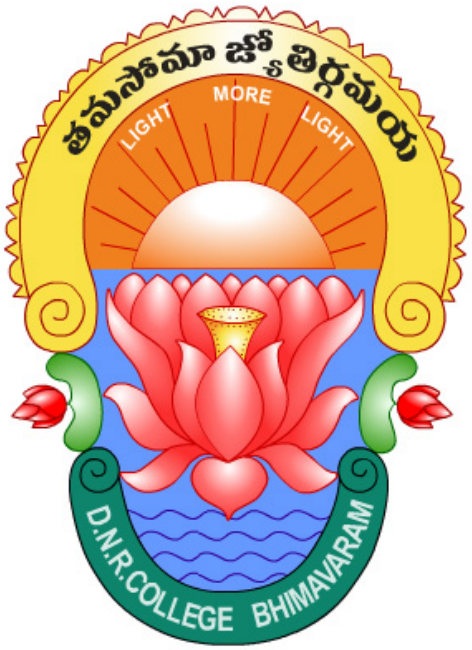
PAPER –III

MODERN ORGANIC SYNTHESIS



By

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ENOLATES

Introduction

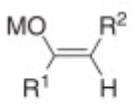
Enolates, or oxyallyl anions, are versatile reagents for the formation of α-substituted carbonyl compounds and are therefore important intermediates for the synthesis of complex molecules. The stereochemical outcome of an enolate reaction often depends on the geometry of the enolate and therefore the selective formation of enolates is a key step in many bond-forming processes.[1]

The counterion of an enolate has a pronounced influence on competing transition states of enolate reactions. The effect is often the result of cation chelation by the carbonyl oxygen atom and one or more additional basic portions of the reactants. For example, alkylation of chiral enolates may lead to more or less diastereomerically pure products and selectivity often depends on the countercation. The importance of the countercation in controlling enolate reaction product distributions requires that the synthetic chemist has at hand stereoselective methods for the preparation of enolate anions with a wide variety of counterions. This chapter is divided into several sections. The 10 following sections describe important current methods for preparing Li, Mg, B, Al, Sn, Ti, Zr, Cu, Zn and other transition metal enolates.

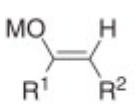
Enolates occur commonly in only two forms: the metal may be found either closer to the oxygen or closer to the carbon atom. Groups I, II and III enolates exist as O-metal tautomers. These strongly electropositive metals bind closely to the oxygen atom. Among transition metal enolates both types of enolates are observed. In a few transition metal enolates the cation is associated with a delocalized enolate anion (η^3-enolate complexes).

The structures of enolates have been examined through magnetic resonance studies (NMR) and with X-ray crystallography.[2–12] It has been observed that solvated enolates exist as dimers, tetramers or hexamers, depending on the enolate structure, the nature of the cation and the solvent.

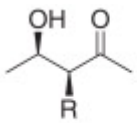
The following nomenclature for enolate stereoisomers is adopted throughout this chapter: the (*E*)/(*Z*) nomenclature is used according to the Cahn-Ingold-Prelog rules, with one change. At the carbonyl C-atom, the OM (oxy-metal) group is defined to be of highest priority without regard to the nature of the metal,[1] for example, (**1**) and (**2**). This has the advantage that changing the metal associated with a given enolate does not affect the (*E*)/(*Z*) nomenclature.



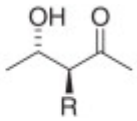
(**1**) (*Z*)



(**2**) (*E*)



(**3**) *syn/erythro*

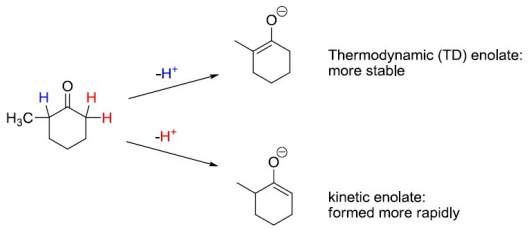


(**4**) *anti/threo*

Kinetic vs Thermodynamic Enolates

An asymmetric ketone with hydrogens at both α-carbons can form two regioisomeric enolates.

If the two α-carbons differ in their degree of substitution, it may be possible to control which of the two regioisomers predominates.



Removal of a proton from the more substituted (and more hindered) α -carbon gives the enolate with the more substituted C=C double bond. This enolate is the more thermodynamically stable, and is referred to as the thermodynamic (TD) enolate. Compare this with Zaitsev's rule, which predicts that reactions that form alkenes favour the production of the more substituted alkene.

Removal of a proton from the less substituted (and less hindered) α -carbon gives the enolate with the less substituted C=C double bond. This enolate is less stable than the TD enolate, but it is formed more rapidly because the hydrogen being removed is more sterically accessible.

In reactions where one product is kinetically favoured and another thermodynamically favoured, the kinetic result is favoured by low temperatures and an irreversible reaction. However, if the reaction is reversible, the kinetic product can revert back to starting material and react again, possibly forming the thermodynamic product. Higher temperatures would then increase the rate at which the two products interconvert.

In the case of enolate formation: if deprotonation is rapid, quantitative, and irreversible, the kinetic enolate predominates because it is formed more rapidly. The pKa difference between diisopropylamine (36) and a ketone (18-20) indicates that the deprotonation of a ketone with LDA will meet these criteria. Once "locked" as the kinetic enolate, it doesn't matter that it's also the less stable enolate. Thus a strong, hindered base like LDA, at low temperatures, typically will favour formation of the kinetic enolate.

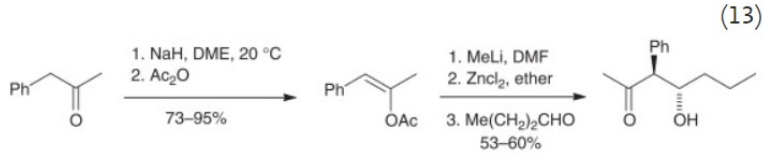
However, if the pKa difference between the base and the enolate is not great, then enolate formation is reversible. The enolates can interconvert between the TD and kinetic, and over time the more stable TD enolate will predominate. Weaker bases such as alkoxides or amines, and higher temperatures, favour formation of the TD enolate.

Alkylation of Enolate Ions

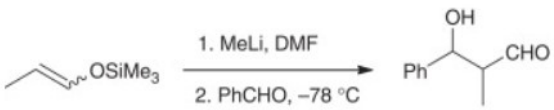
Enolates, formed by the abstraction of the α hydrogen atom by a strong base, are nucleophiles. Lithium diisopropylamide (LDA) or sodium hydride are required as bases. The site of proton abstraction is related to the acidity of the two possible α hydrogen atoms, which is in the order primary > secondary > tertiary. Reaction of the enolate with an alkyl halide forms a alkylated ketones. Multiple alkylation can occur as the result of proton exchange between the original enolate and the alkylated ketone, followed by alkylation of that enolate ion.

Enolates from Enol Esters and Silyl Enol Ethers

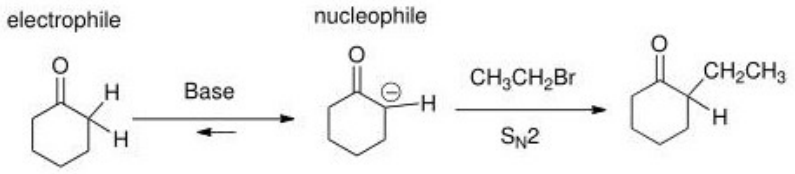
Enolates can also be prepared by reaction of enol esters[16,22,23] or silyl enol ethers[16,24] with alkyllithium reagents. House has worked out a protocol wherein these enolates are allowed to react with aldehydes to give the corresponding aldols.[25] Higher yields of aldol products are obtained when the lithium enolate is generated in ether or 1,2-dimethoxyethane (DME) by reaction of an enol acetate with methyllithium. Lower yields are obtained if the enolate is produced by reaction of a silyl enol ether with methyllithium. For the aldol reaction, ether or mixtures of ether and DME are superior to THF. Acceptable yields of aldol adducts are obtained in ether at low temperatures (–20 to −50 °C). In the more polar solvents DME or THF, the addition of anhydrous $ZnCl_2$ or $MgBr_2$ results in higher yields. An example is seen in equation 13.[25b] The stereochemistry of this process is discussed in Section 2.08.5.

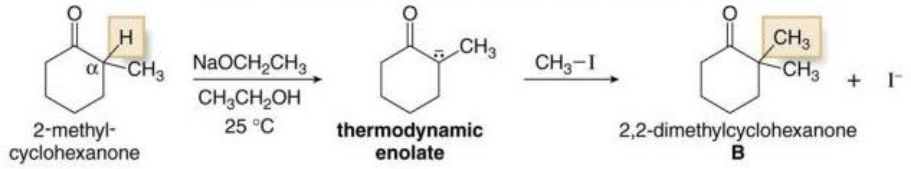


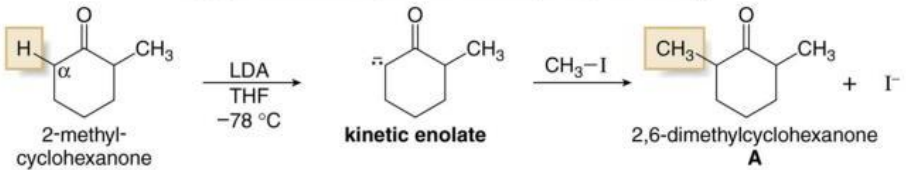
The enol ester or silyl enol ether route to enolates has advantages over direct deprotonation in certain cases. If direct deprotonation provides a mixture of regio- or stereo-isomers, it is often possible to trap the enolate mixture by esterification or silylation, separate the desired enol ester or silyl enol ether and regenerate the enolate by reaction with methyllithium. It is also useful for preparation of enolates from substances that are so electrophilic that direct deprotonation is complicated by self-aldolization. For example, aldehyde enolates have been prepared in this manner (equation 14).[9c]

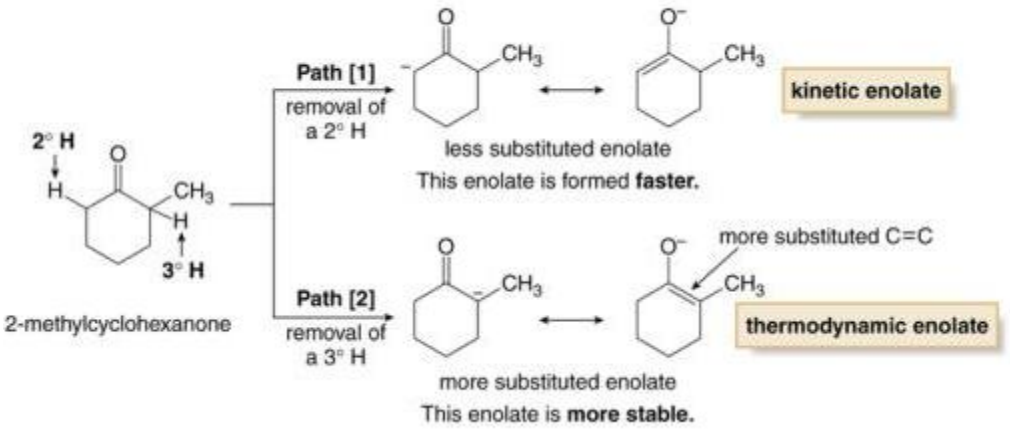


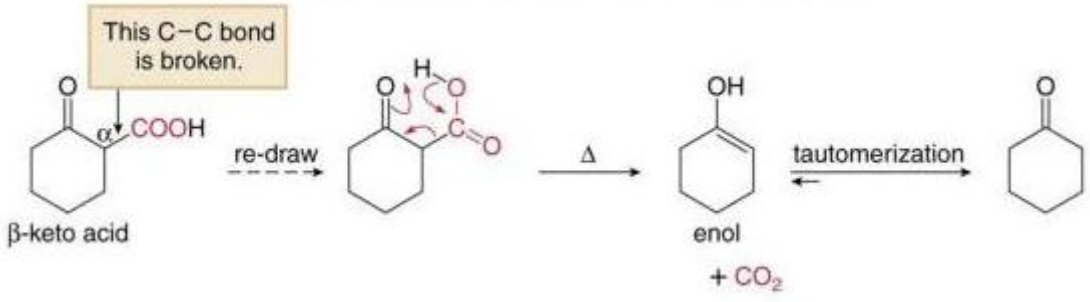
Applications :









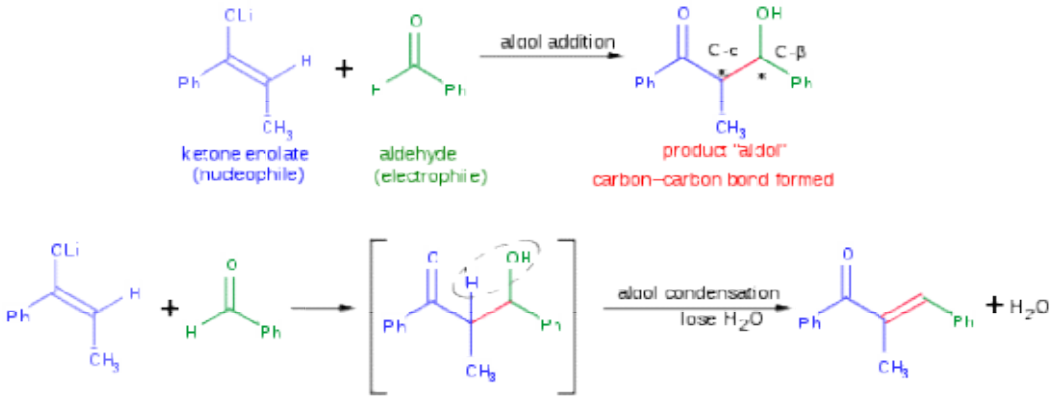


Aldol reaction :

The aldol reaction is a means of forming carbon–carbon bonds in organic chemistry.[1][2][3] Discovered independently by the Russian chemist Alexander Borodin in 1869[4] and by the French chemist Charles-Adolphe Wurtz in 1872,[5][6][7] the reaction combines two carbonyl compounds (the original experiments used aldehydes) to form a new β-hydroxy carbonyl compound. These products are known as *aldols*, from the *ald*ehyde + alcoh*ol*, a structural motif seen in many of the products. Aldol structural units are found in many important molecules, whether naturally occurring or synthetic.[8][9][10] For example, the aldol reaction has been used in the large-scale production of the commodity chemical pentaerythritol[11] and the synthesis of the heart disease drug Lipitor (atorvastatin, calcium salt).[12][13]

The aldol reaction unites two relatively simple molecules into a more complex one. Increased complexity arises because up to two new stereogenic centers (on the α- and β-carbon of the aldol adduct, marked with asterisks in the scheme below) are formed. Modern methodology is capable of not only allowing aldol reactions to proceed in high yield but also controlling both the relative and absolute configuration of these stereocenters.[14] This ability to selectively synthesize a particular stereoisomer is significant because different stereoisomers can have very different chemical and biological properties.

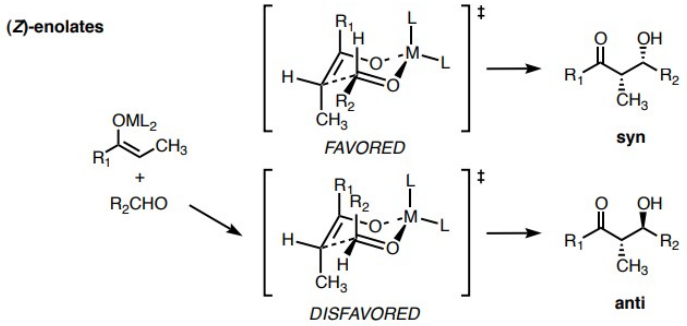
For example, stereogenic aldol units are especially common in polyketides, a class of molecules found in biological organisms. In nature, polyketides are synthesized by enzymes that effect iterative Claisen condensations. The 1,3-dicarbonyl products of these reactions can then be variously derivatized to produce a wide variety of interesting structures. Often, such derivitization involves the reduction of one of the carbonyl groups, producing the aldol subunit. Some of these structures have potent biological properties: the immunosuppressant FK506, the anti-tumor agent discodermolide, or the antifungal agent amphotericin B, for example. Although the synthesis of many such compounds was once considered nearly impossible, aldol methodology has allowed their efficient synthesis in many cases.[15]



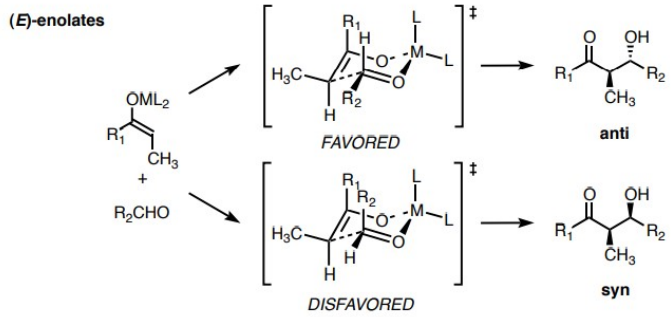
A typical modern aldol addition reaction, shown above, might involve the nucleophilic addition of a ketone enolate to an aldehyde. Once formed, the aldol product

can sometimes lose a molecule of water to form an α,β-unsaturated carbonyl compound. This is called *aldol condensation*. A variety of nucleophiles may be employed in the aldol reaction, including the enols, enolates, and enol ethers of ketones, aldehydes, and many other carbonyl compounds. The electrophilic partner is usually an aldehyde or ketone (many variations, such as the Mannich reaction, exist). When the nucleophile and electrophile are different, the reaction is called a *crossed aldol reaction*; on the converse, when the nucleophile and electrophile are the same, the reaction is called an *aldol dimerization*.

Zimmerman-Traxler Chair-Like Transition States



The enantiomeric transition states (not shown) are, by definition, of equal energies. The pericyclic transition state determines syn/anti selectivity. To differentiate two syn or two anti transition states, a chiral element must be introduced (e.g., R1, R2, or L), thereby creating diastereomeric transition states which, by definition, are of different energies.



Zimmerman and Traxler proposed that the aldol reaction with metal enolates proceeds via a chair-like, pericyclic process. In practice, the stereochemistry can be highly metal dependent. Only a few metals, such as boron, reliably follow the indicated pathways. • (Z)- and (E)-enolates afford syn- and anti-aldol adducts, respectively, by minimizing 1,3-diaxial interactions between R1 and R2 in each chair-like TS

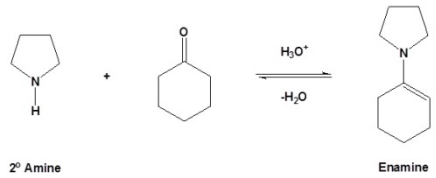
Stork Enamine Reaction

Ketones cannot be directly alkylated or acylated but when treated with secondary amines they are converted into enamines which can further react with various reagents. Thus, enamines can react with alkyl halides forming alkylated carbonyl compounds, and also can react with α,β-unsaturated aldehydes or ketones forming acylated carbonyl compounds.

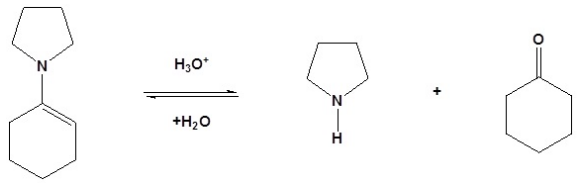
This process involves:

1) From ketone *or* aldehyde;
2) Addition of the enamine to an α,β-unsaturated aldehyde *or* ketone or alkyl halide;
3) Hydrolysis of alkylated/acylated enamine back to starting ketone *or* aldehyde.

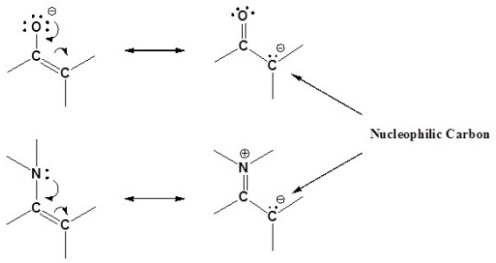
The beginning of the mechanism is the same for all further reactions regardless of which reagents are added.



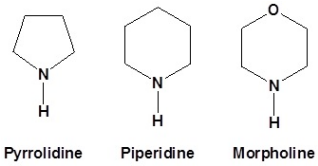
Reversible



Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an eletrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over and enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. These reactions are generally known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.



Typically we use the following 2° amines for enamine reactions

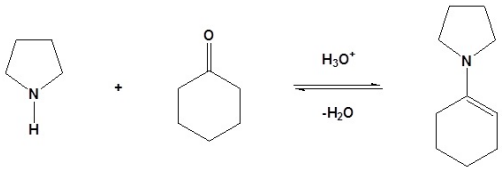


Alkylation of an Enamine

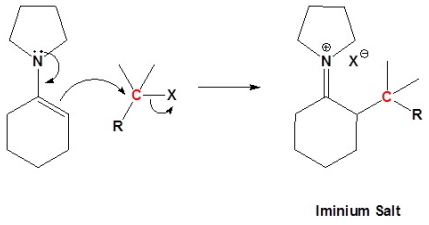
Enamined undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

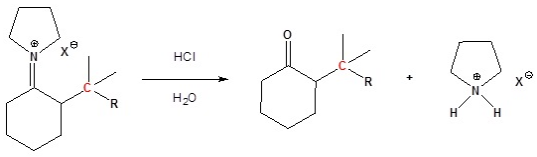
1) Formation of an enamine



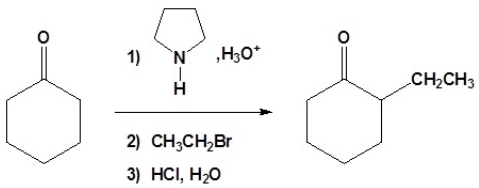
2) S_N2 Alkylation



3) Reform the carbonyl by hydrolysis



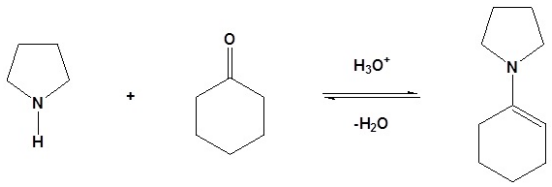
All three steps together:



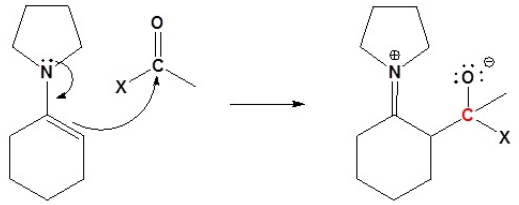
Acylation of Enamines

Enamine can react with acid halides to form β-dicarbonyls

1) Formation of the enamine

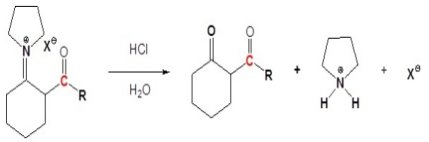


2) Nucleophilic attack

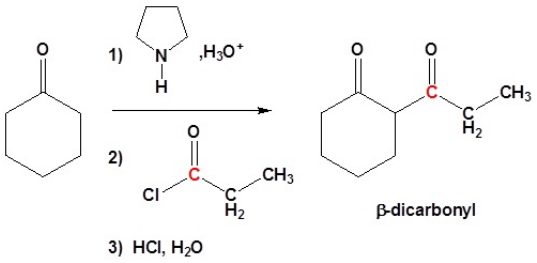


Iminium Salt

3) Reform the carbonyl by hydrolysis

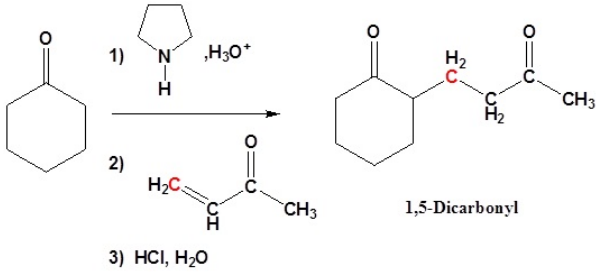


All three steps together:



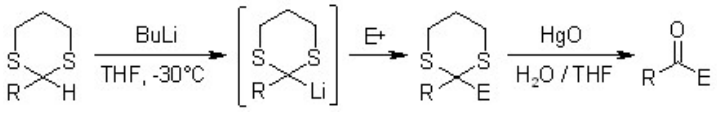
Michael Addition using Enamines

Enamines, like other weak bases, add 1,4 to enones. The end product is a 1,5 dicarbonyl compound.



SULPHUR CHEMISTRY

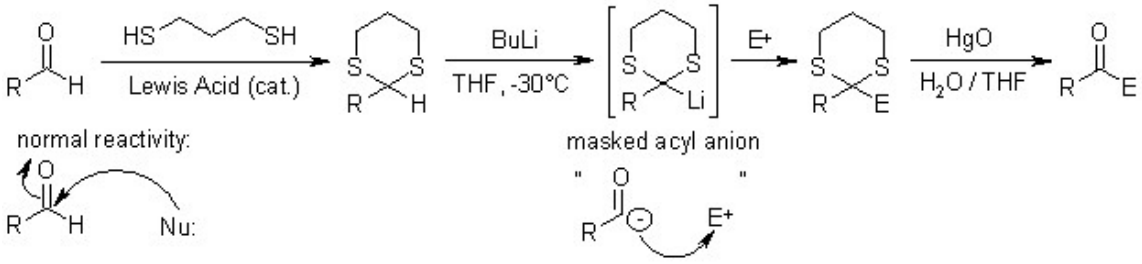
Corey-Seebach Reaction
Seebach Umpolung



The Corey-Seebach Reaction uses lithiated 1,3-dithianes as nucleophilic acylating agents.

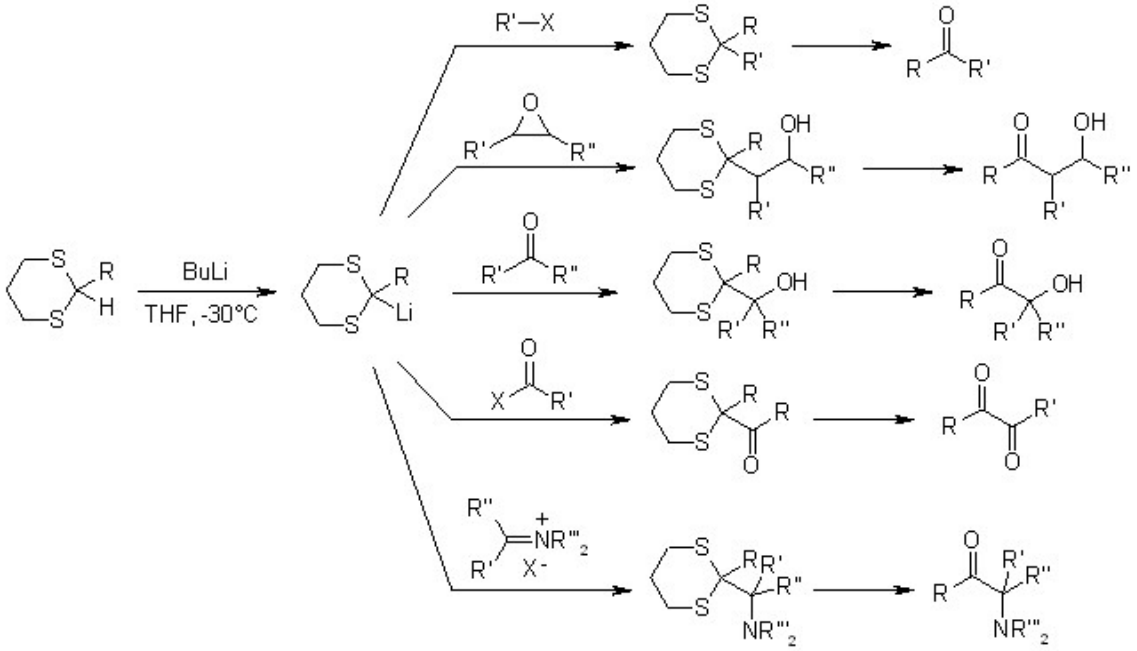
Mechanism of the Corey-Seebach Reaction

The Corey-Seebach Reaction allows a reversal of the normal reactivity of acyl carbon atoms, which combine only with nucleophiles. The German term "Umpolung" is widely used for this inversion of reactivity.



The lithiated 1,3-dithiane can be viewed as an masked acyl anion that is able to react with various electrophiles.

The acidity difference of hydrogen atoms adjacent to divalent sulfur compared to oxygen stems from the greater polarizability of sulfur and the longer C-S-bond length; d-orbitals are not involved. In most cases treatment of dithianes with *n*-BuLi at temperatures of -30 °C is sufficient for the preparation of the lithio-derivatives. With pK_A values of approximately 30, lithiated dithianes can react with aldehydes or ketones, epoxides and acid derivatives, but also with alkyl halides without competing elimination reactions.



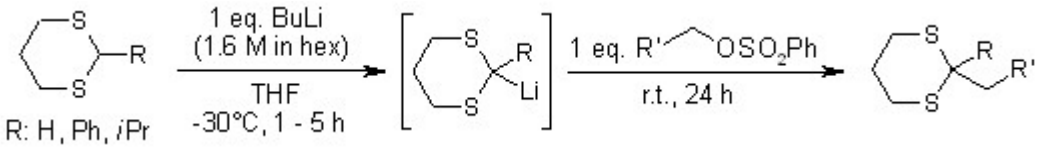
Umpolung offers access to a wide range of products, especially 1,2-diketones and α-hydroxy ketones, products that cannot be obtained using the normal reactivity (for example through aldol addition).

Among the other thioacetals that could be used for Umpolung, metallated dithiolanes undergo fragmentation and disproportionate to ethene and dithiocarboxylates:

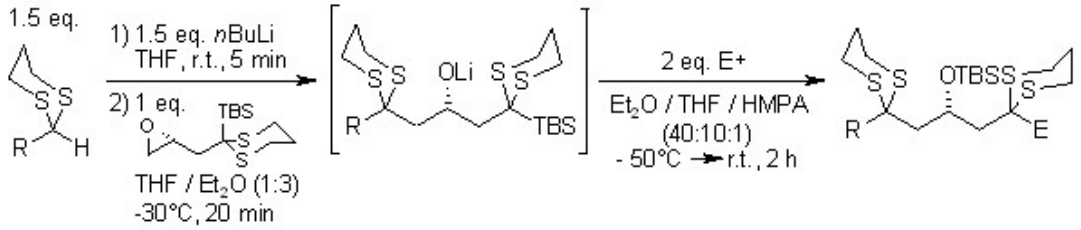
1,3-Dithianes are readily prepared from aldehydes (for an overview, see 1,3-dithianes as protecting group) and offer high stability towards acids and bases. Therefore, use of the S,S-acetal unit is especially useful in multistep synthesis. A crucial step is the hydrolysis of S,S-acetals, the difficulty of which is due to the excellent nucleophilicity of sulfur.

Only irreversible removal of the dithiol or of the solvolysis products can push the equilibrium to the right. Methods of choice are transacetalization to a highly reactive carbonyl derivative, alkylation to sulfide, oxidation of the thiol (for recent methods see deprotection of 1,3-dithianes) and formation of metal thiolates, for which mercury(II) salts are frequently used.

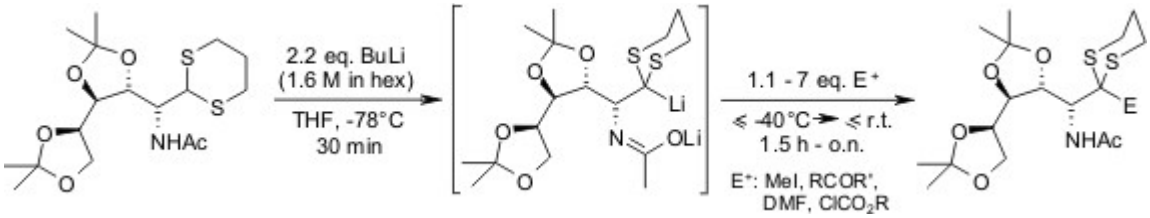
Alkylation of 2-Lithio-1,3-dithianes with Arenesulfonates of Primary Alcohols



Anion Relay Chemistry: An Effective Tactic for Diversity Oriented Synthesis



Trimethylene Dithioacetals of Carbohydrates, Part 6: C-C Coupling Reactions of Dilithiated *N*-Acetyl-D-glucosamine Trimethylene Dithioacetal Derivatives



SULPHUR YLIDES

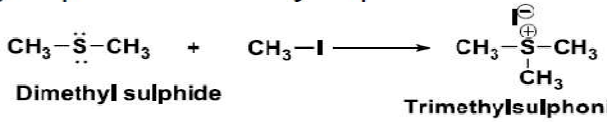
Synthesis of Epoxides and Cyclopropanes

The most important sulphur ylides are dimethylsulfonium methylide and dimethylsulfoxonium methylide (Corey-Chaykovsky reagent).

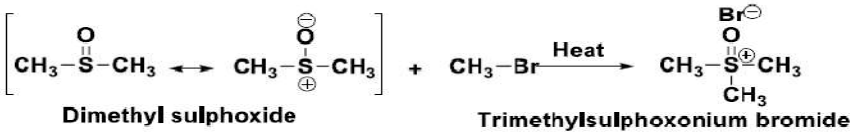
Dimethylsulfonium methylide — **Sulphonium ylide**

Dimethylsulfoxonium methylide — **Sulphoxonium ylide**

These ylides are prepared by deprotonation of the corresponding sulfonium salts, which can be prepared from the reaction of either dimethylsulphide or dimethylsulphoxide with methyl iodide.

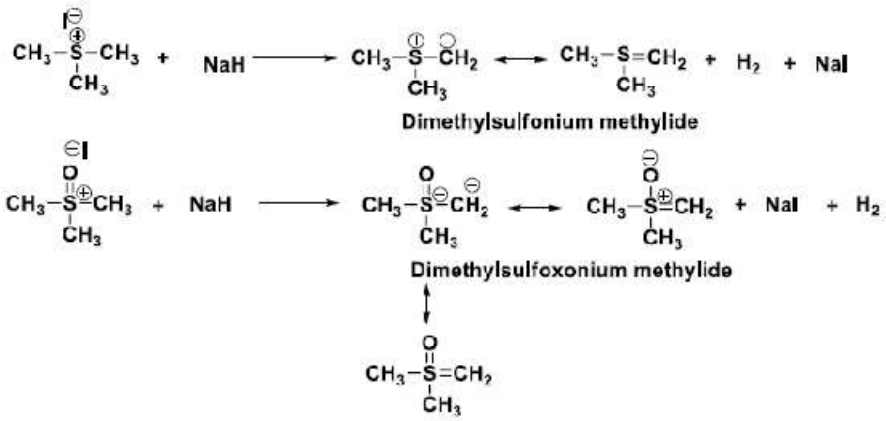


Dimethyl sulphide — **Trimethylsulphonium iodide**

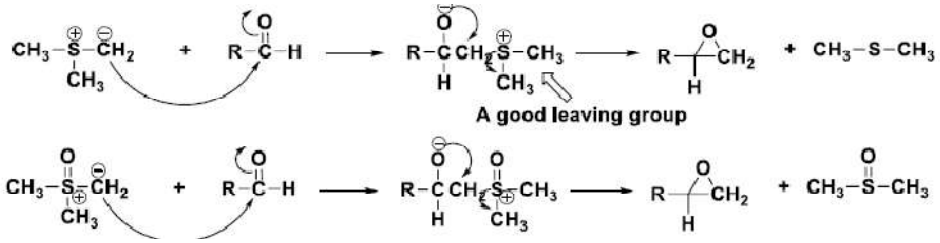


Dimethyl sulphoxide — **Trimethylsulphoxonium bromide**

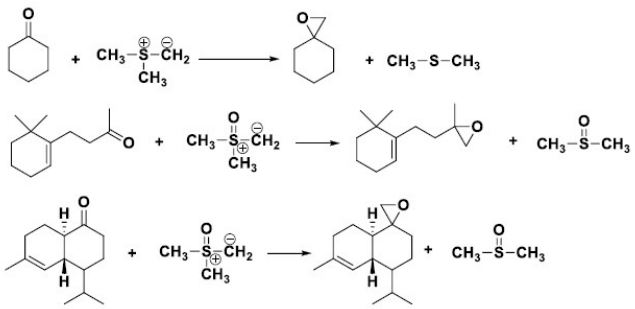
Synthesis of Epoxides from Aldehydes and Ketones from Sulphur Ylides



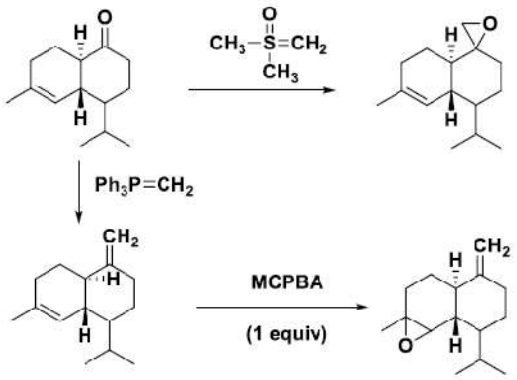
Whereas phosphorous ylides react to provide alkenes, sulphur ylides (dimethylsulfonium methylide and dimethylsulfoxonium methylide) react with saturated aldehydes and ketones to provide epoxides.



Synthesis of Epoxides from Sulphur Ylides



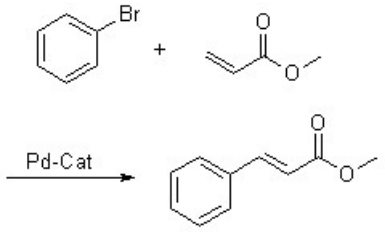
Envisage an alternative attempt through epoxidation of an alkene



Organopalladium chemistry

Organopalladium chemistry is a branch of organometallic chemistry that deals with organic palladium compounds and their reactions. Palladium is often used as a catalyst in the reduction of alkenes and alkynes with hydrogen. This process involves the formation of a palladium-carbon covalent bond. Palladium is also prominent in carbon-carbon coupling reactions, as demonstrated in tandem reactions.

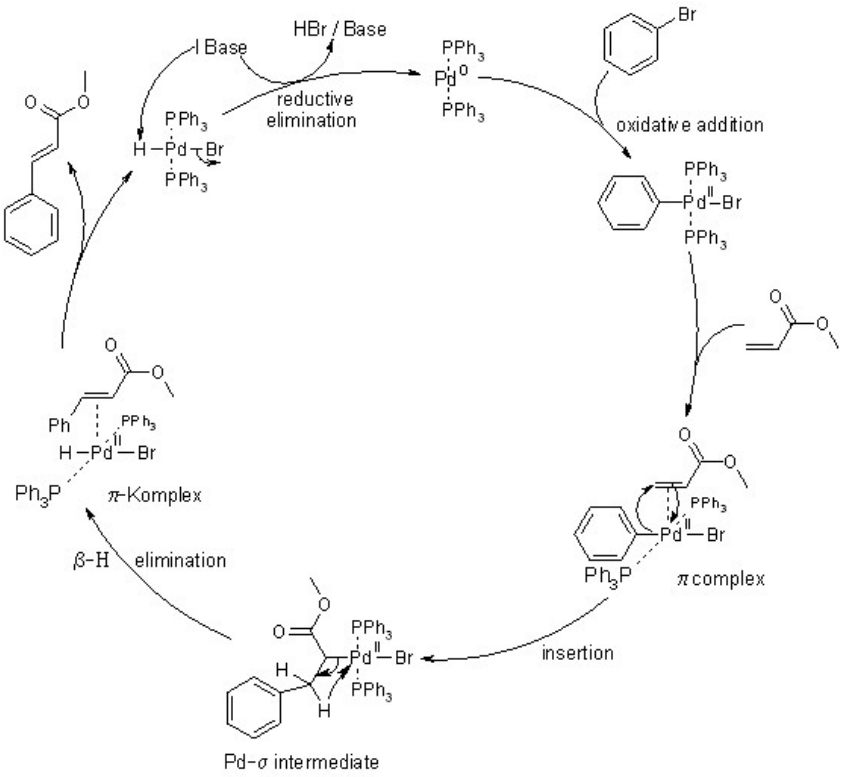
Heck Reaction



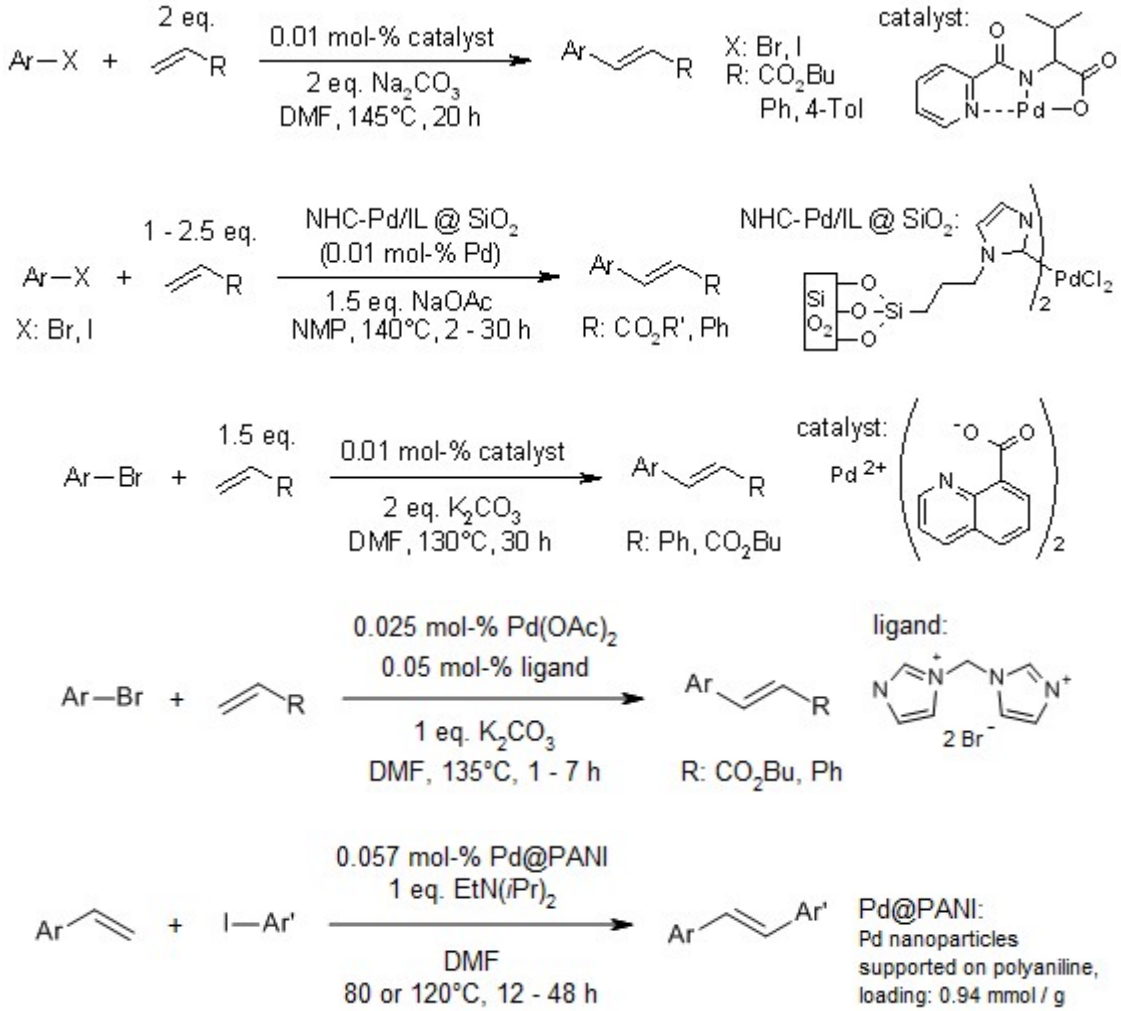
The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the "Heck Reaction". Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.

One of the benefits of the Heck Reaction is its outstanding *trans* selectivity.

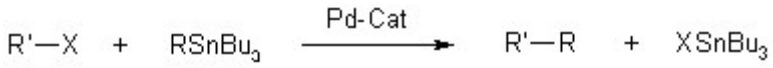
Mechanism of the Heck Reaction



Applications :

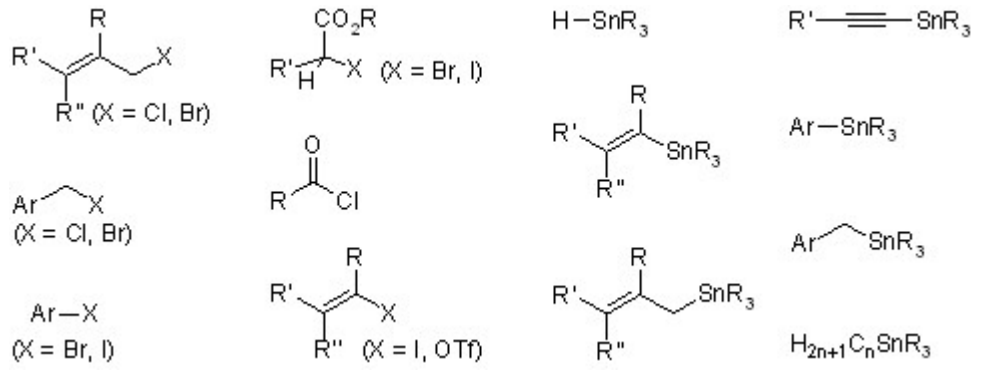


Stille Coupling

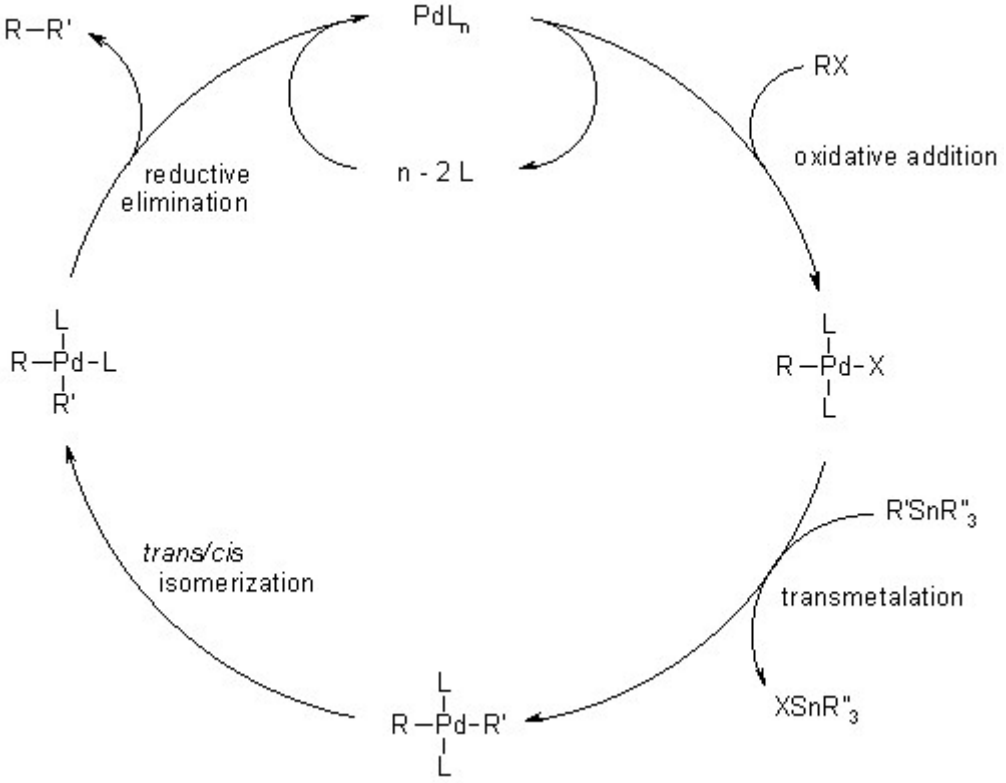


The Stille Coupling is a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, with very few limitations on the R-groups. Well-elaborated methods allow the preparation of different products from all of the combinations of halides and stannanes depicted below. The main drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki Coupling. Improvements in the Suzuki Coupling may soon lead to the same versatility without the drawbacks of using tin compounds.

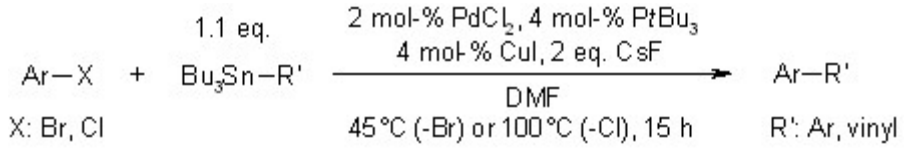
Convenient electrophiles and stannanes:

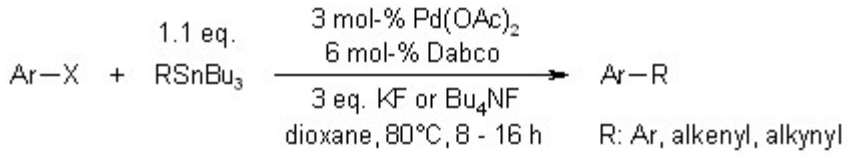


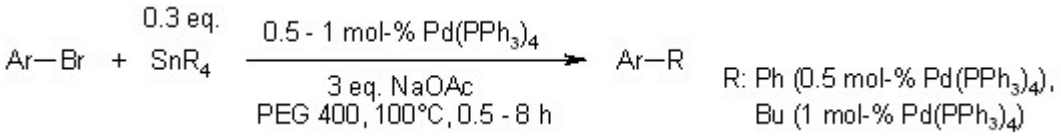
Mechanism of the Stille Coupling

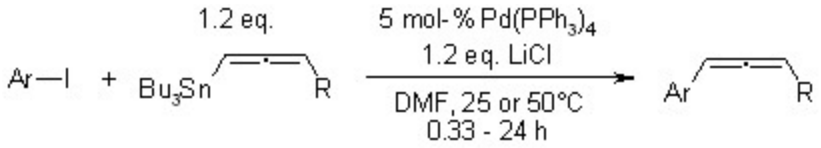


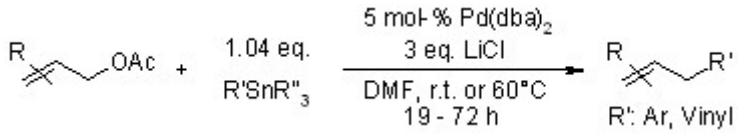
Applications

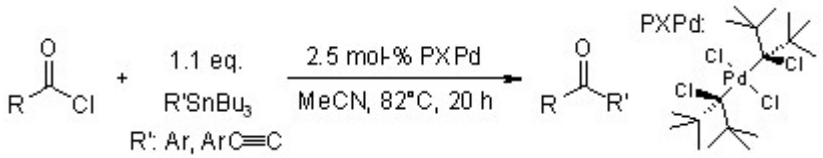




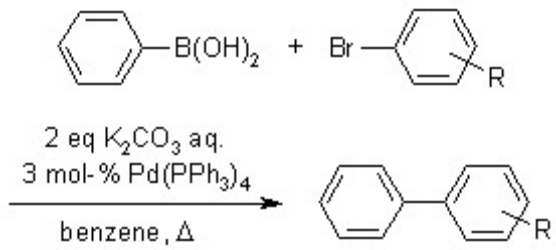








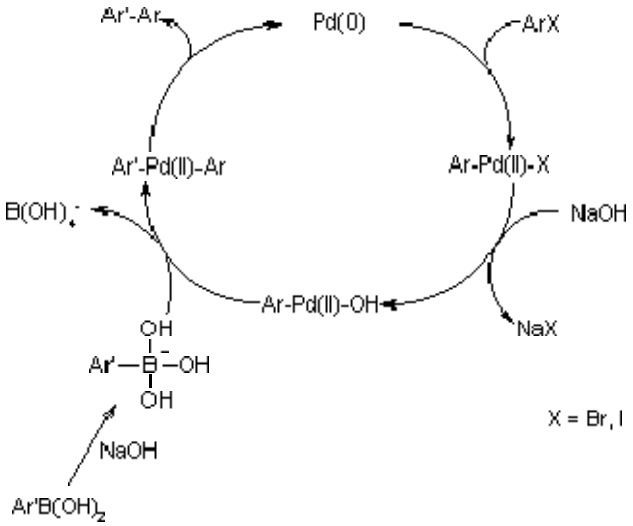
Suzuki Coupling



The scheme above shows the first published Suzuki Coupling, which is the palladium-catalysed cross coupling between organoboronic acid and halides. Recent catalyst and methods developments have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners.

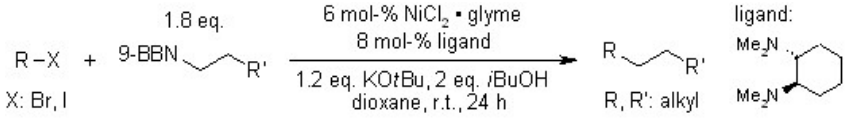
Mechanism of the Suzuki Coupling

One difference between the Suzuki mechanism and that of the Stille Coupling is that the boronic acid must be activated, for example with base. This activation of the boron atom enhances the polarisation of the organic ligand, and facilitates transmetallation. If starting materials are substituted with base labile groups (for example esters), powdered KF effects this activation while leaving base labile groups unaffected.

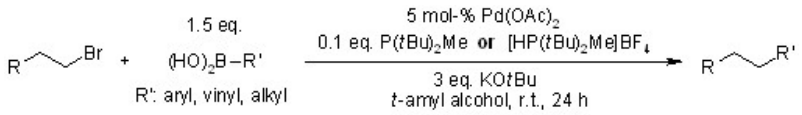


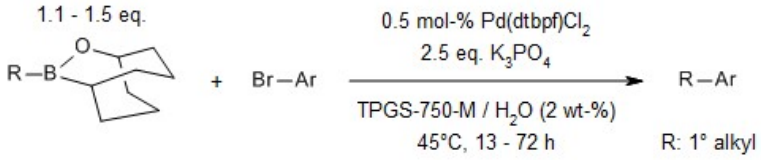
In part due to the stability, ease of preparation and low toxicity of the boronic acid compounds, there is currently widespread interest in applications of the Suzuki Coupling, with new developments and refinements being reported constantly.

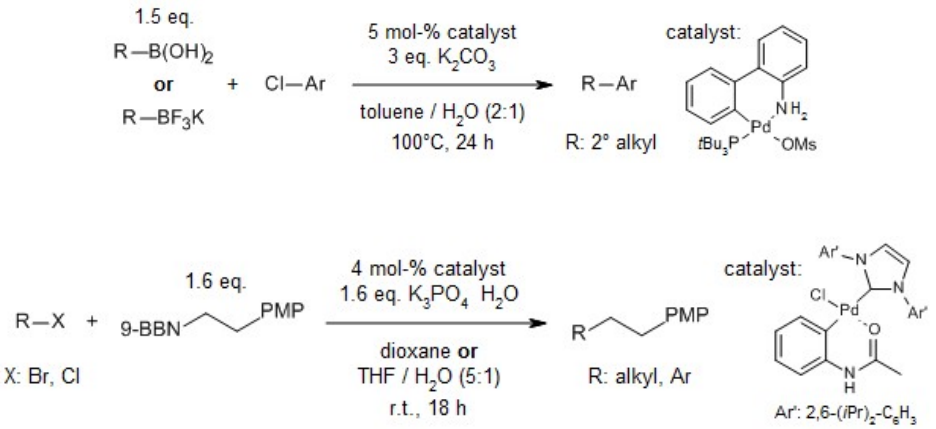
Applications :



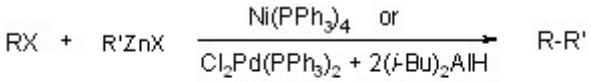
Alkyl-Alkyl Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides at Room Temperature







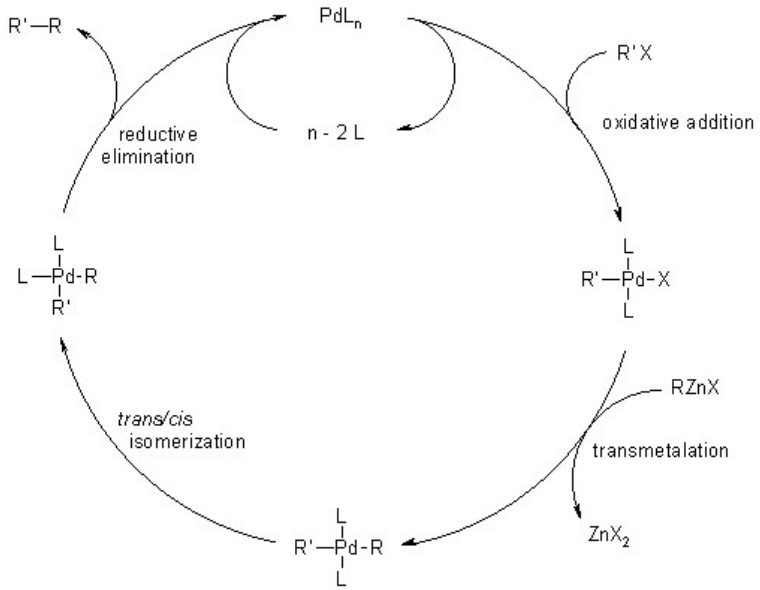
Negishi Coupling



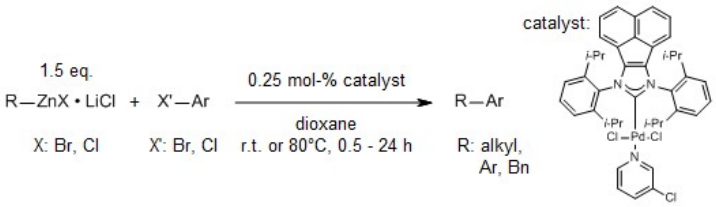
R = alkenyl, aryl, allyl, benzyl, propargyl
R' = akenyl, aryl, alkynyl, alkyl, benzyl, allyl

The Negishi Coupling, published in 1977, was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. The versatile nickel- or palladium-catalyzed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl) has broad scope, and is not restricted to the formation of biaryls.

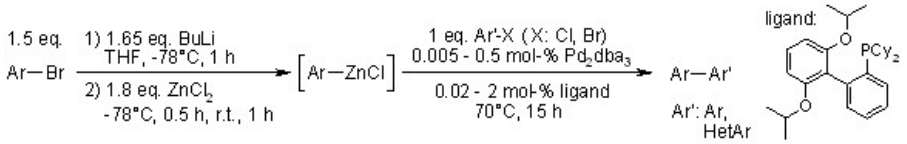
Mechanism of the Negishi Coupling



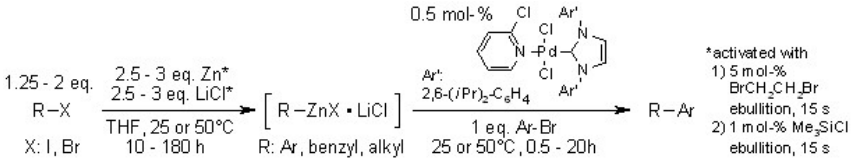
Applications



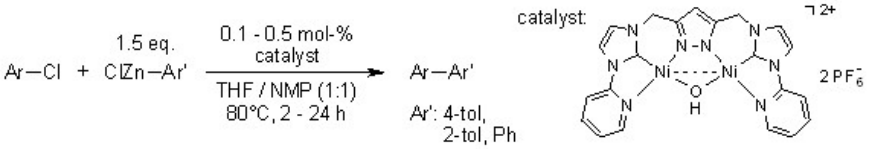
Mild Negishi Cross-Coupling Reactions Catalyzed by Acenaphthoimidazolylidene Palladium Complexes at Low Catalyst Loadings



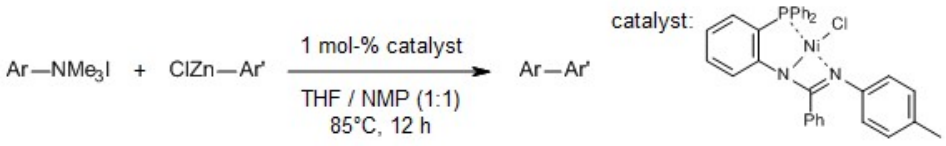
An Extremely Active Catalyst for the Negishi Cross-Coupling Reaction



One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates

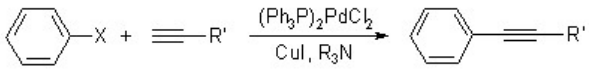


Efficient Negishi Coupling Reactions of Aryl Chlorides Catalyzed by Binuclear and Mononuclear Nickel-N-Heterocyclic Carbene Complexes

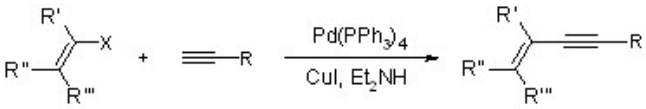


Cross-Coupling of Aryltrimethylammonium Iodides with Arylzinc Reagents Catalyzed by Amido Pincer Nickel Complexes

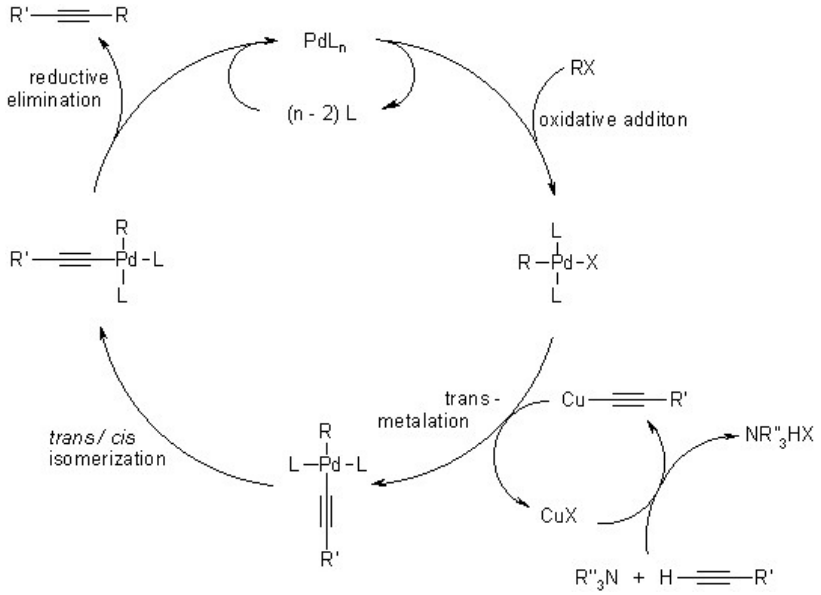
Sonogashira Coupling



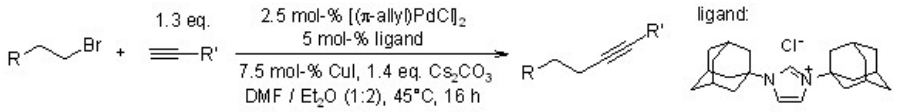
This coupling of terminal alkynes with aryl or vinyl halides is performed with a palladium catalyst, a copper(I) cocatalyst, and an amine base. Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions are not important.



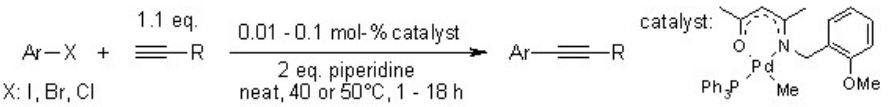
Mechanism of the Sonogashira Coupling



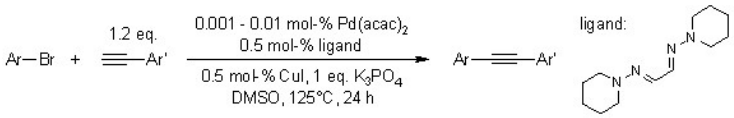
Applications :



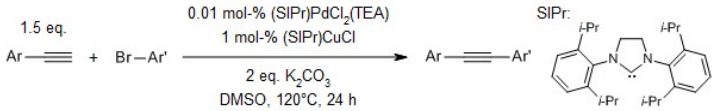
The First Applications of Carbene Ligands in Cross-Couplings of Alkyl Electrophiles: Sonogashira Reactions of Unactivated Alkyl Bromides and Iodides



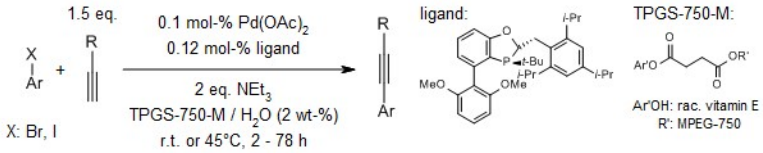
Efficient Sonogashira Coupling Reaction Catalyzed by Palladium(II) β-Oxoiminatophosphane Complexes under Mild Conditions



Hydrazone-Promoted Sonogashira Coupling Reaction with Aryl Bromides at Low Palladium Loadings

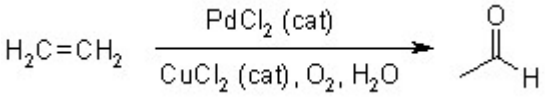


Sonogashira Couplings Catalyzed by Collaborative (*N*-Heterocyclic Carbene)-Copper and -Palladium Complexes

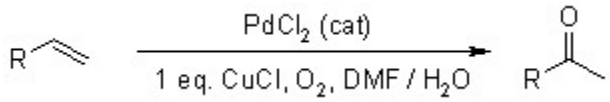


Sustainable HandaPhos-*ppm* Palladium Technology for Copper-Free Sonogashira Couplings in Water under Mild Conditions

Wacker-Tsuji Oxidation



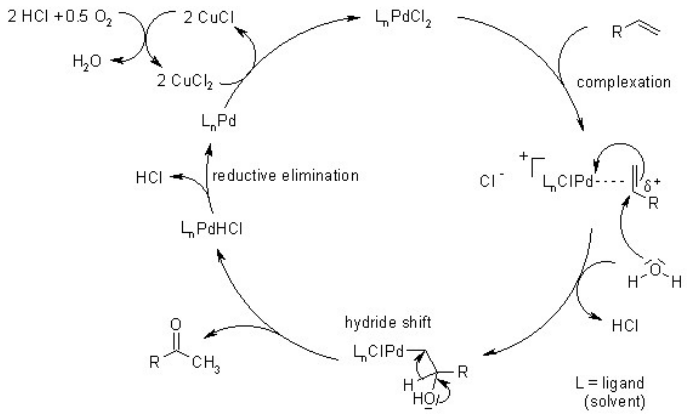
The Wacker Oxidation is an industrial process, which allows the synthesis of ethanal from ethene by palladium-catalyzed oxidation with oxygen. Copper serves as redox cocatalyst.



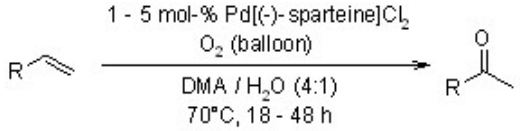
The lab scale modification - the Wacker-Tsuji Oxidation - is useful for the synthesis of various ketones.

Mechanism of the Wacker-Tsuji Oxidation

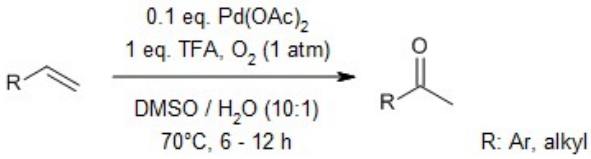
The mechanism is typical of palladium olefin chemistry, and water serves as the oxygen source; the reduced palladium is reoxidized by Cu(II) and ultimately by atmospheric oxygen.



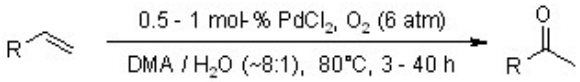
Applications :



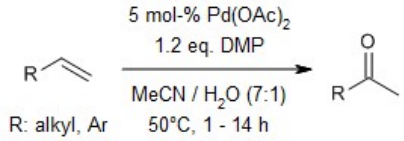
Discovery of a Practical Direct O_2-Coupled Wacker Oxidation with Pd[(-)-sparteine]Cl_2



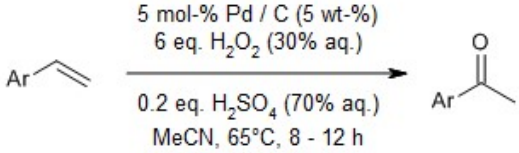
Wacker-Type Oxidation and Dehydrogenation of Terminal Olefins Using Molecular Oxygen as the Sole Oxidant without Adding Ligand



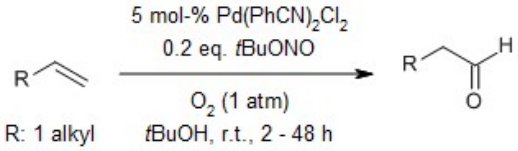
Convenient and Efficient Pd-Catalyzed Regioselective Oxyfunctionalization of Terminal Olefins by Using Molecular Oxygen as Sole Reoxidant



Hypervalent Iodine as a Terminal Oxidant in Wacker-Type Oxidation of Terminal Olefins to Methyl Ketones



Selective Oxidation of Styrene Derivatives to Ketones over Palladium(0)/Carbon with Hydrogen Peroxide as the Sole Oxidant



tert-Butyl Nitrite: Organic Redox Cocatalyst for Aerobic Aldehyde-Selective Wacker-Tsuji Oxidation

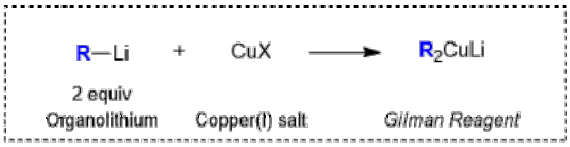
ORGANOCOPPER CHEMISTRY

Organocopper compounds in organometallic chemistry contain carbon to copper chemical bonds. Organocopper chemistry is the science of organocopper compounds describing their physical properties, synthesis and reactions.[1][2][3] They are reagents in organic chemistry.

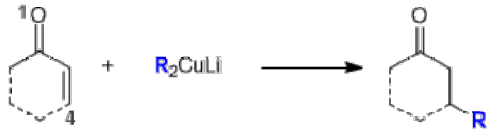
The first organocopper compound, the explosive copper(I) acetylide Cu_2C_2 (Cu-C≡C-Cu), was synthesized by Rudolf Christian Böttger in 1859 by passing acetylene gas through copper(I) chloride solution:[4]

$$C_2H_2 + 2\ CuCl \rightarrow Cu_2C_2 + 2\ HCl$$

A **Gilman reagent** is a lithium and copper (diorganocopper) reagent compound, R_2CuLi, where R is an alkyl or aryl. These reagents are useful because, unlike related Grignard reagents and organolithium reagents, they react with organic halides to replace the halide group with an R group (the Corey–House reaction). Such displacement reactions allow for the synthesis of complex products from simple building blocks.[1]

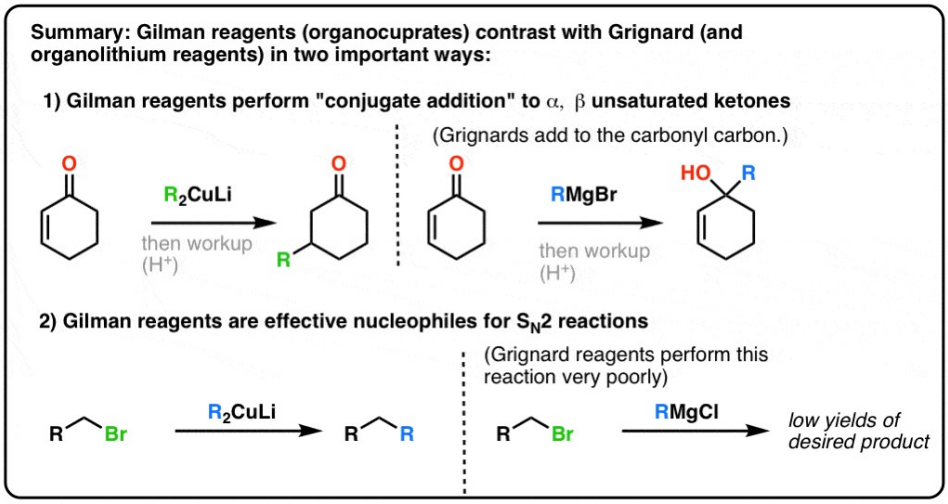


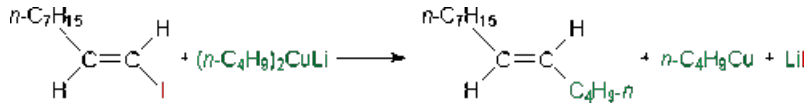
1,4-addition of α,β-unsaturated carbonyl compounds

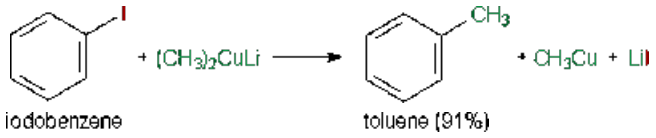


S_N2-type addition of alkyl halides

Applications :



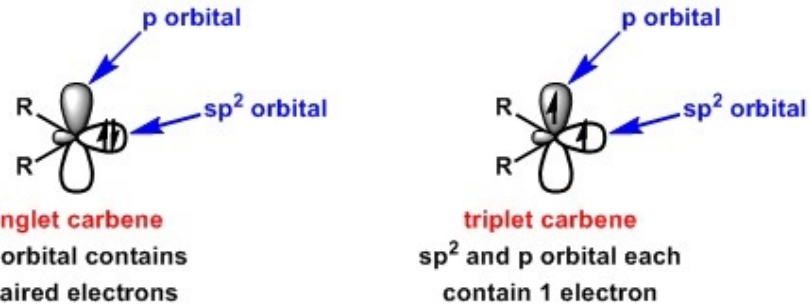




Carbenes/Carbenoids

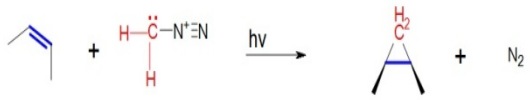
Carbenes are highly reactive species in which the central carbon only has 6 electrons. The electrons are distributed around the carbon so that 4 electrons are in bonds and the remaining 2 are in a non-bonding orbital. However, this representation can be misleading.

Carbenes actually exist in 2 forms; the singlet and triplet form. These are different electronically and also in their chemical reactivity. Which you have can affect the stereochemical outcome of a reaction.

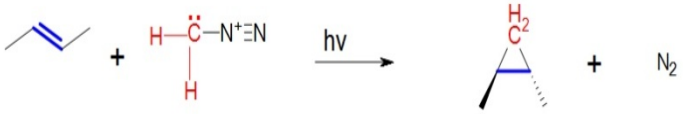


Carbene reaction with alkenes

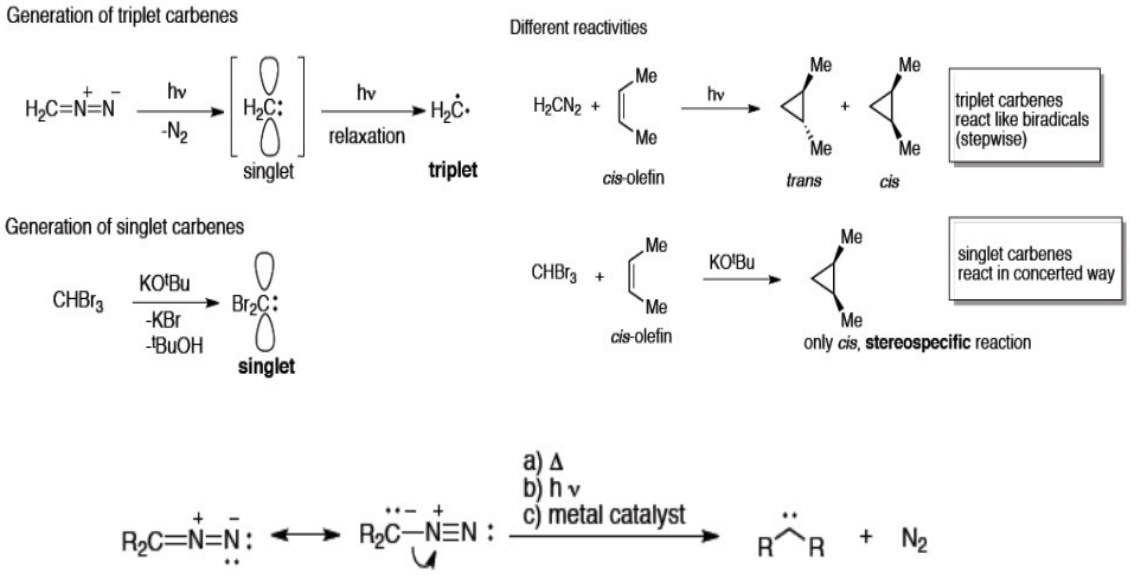
A carbene such as methlyene will react with an alkene which will break the double bond and result with a cyclopropane. The reaction will usually leave stereochemistry of the double bond unchanged. As stated before, carbenes are generally formed along with the main reaction; hence the starting material is diazomethane not methylene.



In the above case *cis*-2-butene is converted to *cis*-1,2-dimethylcyclopropane. Likewise, below the *trans* configuration is maintained.



Generation and reactivity differences of singlet vs triplet carbenes

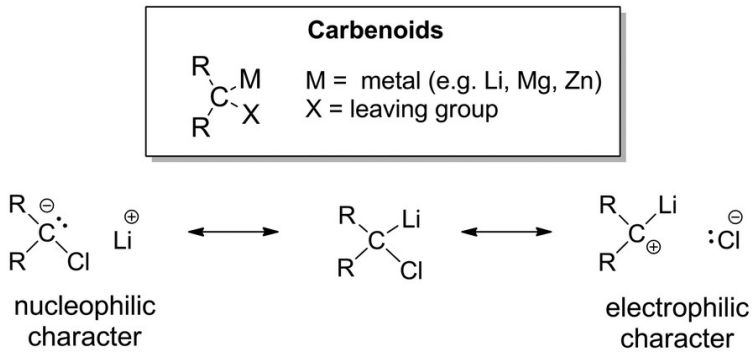


In chemistry a **carbenoid** is a reactive intermediate that shares reaction characteristics with a carbene.[1] In the Simmons–Smith reaction the carbenoid intermediate is a zinc / iodine complex that takes the form of

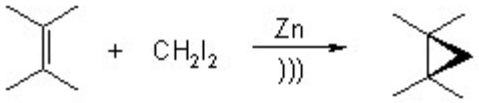
$$I\text{-}CH_2\text{-}Zn\text{-}I$$

This complex reacts with an alkene to form a cyclopropane just as a carbene would do.

Carbenoids appear as intermediates in many other reactions. In one system a carbenoid chloroalkyllithium reagent is prepared in situ from a sulfoxide and t-BuLi which reacts the boronic ester to give an ate complex. The ate complex undergoes a 1,2-metallate rearrangement to give the homologated product, which is then further oxidised to a secondary alcohol.



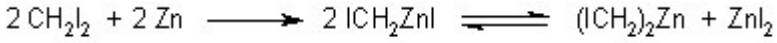
Simmons-Smith Reaction



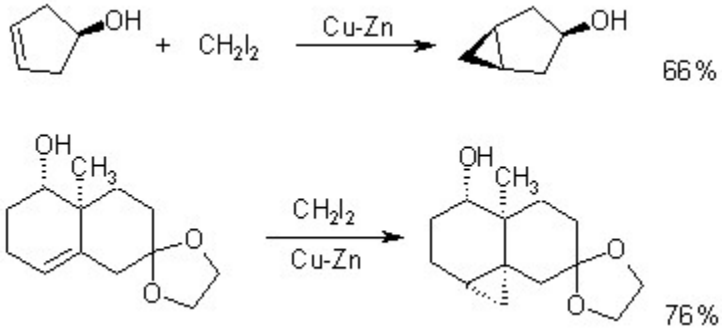
This reaction affords the cyclopropanation of olefins.

Mechanism of the Simmons-Smith Reaction

Ultrasonication improves the rate of formation of these organozinc compounds, as with many organometallic reactions occurring at a surface.

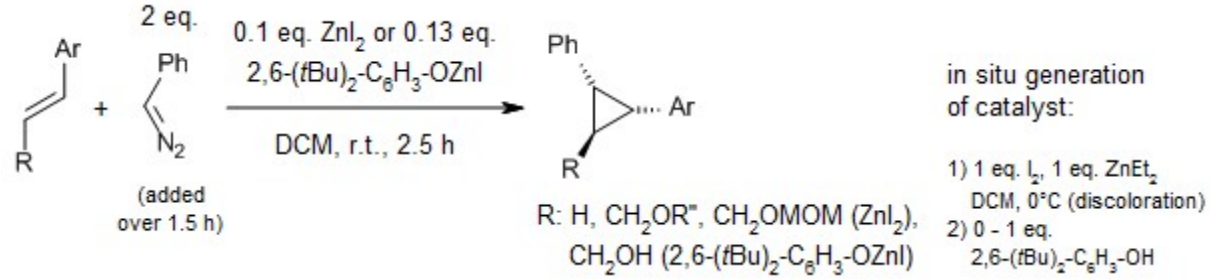


The mechanism has not been fully clarified, but pure carbenes can be excluded, and a metal carbenoid is likely to be involved. The following results may be interpreted to indicate a possible complexation of the active species by hydroxy groups leading to reaction on the same face as this substituent. This would only be possible if an organozinc reagent is present.

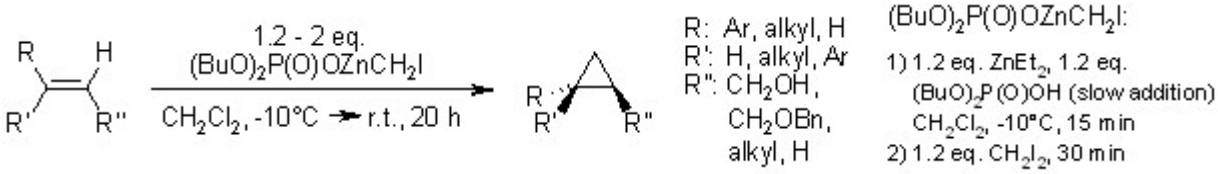


Various research groups have developed variants of the Simmons-Smith cyclopropanating reagent through the replacement of the iodide ligand on the zinc atom with a strongly electron-withdrawing substituent. Whereas the original reagent often requires a directing group such as the hydroxyl of an allylic alcohol, carbenoids such as $CF_3CO_2ZnCH_2I$ and $(PhO)_2P(O)OZnCH_2I$ enable a rapid cyclopropanation of alkenes without the need for such a directing group.

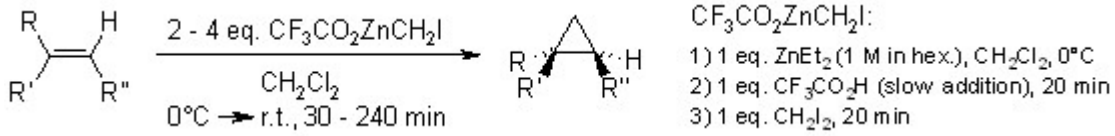
Applications :



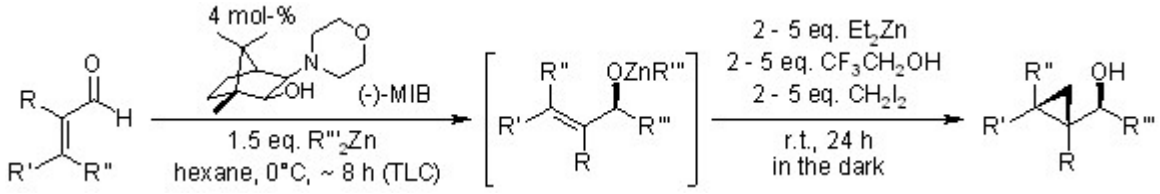
Improved Zinc-Catalyzed Simmons-Smith Reaction: Access to Various 1,2,3-Trisubstituted Cyclopropanes



Preparation of a Storable Zinc Carbenoid Species and Its Application in Cyclopropanation, Chain Extension, and [2,3]-Sigmatropic Rearrangement Reactions



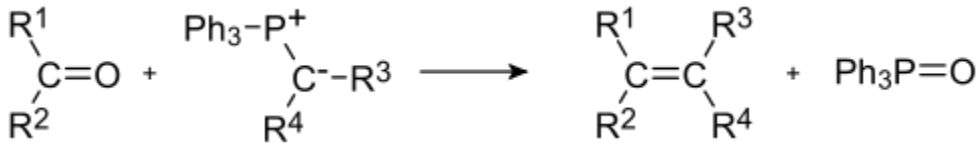
A Novel Class of Tunable Zinc Reagents ($RXZnCH_2Y$) for Efficient Cyclopropanation of Olefins



Highly Enantio- and Diastereoselective Tandem Generation of Cyclopropyl Alcohols with up to Four Contiguous Stereocenters

Wittig reaction

The **Wittig reaction** or Wittig olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a **Wittig reagent**) to give an alkene and triphenylphosphine oxide.



It is widely used in organic synthesis for the preparation of alkenes.[1][2][3] It should not be confused with the Wittig rearrangement.

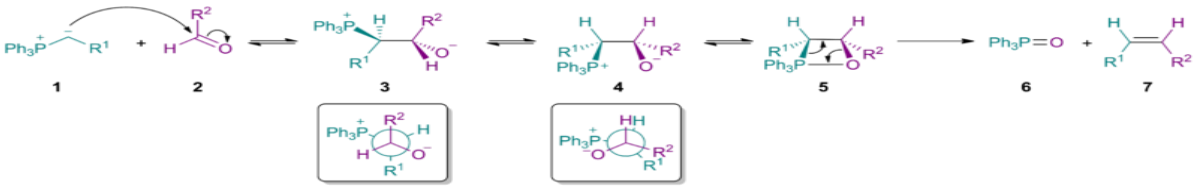
Wittig reactions are most commonly used to couple aldehydes and ketones to singly-substituted triphenylphosphonium ylides. For the reaction with aldehydes, the double bond geometry is readily predicted based on the nature of the ylide. With unstabilised ylides (R^3 = alkyl) this results in (*Z*)-alkene product with moderate to high selectivity. With stabilized ylides (R^3 = ester or ketone), the (*E*)-alkene is formed with high selectivity. The (*E*)/(*Z*) selectivity is often poor with semistabilized ylides (R^3 = aryl).[4]

To obtain the (*E*)-alkene for unstabilized ylides, the Schlosser modification of the Wittig reaction can be used. Alternatively, the Julia olefination and its variants also provide the (*E*)-alkene selectively. Ordinarily, the Horner–Wadsworth–Emmons reaction provides the (*E*)-enoate (α,β-unsaturated ester), just as the Wittig reaction does. To obtain the (*Z*)-enoate, the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction can be used.

Classical mechanism

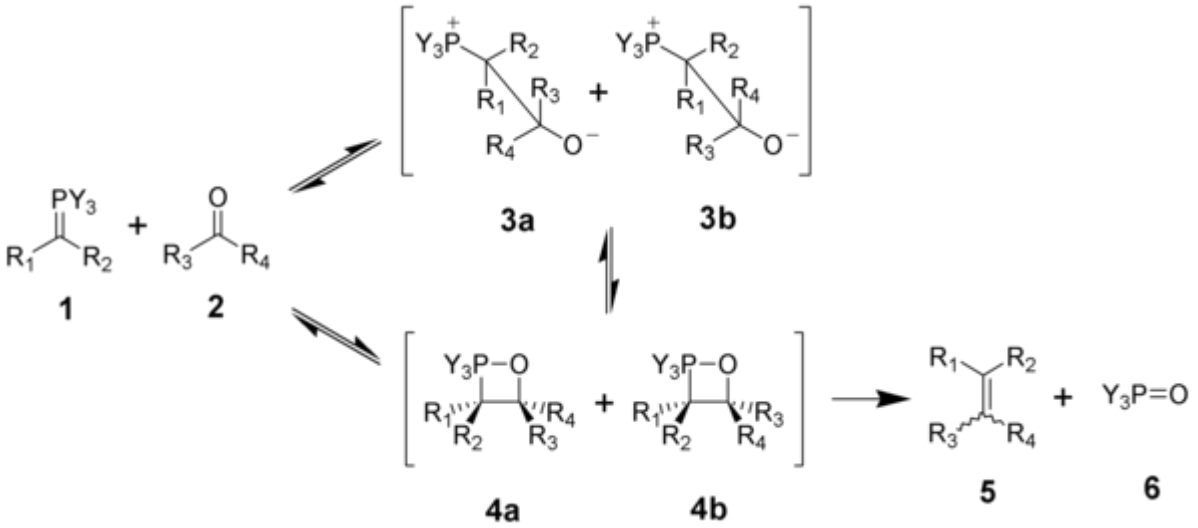
The steric bulk of the ylide **1** influences the stereochemical outcome of nucleophilic addition to give a predominance of the betaine **3** (cf. Bürgi–Dunitz angle). Note that for betaine **3** both R_1 and R_2 as well as PPh_3^+ and O^- are positioned anti to one another.

Carbon-carbon bond rotation gives the betaine **4**, which then forms the oxaphosphetane **5**. Elimination gives the desired Z-alkene **7** and triphenylphosphine oxide **6**. With simple Wittig reagents, the first step occurs easily with both aldehydes and ketones, and the decomposition of the betaine (to form **5**) is the rate-determining step. However, with stabilised ylides (where R_1 stabilises the negative charge) the first step is the slowest step, so the overall rate of alkene formation decreases and a bigger proportion of the alkene product is the E-isomer. This also explains why stabilised reagents fail to react well with sterically hindered ketones.



Mechanism

Mechanistic studies have focused on unstabilized ylides, because the intermediates can be followed by NMR spectroscopy. The existence and interconversion of the betaine (**3a** and **3b**) is subject of ongoing research.[5] For lithium-free Wittig reactions, most recent studies support a concerted formation of the oxaphosphetane without intervention of a betaine. In particular, phosphonium ylides **1** react with carbonyl compounds **2** via a [2+2] cycloaddition that is sometimes described as having $[\pi 2_s + \pi 2_a]$ topology to directly form the oxaphosphetanes **4a** and **4b**. Under lithium-free conditions, the stereochemistry of the product **5** is due to the kinetically controlled addition of the ylide **1** to the carbonyl **2**. When lithium is present, there may be equilibration of the intermediates, possibly via betaine species **3a** and **3b**.[6][7][8] Bruce E. Maryanoff and A. B. Reitz identified the issue about equilibration of Wittig intermediates and termed the process "stereochemical drift". For many years, the stereochemistry of the Wittig reaction, in terms of carbon-carbon bond formation, had been assumed to correspond directly with the Z/E stereochemistry of the alkene products. However, certain reactants do not follow this simple pattern. Lithium salts can also exert a profound effect on the stereochemical outcome.[9]

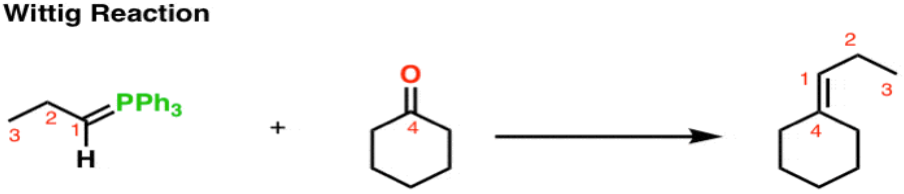


Mechanisms differ for aliphatic and aromatic aldehydes and for aromatic and aliphatic phosphonium ylides. Evidence suggests that the Wittig reaction of unbranched aldehydes under lithium-salt-free conditions do not equilibrate and are therefore under kinetic reaction control.[10][11] E. Vedejs has put forth a theory to explain the stereoselectivity of stabilized and unstabilized Wittig reactions.[12]

Strong evidence indicated that under Li-free conditions, Wittig reactions involving unstabilized (R_1= alkyl, H), semistabilized (R_1 = aryl), and stabilized (R_1 = EWG) Wittig reagents all proceed via a [2+2]/retro-[2+2] mechanism under kinetic control, with oxaphosphetane as the one and only intermediate.[13]

Applications

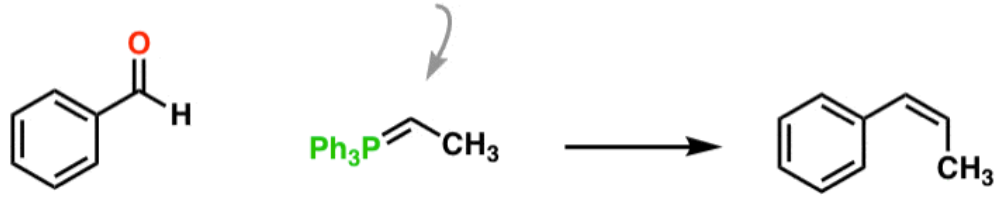
Wittig Reaction



What about stereochemistry of the Wittig reaction?

- *Z products tend to dominate for ylides lacking electron-withdrawing groups*

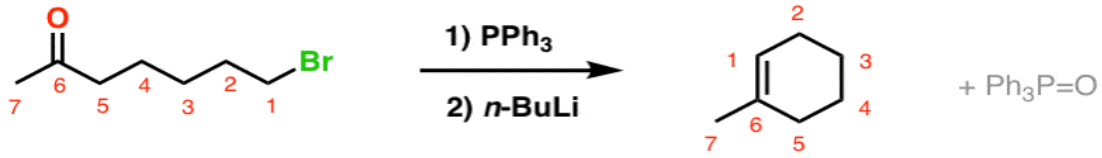
"unstabilized" ylide



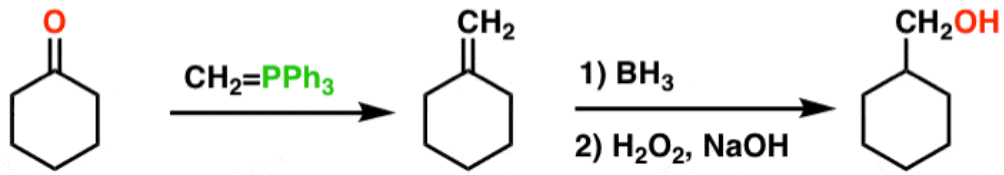
the method in which the ylide is created matters; Na^+ salts give higher *Z:E* ratios than Li^+ salts

Z : E **87:13** + $Ph_3P{=}O$

an intramolecular Wittig:

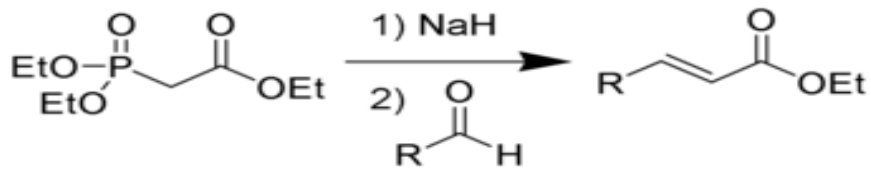


Example in synthesis



Horner–Wadsworth–Emmons reaction

The **Horner–Wadsworth–Emmons (HWE) reaction** is a chemical reaction used in organic chemistry of stabilized phosphonate carbanions with aldehydes (or ketones) to produce predominantly E-alkenes.[1]

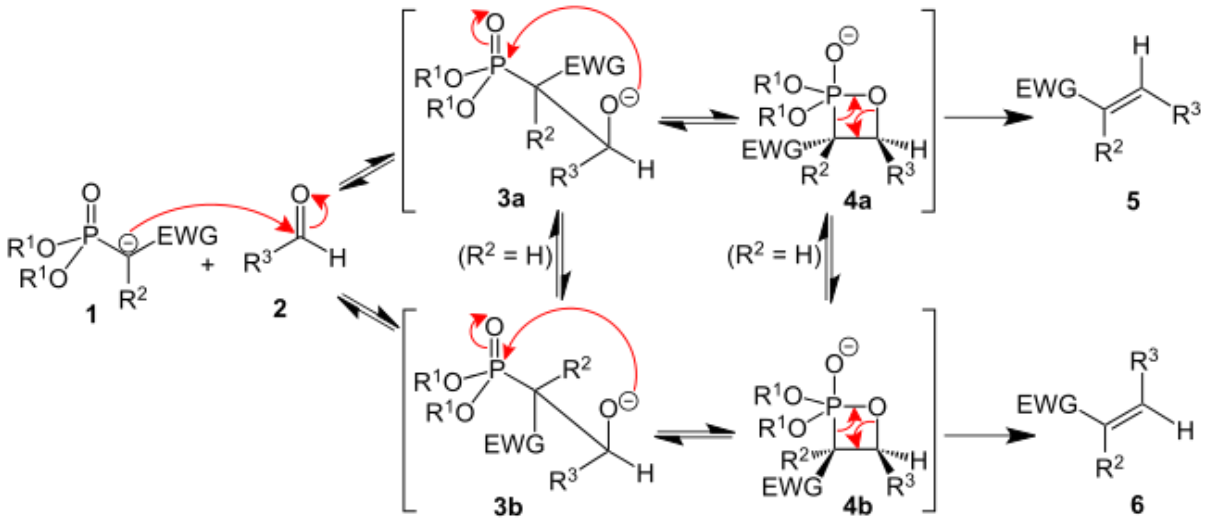


In 1958, Leopold Horner published a modified Wittig reaction using phosphonate-stabilized carbanions.[2][3] William S. Wadsworth and William D. Emmons further defined the reaction.[4][5]

In contrast to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic but less basic. Likewise, phosphonate-stabilized carbanions can be alkylated. Unlike phosphonium ylides, the dialkylphosphate salt byproduct is easily removed by aqueous extraction.

Reaction mechanism

The Horner–Wadsworth–Emmons reaction begins with the deprotonation of the phosphonate to give the phosphonate carbanion **1**. Nucleophilic addition of the carbanion onto the aldehyde **2** (or ketone) producing **3a** or **3b** is the rate-limiting step.[12] If R^2 = H, then intermediates **3a** and **4a** and intermediates **3b** and **4b** can interconvert with each other.[13] The final elimination of **4a** and **4b** yield (*E*)-alkene **5** and (*Z*)-alkene **6**, with the by-product being a dialkyl-phosphate.



The ratio of alkene isomers **5** and **6** is dependent upon the stereochemical outcome of the initial carbanion addition and upon the ability of the intermediates to equilibrate.

The electron-withdrawing group (EWG) alpha to the phosphonate is necessary for the final elimination to occur. In the absence of an electron-withdrawing group, the final product is the α-hydroxyphosphonate **3a** and **3b**.[14] However, these α-hydroxyphosphonates can be transformed to alkenes by reaction with diisopropylcarbodiimide.[15]

Stereoselectivity

The Horner–Wadsworth–Emmons reaction favours the formation of (*E*)-alkenes. In general, the more equilibration amongst intermediates, the higher the selectivity for (*E*)-alkene formation.

Disubstituted alkenes

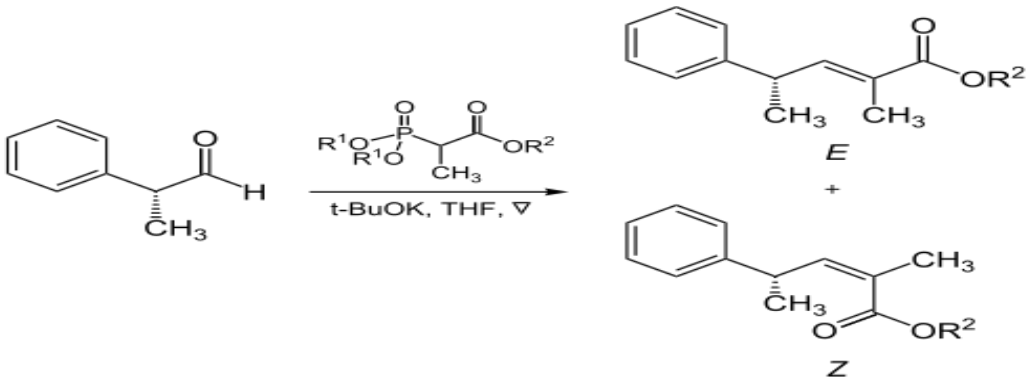
Thompson and Heathcock have performed a systematic study of the reaction of methyl 2-(dimethylphosphono)acetate with various aldehydes.[16] While each effect was small, they had a cumulative effect making it possible to modify the stereochemical outcome without modifying the structure of the phosphonate. They found greater (*E*)-stereoselectivity with the following conditions:

- Increasing steric bulk of the aldehyde
- Higher reaction temperatures (23 °C over −78 °C)
- Li > Na > K salts
- Using the solvent DME over THF

In a separate study, it was found that bulky phosphonate and bulky electron-withdrawing groups enhance E-alkene selectivity.

Trisubstituted alkenes

The steric bulk of the phosphonate and electron-withdrawing groups plays a critical role in the reaction of α-branched phosphonates with aliphatic aldehydes.[17]

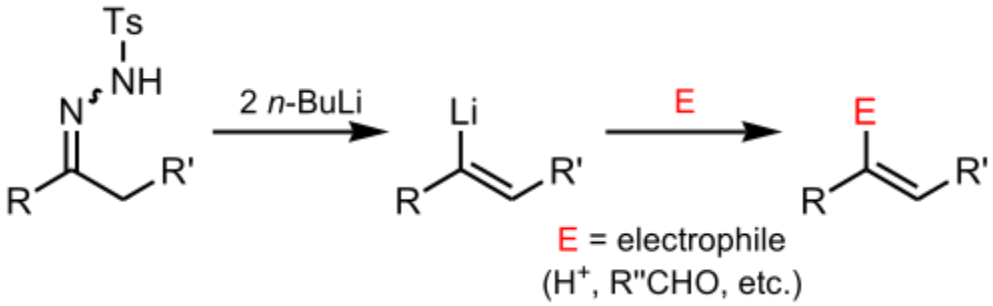


R^1	R^2	Ratio of alkenes (E : Z)
Methyl	Methyl	5 : 95
Methyl	Ethyl	10 : 90
9Ethyl	Ethyl	40 : 60
Isopropyl	Ethyl	90 : 10
Isopropyl	Isopropyl	95 : 5

Aromatic aldehydes produce almost exclusively (*E*)-alkenes. In case (*Z*)-alkenes from aromatic aldehydes are needed, the Still–Gennari modification (see below) can be used.

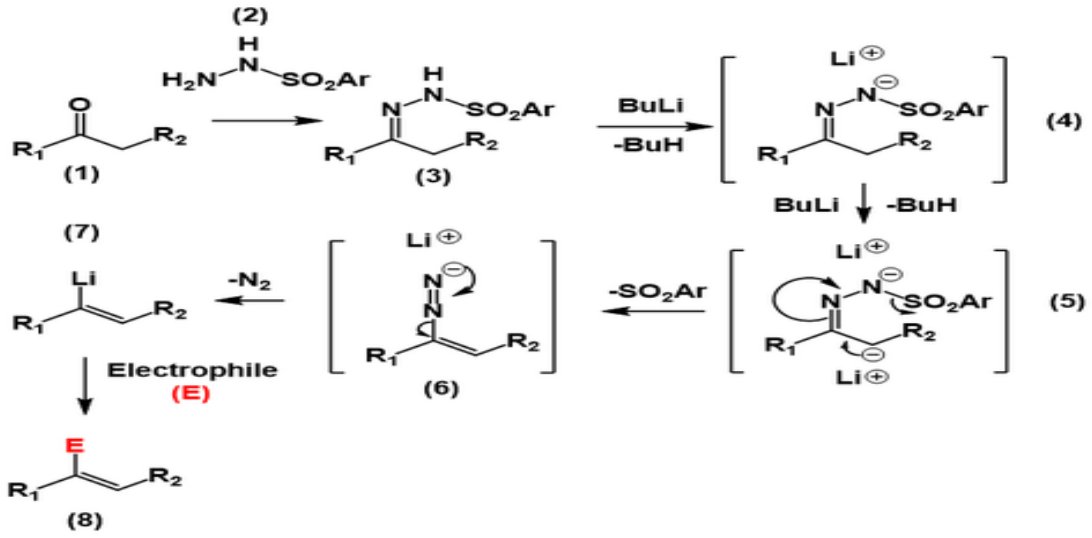
Shapiro reaction

The **Shapiro reaction** or **tosylhydrazone decomposition** is an organic reaction in which a ketone or aldehyde is converted to an alkene through an intermediate hydrazone in the presence of 2 equivalents of organolithium reagent.[1][2][3] The reaction was discovered by Robert H. Shapiro in 1967.[4] The Shapiro reaction was used in the Nicolaou Taxol total synthesis.[5] This reaction is very similar to the Bamford–Stevens reaction, which also involves the basic decomposition of tosyl hydrazones.



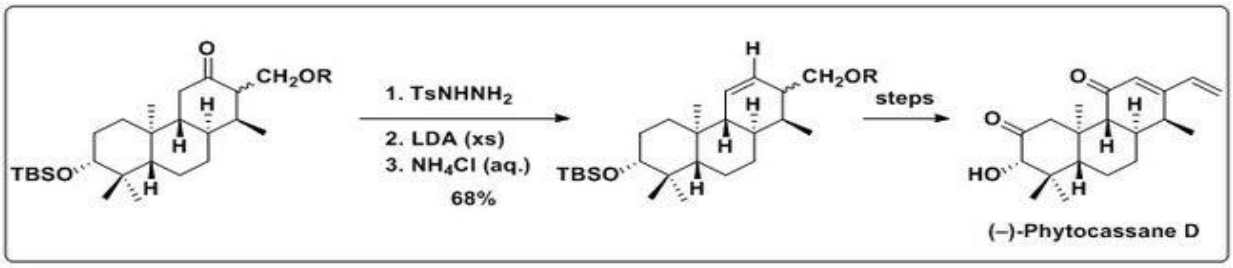
Reaction mechanism

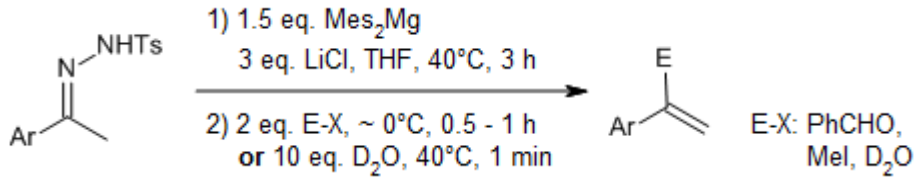
In a prelude to the actual Shapiro reaction, a ketone or an aldehyde **(1)** is reacted with *p*-toluenesulfonylhydrazide[6]**(2)** to form a *p*-toluenesulfonylhydrazone (or tosylhydrazone) which is a hydrazone **(3)**. Two equivalents of strong base such as *n*-butyllithium abstract the proton from the hydrazone **(4)** followed by the less acidic proton α to the hydrazone carbon **(5)**, forming a carbanion. The carbanion then undergoes an elimination reaction producing a carbon–carbon double bond and ejecting the tosyl anion, forming a diazonium anion **(6)**. This diazonium anion is then lost as molecular nitrogen resulting in a vinyllithium species **(7)**, which can then be reacted with various electrophiles, including simple neutralization with water or an acid **(8)**.

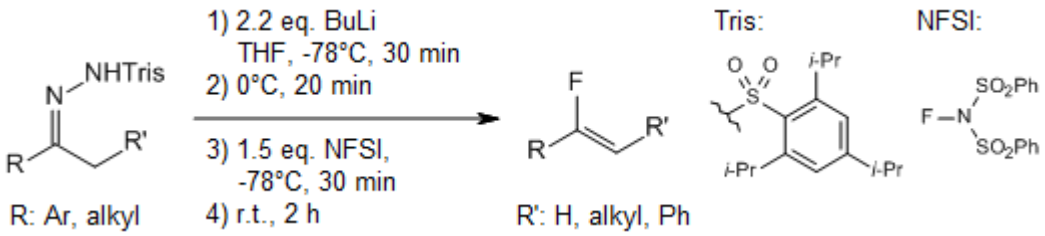


Applications:

The Shapiro reaction has been used to generate olefins towards to complex natural products. K. Mori and coworkers wanted to determine the absolute configuration of the phytocassane group of a class of natural products called phytoalexins. This was accomplished by preparing the naturally occurring (–)-phytocassane D from (*R*)-Wieland-Miescher ketone. On the way to (–)-phytocassane D, a tricyclic ketone was subjected to Shapiro reaction conditions to yield the cyclic alkene product. [12]

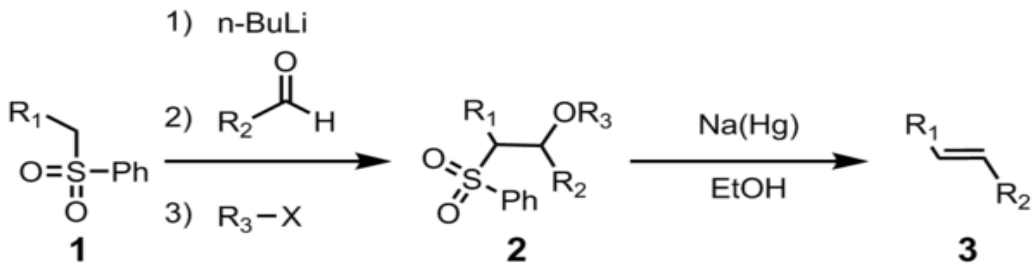






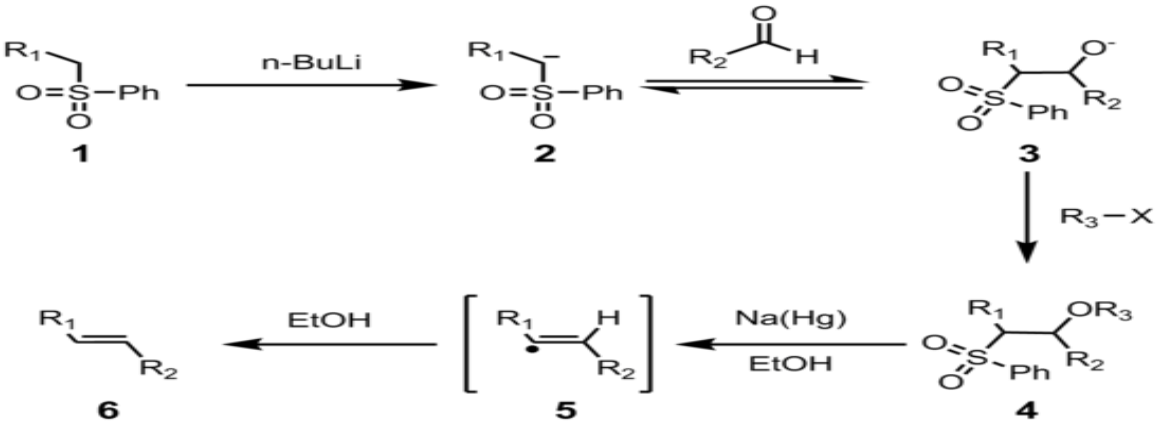
Julia-Lythgoe Reaction

The **Julia olefination** (also known as the **Julia–Lythgoe** olefination) is the chemical reaction used in organic chemistry of phenyl sulfones (1) with aldehydes (or ketones) to give alkenes (olefins)(3) after alcohol functionalization and reductive elimination using sodium amalgam[1][2] or SmI_2.[3] The reaction is named after the French chemist Marc Julia.

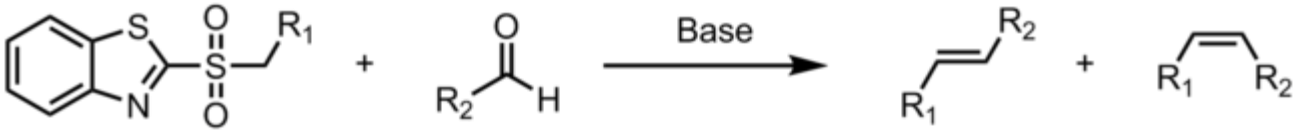


Reaction mechanism

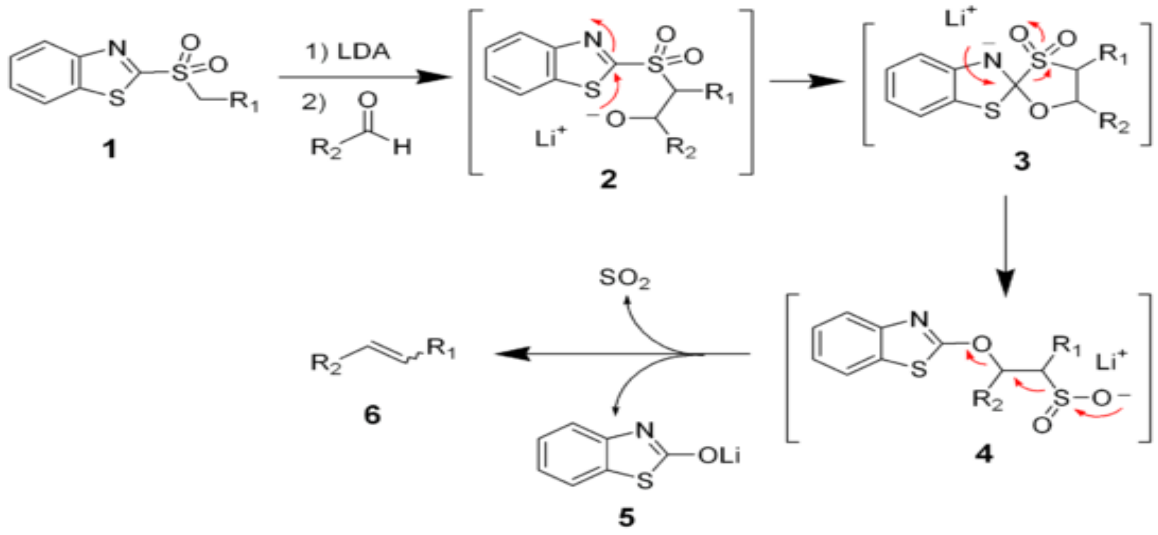
The initial steps are straightforward. The phenyl sulfone anion (2) reacts with an aldehyde to form the alkoxide (3). The alkoxide is functionalized with R_3-X to give the stable intermediate (4). The exact mechanism of the sodium amalgam reduction is unknown but has been shown to proceed through a vinylic radical species (5)[11]. Protonation of the vinylic radical gives the desired product (6).



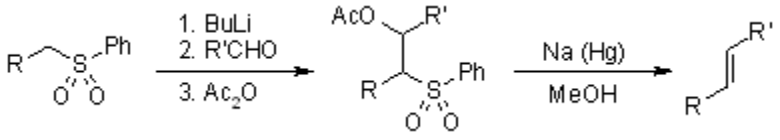
The stereochemistry of the alkene (6) is independent of the stereochemistry of the sulfone intermediate 4. It is thought that the radical intermediates are able to equilibrate so that the more thermodynamically stable trans-olefin is produced most often. This transformation highly favors formation of the *E*-alkene.[12]

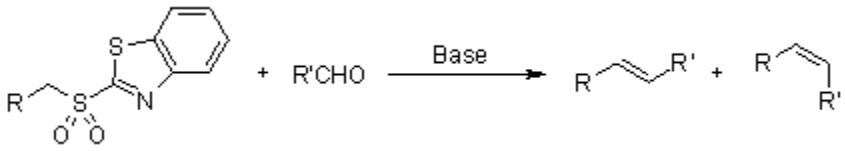


The modified Julia olefination, also known as the one-pot Julia olefination is a modification of the classical Julia olefination. The replacement of the phenyl sulfones with heteroaryl sulfones greatly alters the reaction pathway.[13] The most popular example is the benzothiazole sulfone.[14] The reaction of the benzothiazole sulfone (1) with lithium diisopropylamide (LDA) gives a metallated benzothiazolyl sulfone, which reacts quickly with aldehydes (or ketones) to give an alkoxide intermediate (2). Unlike the phenyl sulfones, this alkoxide intermediate (2) is more reactive and will undergo a Smiles rearrangement[15] to give the sulfinate salt (4). The sulfinate salt (4) will spontaneously eliminate sulfur dioxide and lithium benzothiazolone (5) producing the desired alkene (6).



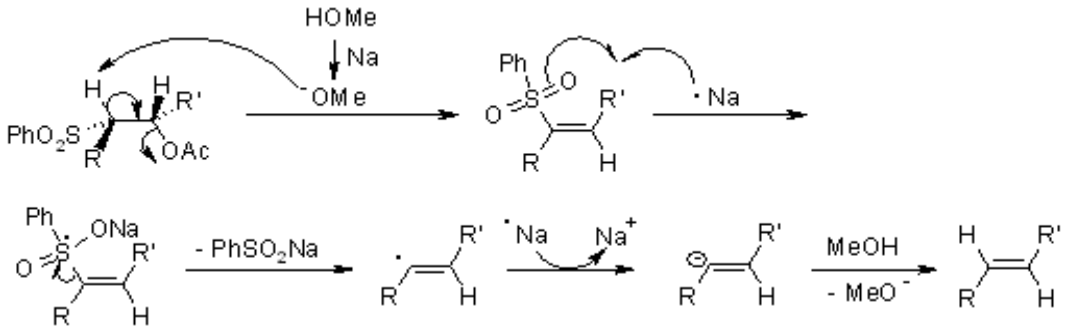
Applications:





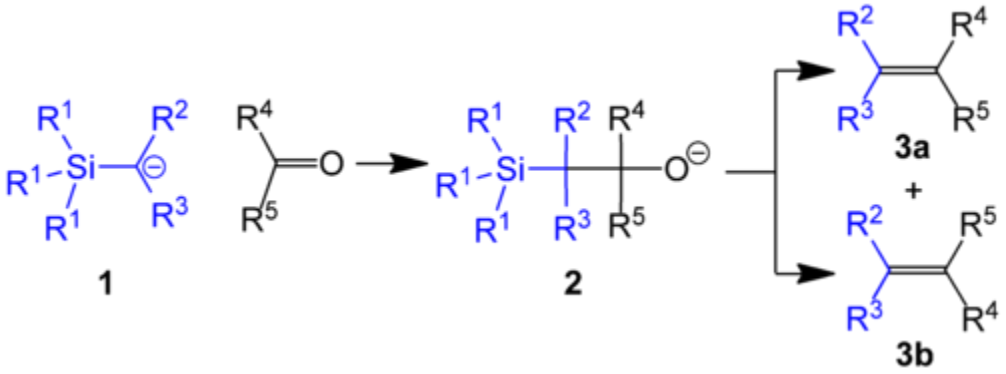
Deuterium Incorporation in Reductions of Acetoxy Sulfones

reaction conditions	*E*:*Z*	deuterium incorpn (%)
8 eq. SmI_2, THF, DMPU, CD_3OD, 60 min	2.3 : 1	0
5% Na/Hg, Na_2HPO_4, THF/CD_3OD (4:1)	9.1 : 1	91



Peterson olefination

The **Peterson olefination** (also called the **Peterson reaction**) is the chemical reaction of α-silyl carbanions (**1** in diagram below) with ketones (or aldehydes) to form a β-hydroxysilane (**2**) which eliminates to form alkenes (**3**).[1]

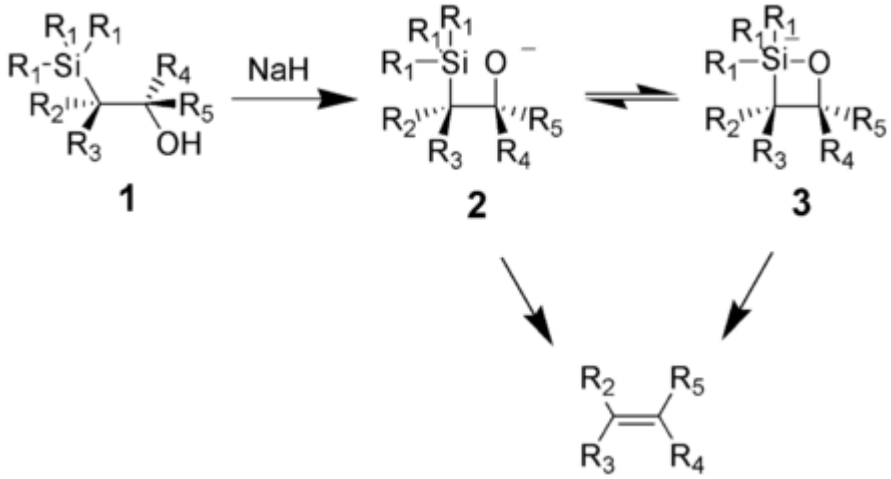


Reaction mechanism

One attractive feature of the Peterson olefination is that it can be used to prepare either cis- or trans-alkenes from the same β-hydroxysilane. Treatment of the β-hydroxysilane with acid will yield one alkene, while treatment of the same β-hydroxysilane with base will yield the alkene of opposite stereochemistry.

Basic elimination

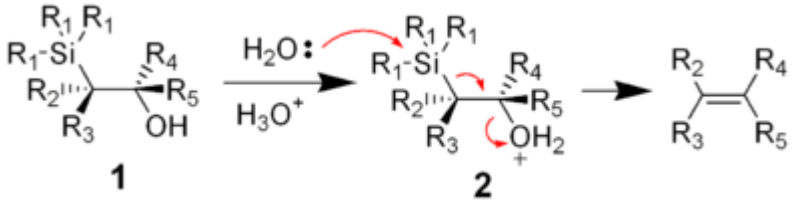
The action of base upon a β-hydroxysilane (**1**) results in a concerted *syn* elimination of (**2**) or (**3**) to form the desired alkene. The penta-coordinate silicate intermediate (**3**) is postulated, but no proof exists to date.[*when?*]



Potassium alkoxides eliminate quickly, while sodium alkoxides generally require heating. Magnesium alkoxides only eliminate in extreme conditions. The order of reactivity of alkoxides, K > Na >> Mg, is consistent with higher electron density on oxygen, hence increasing the alkoxide nucleophilicity.

Acidic elimination

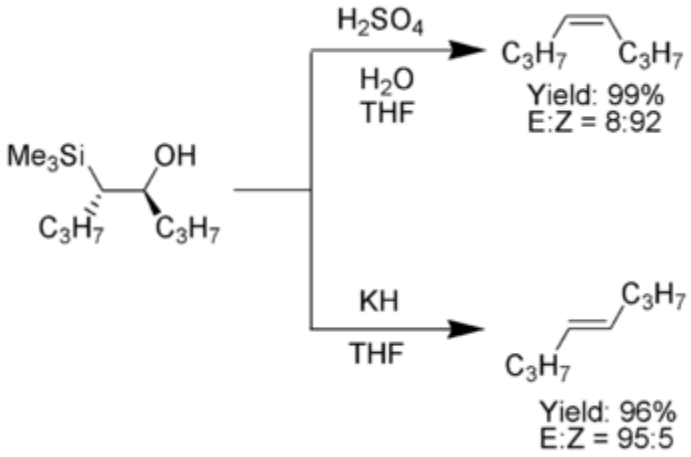
The treatment of the β-hydroxysilane (**1**) with acid results in protonation and an *anti* elimination to form the desired alkene.



Alkyl substituents

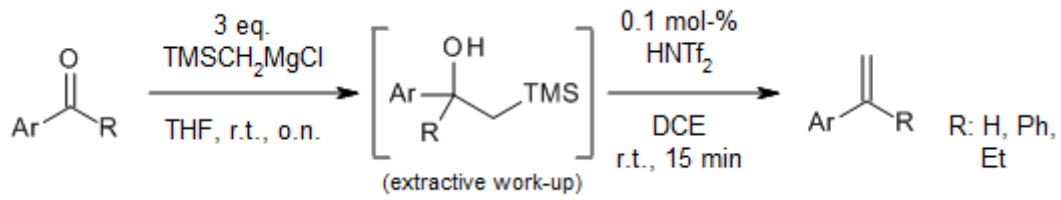
When the α-silyl carbanion contains only alkyl, hydrogen, or electron-donating substituents, the stereochemical outcome of the Peterson olefination can be controlled,[7] because at low temperature the elimination is slow and the intermediate β-hydroxysilane can be isolated.

Once isolated, the diastereomeric β-hydroxysilanes are separated. One diastereomer is treated with acid, while the other is treated with base, thus converted the material to an alkene with the required stereochemistry.[4]

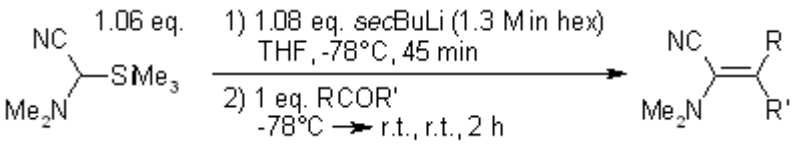


Applications:

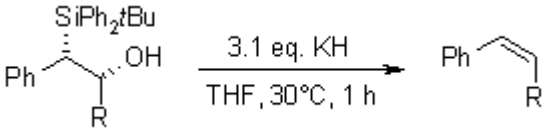
External Chiral Ligand-Mediated Enantioselective Peterson Reaction of α-Trimethylsilanylacetate with Substituted Cyclohexanones.



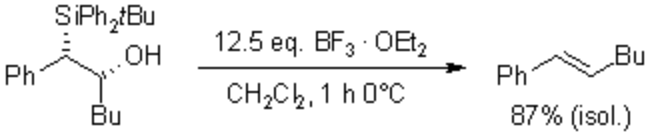
Brønsted Acid Catalyzed Peterson Olefinations.



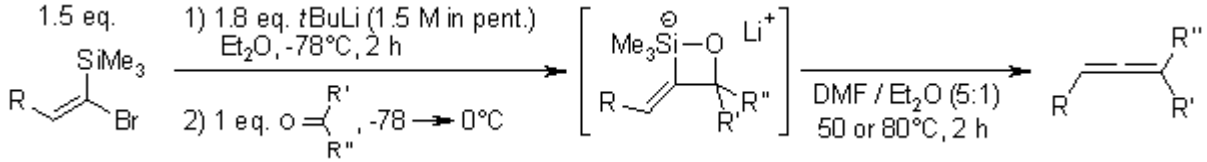
An Effective Synthesis of α-Cyanoenamines by Peterson Olefination.



The Peterson Olefination Using the *tert*-Butyldiphenylsilyl Group: Stereoselective Synthesis of Di- and Trisubstituted Alkenes.



The Peterson Olefination Using the *tert*-Butyldiphenylsilyl Group: Stereoselective Synthesis of Di- and Trisubstituted Alkenes.



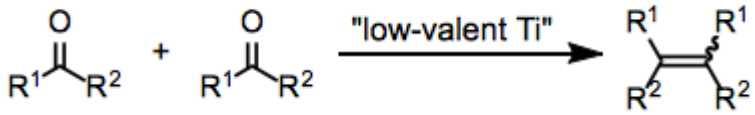
Peterson Allenation Using (*Z*)-(1-Lithio-1-alkenyl)trimethylsilanes.

McMurry coupling

The **McMurry coupling** is the reaction of two carbonyl functional groups to establish a new double bond between the carbons of the carbonyl groups. The reaction is mediated by low-valent titanium reagents, which may be generated through the combination of titanium chlorides with any of a number of reducing agents. The McMurry coupling is useful for the construction of sterically hindered alkenes, but has limited scope due to a lack of stereochemical control and statistical mixtures of products in mixed-coupling reactions.[1]

The formation of alkenes as minor products in pinacol couplings of aromatic carbonyl compounds with aluminum amalgam was first reported in 1970.[2] Since then, the reductive coupling of carbonyl compounds to afford alkenes has been developed into a useful synthetic method, most notably by McMurry and colleagues. The modern McMurry coupling employs low-valent titanium generated from a titanium source and a reducing agent (Eq. 1), and the scope of the reaction has benefited from the development of several titanium-reductant combinations. Aldehydes and ketones may be coupled in an intra- or intermolecular fashion to afford alkenes that may be difficult to access using other methods. Carboxylic acid derivatives such as esters, amides, and thioesters are amenable to coupling in some cases.

(1)

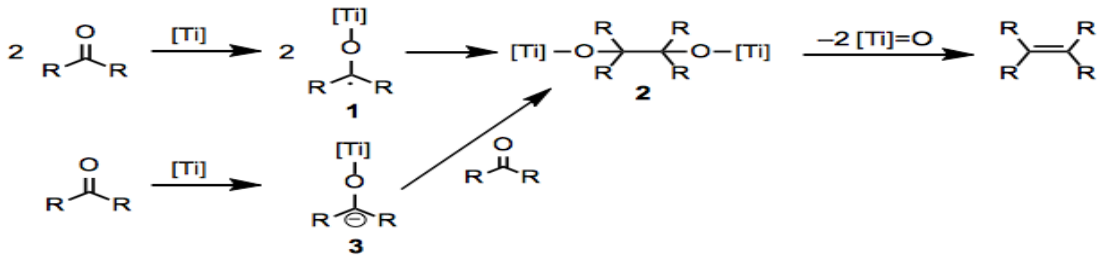


In general, the (*E*)-isomer of product is favored over the (*Z*)-isomer, although mixtures may result when the substituents of the carbonyl groups are similarly sized. One- and two-electron transfer mechanisms have been postulated for the McMurry coupling and the details of its mechanism remain unknown. When the steric environments and reduction potentials of the carbonyl groups involved are similar, achievining selective mixed coupling (rather than a statistical mixture of homocoupling and mixed-coupling products) is often difficult. Methods that circumvent this issue have relied on the use of carbonyl equivalents such as thioacetals and geminal dihalides.

Mechanism and Stereochemistry

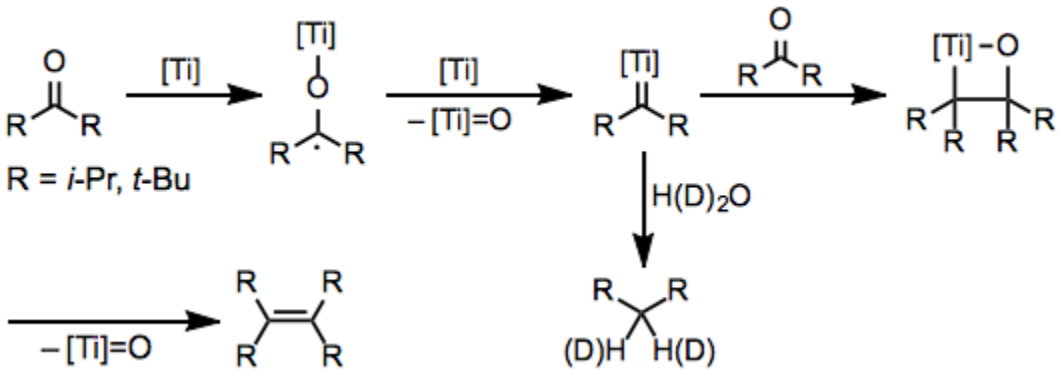
The mechanism of the McMurry coupling is unclear at present, and isolated observations have pointed to both one-electron and two-electron mechanisms. In either case, reduction of the carbonyl group yielding an organometallic intermediate is a key first step of the process, and deoxygenation likely follows. One-electron reduction may afford two titanium ketyl radicals **1**, which could subsequently couple with one another to yield titanium pinacolate **2**. Elimination of two titanium oxo molecules would then occure to afford the product olefin. This mechanism is likely for aliphatic carbonyl compounds, and has been supported by electron paramagnetic resonance spectroscopy.[3] More readily reducible aromatic carbonyl compounds undergo two-electron reduction to produce titanium ketyl anion **3**, which leads to the same pinacolate **2** after addition to a second molecule of the carbonyl compound (Eq. 2).[4]

(2)



A mechanism reminiscent of olefin metathesis involving titanium carbene complexes has also been identified for hindered ketones (Eq. 3).[5] Pinacolate **2** is not an intermediate in these reactions—the corresponding titanium pinacolates generated through other means decompose to the starting ketones rather than alkenes. Quenching the carbene intermediate with water affords the corresponding alkane.

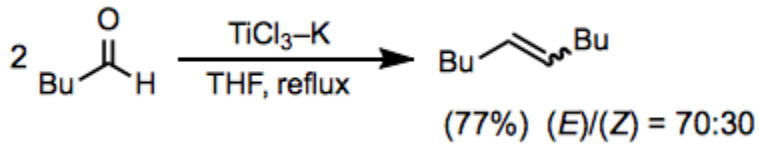
(3)



Stereochemistry

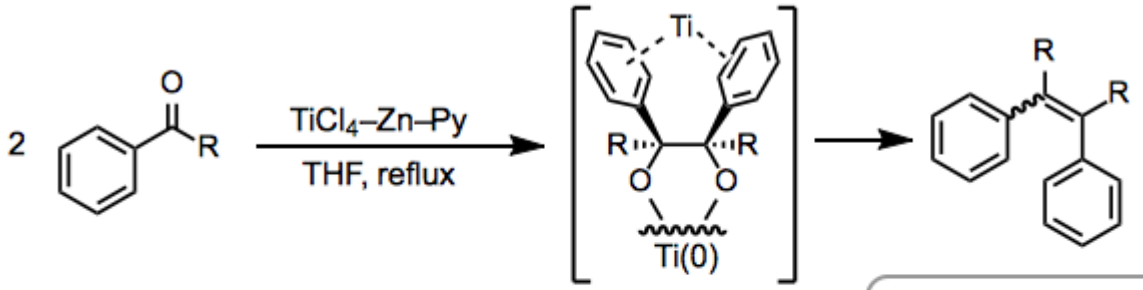
McMurry couplings generally produce mixtures of (*E*)- and (*Z*)-isomers, with the (*E*)-isomer predominating. Increasing the size difference between the substituents increases the selectivity for the less sterically hindered (*E*)-isomer.[6]

(4)



Coupling reactions between monoaryl ketones are an interesting and important exception to this rule. The tendency of these reactions to yield the (*Z*)-isomer as the major product when R is small has been attributed to coordination of the aryl groups to the titanium center (Eq. 5).[7]

(5)



R	Yield (%)	(*E*)/(*Z*)
Me	81	26:74
Et	59	27:73
Pr	55	11:89
i-Pr	25	88:12

Scope and Limitations

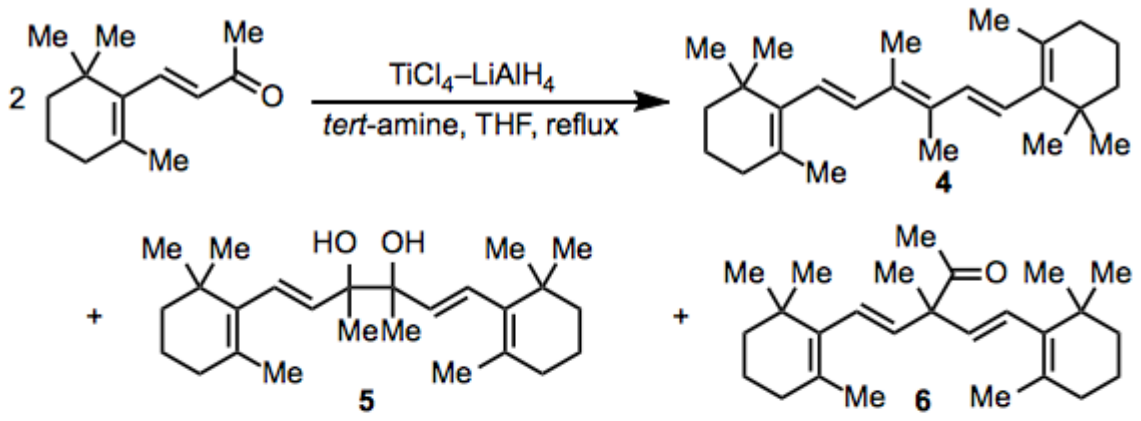
The McMurry coupling employing titanium requires a low-valent species, which is typically generated 'in situ' via treatment of a titanium halide with a reducing agent. A variety of titanium-reductant combinations have been employed for the reaction, and each has a unique scope. Reductants include zinc metal, Zn/Cu, $LiAlH_4$, alkali and alkali earth metals, lithium arenes, and butyllithium. $TiCl_4$ and $TiCl_3$ are the most common titanium sources employed. In general, aliphatic ketones are more difficult to couple than aromatic ketones. For example,

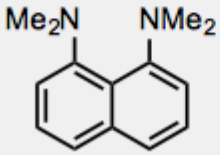
aliphatic ketones exclusively form pinacols in the presence of the low-valent titanium reagent generated from $TiCl_4$ and Zn, and are poor substrates for titanium powder.

Other metals employed in McMurry couplings include zirconium, vanadium,[8] niobium,[9] molybdenum,[10] tungsten,[11] aluminum,[12] and zinc.[13] The practical utility of some of these metals is limited by their cost and availability, but the scope of the reaction certainly benefits from the large number of metallic reagents that may be used.

In some cases, additives can have a beneficial effect on McMurry couplings suffering from reduced yields due to pinacol formation and rearrangement. For example, amines suppress the formation of pinacols and rearrangement in the homocoupling of β-ionone (Eq. 6).[14] Substoichiometric amounts of iodine facilitate the coupling of aliphatic carbonyl compounds by $TiCl_3$–Li at low temperatures and short reaction times.[15]

(6)



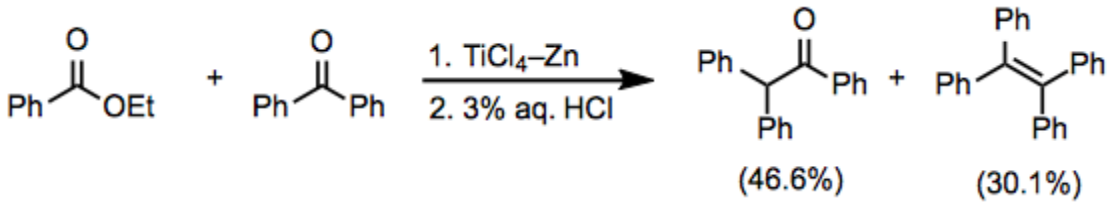
tert-Amine	**4** (%)	**5** (%)	**6** (%)
none	44	8	25
Bu_3N	91	0	0
Py	82	0	0
Et_3N	82	0	0
	94	0	0
DABCO	72	0	0

The scope of the carbonyl substrate is limited by the propensity of low-valent titanium reagents to reduce a substantial number of organic functional groups. For instance, the $TiCl_3$–$LiAlH_4$ system converts epoxides and bromohydrins to alkenes and mediates the deoxygenation of allylic and benzylic alcohols.[16] Carboxylic acid substrates are generally not effective in the McMurry coupling, but intramolecular mixed-couplings of esters and amides are useful for the preparation of heterocyclic compounds (see below).

Unsaturated carbonyl compounds react smoothly in the McMurry coupling with retention of configuration at the carbon-carbon double bond.[17] Although intermolecular coupling between two esters has not yet been reported, mixed-coupling of esters with other carbonyl

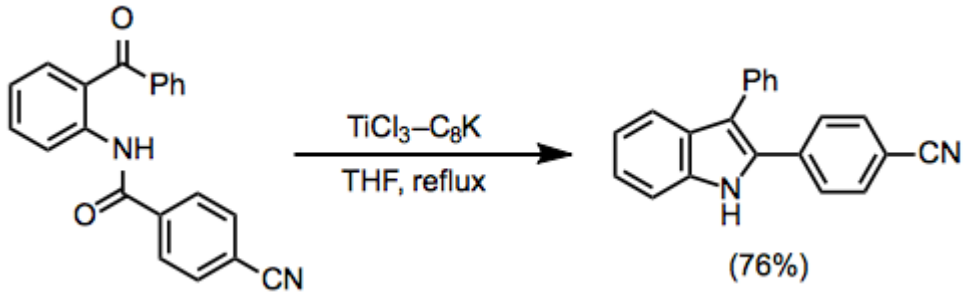
functionality is known. In reactions of ketones with esters, homocoupling of the ketone can be a significant problem (Eq. 7).[18]

(7)



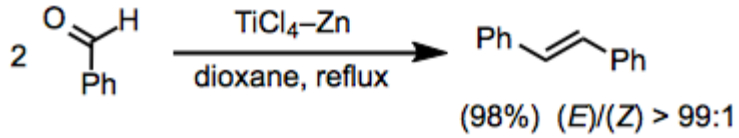
Amides are relatively versatile substrates, and both inter- and intramolecular homocoupling reactions of amides have been reported.[19] The intramolecular coupling of amides with ketones has been employed for the synthesis of indole derivatives (Eq. 8).[20]

(8)



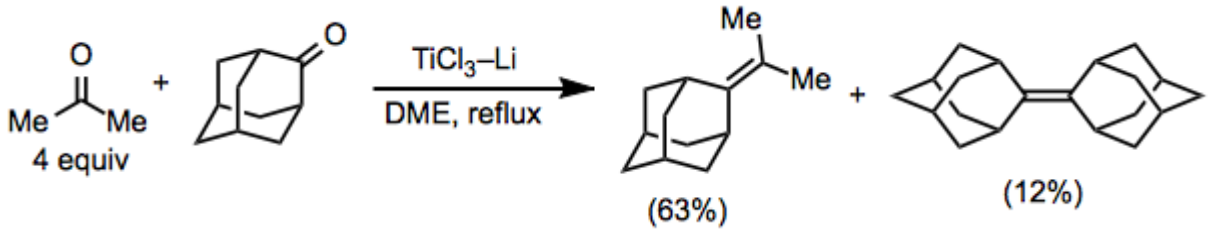
Homocoupling reactions are the most straightforward transformations that can be accomplished under the conditions of the McMurry coupling. Aliphatic and aromatic ketones can be converted into the corresponding symmetric alkenes in high yield and stereoselectivity. In reactions that could form diastereomers, selectivity for the (*E*)-isomer is typical (Eq. 9).[3]

(9)



Mixed-coupling reactions between carbonyl substrates with different substitution patterns often afford a statistical mixture of products unless an excess of one of the coupling partners is employed (Eq. 10).[6] The success of a mixed-coupling also depends on the structures of the substrates; in some cases, an excess of one of the coupling partners does not minimize homocoupling.

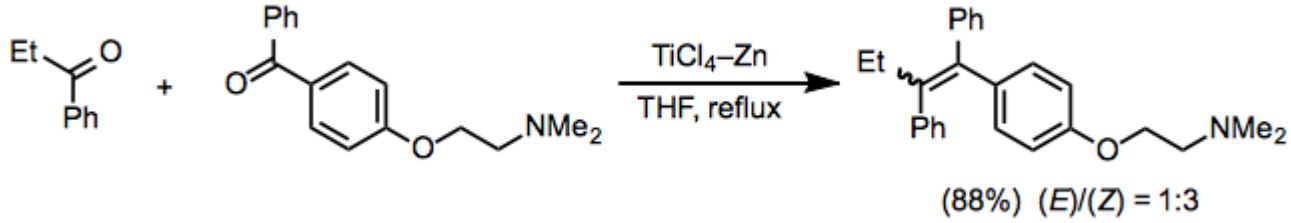
(10)



When the reduction potentials of the two substrates employed are sufficiently different, selective mixed-couplings can be accomplished using equimolar amounts of the two coupling

partners. For example, monoaryl and diaryl ketones readily couple with one another in high yield in the presence of $TiCl_3$–Zn (Eq. 11).[21]

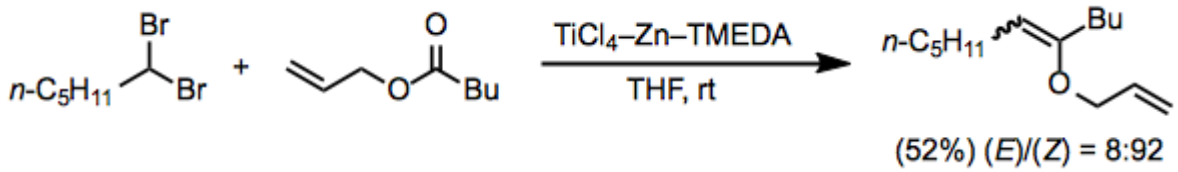
(11)



(88%) (*E*)/(*Z*) = 1:3

The McMurry coupling is severely limited by the drawback that mixed coupling between ketones and aldehydes is difficult to achieve. Reactions employing carbonyl equivalents such as *gem*-dihalides and thioacetals are amenable to mixed coupling and nicely complement the traditional McMurry coupling. Essentially, these reactions are an extension of the strategy of using coupling partners with very different reduction potentials. Esters, amides, and thioesters are useful substrates and afford electron-rich olefins (Eq. 12).[22]

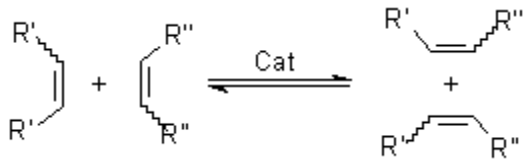
(12)



(52%) (*E*)/(*Z*) = 8:92

Olefin Metathesis Grubbs Reaction

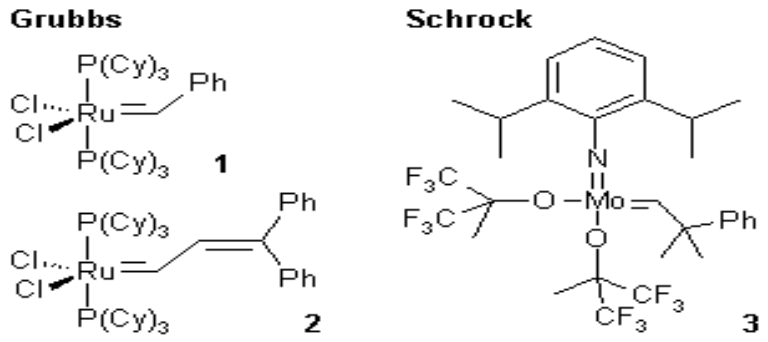
Olefin Metathesis allows the exchange of substituents between different olefins - a transalkylidenation.



This reaction was first used in petroleum reformation for the synthesis of higher olefins (Shell higher olefin process - SHOP), with nickel catalysts under high pressure and high temperatures. Nowadays, even polyenes with MW > 250,000 are produced industrially in this way.

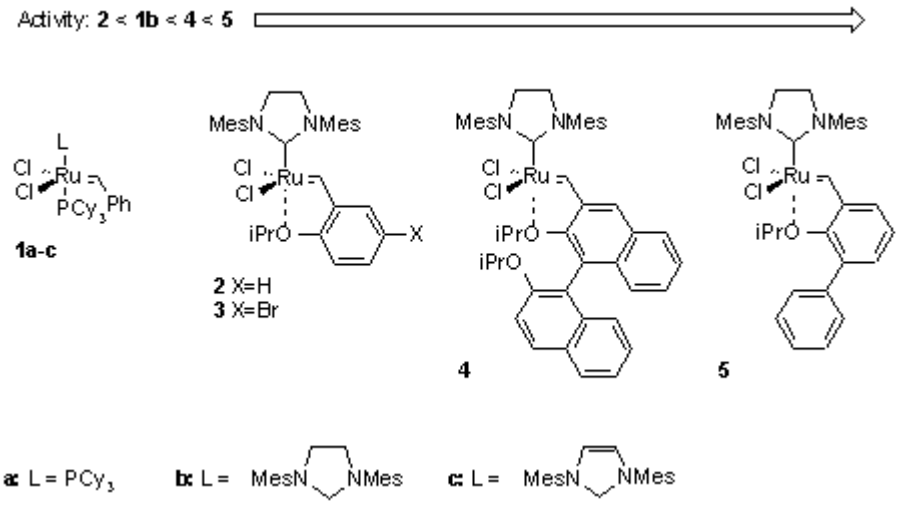
Synthetically useful, high-yield procedures for lab use include ring closure between terminal vinyl groups, cross metathesis - the intermolecular reaction of terminal vinyl groups - and ring opening of strained alkenes. When molecules with terminal vinyl groups are used, the equilibrium can be driven by the ready removal of the product ethene from the reaction mixture. Ring opening metathesis can employ an excess of a second alkene (for example ethene), but can also be conducted as a homo- or co-polymerization reaction. The driving force in this case is the loss of ring strain.

All of these applications have been made possible by the development of new homogeneous catalysts. Shown below are some of these catalysts, which tolerate more functional groups and are more stable and easy to handle.

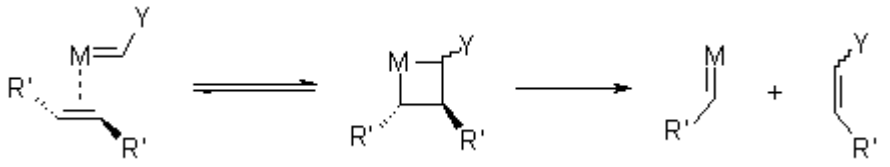


The Schrock catalysts are more active and are useful in the conversion of sterically demanding substrates, while the Grubbs catalysts tolerate a wide variety of functional groups.

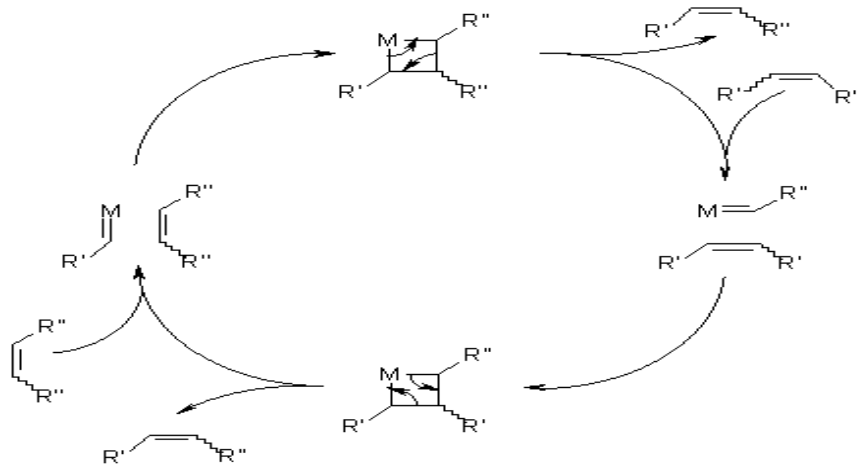
The second generation Grubbs catalysts are even more stable and more active than the original versions. Some of these are depicted:



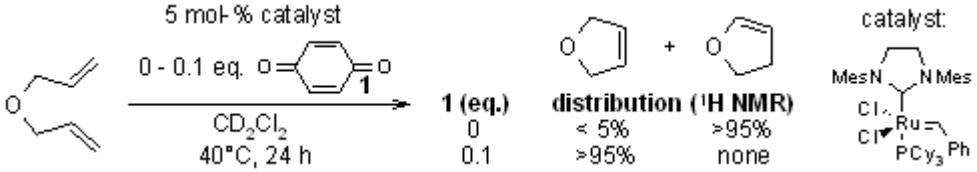
Mechanism of Olefin Metathesis



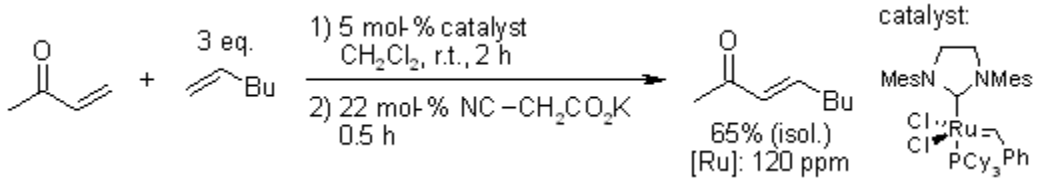
Catalytic Cycle:



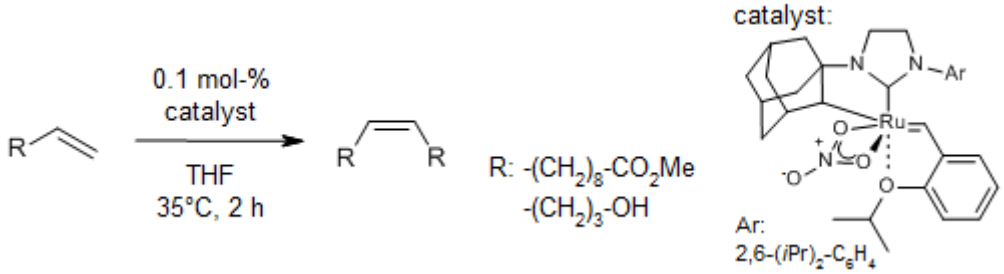
Applications:



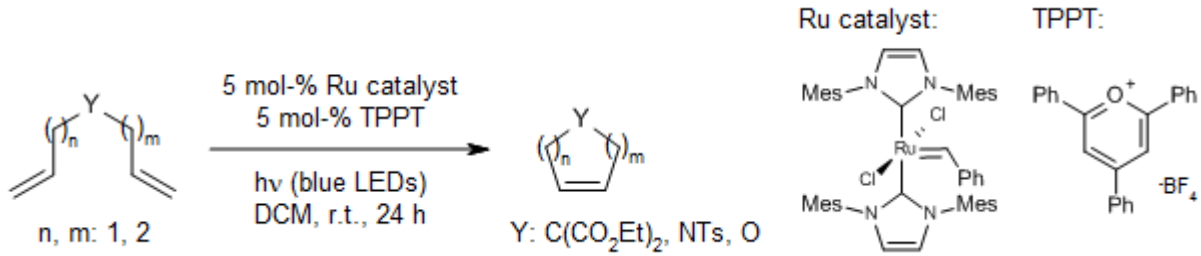
Prevention of Undesirable Isomerization during Olefin Metathesi.



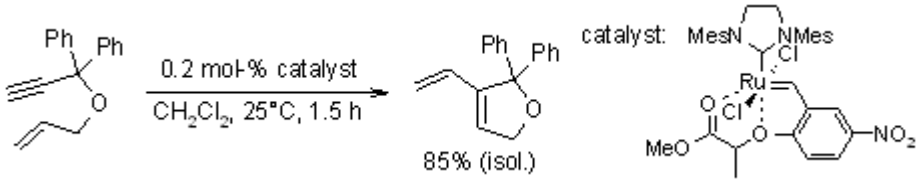
A Rapid and Simple Cleanup Procedure for Metathesis Reactions.



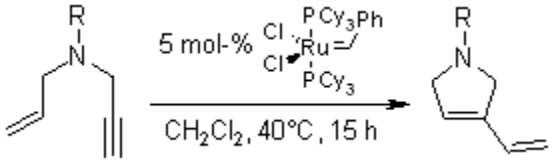
Highly Active Ruthenium Metathesis Catalysts Exhibiting Unprecedented Activity and *Z*-Selectivity.



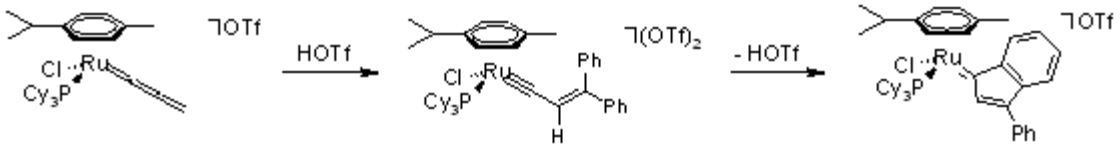
Visible-Light-Controlled Ruthenium-Catalyzed Olefin Metathesis.



Advanced Fine-Tuning of Grubbs/Hoveyda Olefin Metathesis Catalysts: A Further Step toward an Optimum Balance between Antinomic Properties.



Efficient Method for the Synthesis of Chiral Pyrrolidine Derivatives via Ring-Closing Enyne Metathesis Reaction.



Allenylidene-to-Indenylidene Rearrangement in Arene-Ruthenium Complexes: A Key Step to Highly Active Catalysts for Olefin Metathesis Reactions.

Nysted reagent

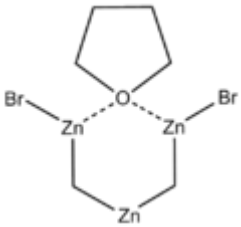
The **Nysted reagent** is a reagent used in organic synthesis for the methenylation of a carbonyl group. It was discovered in 1975 by Leonard N. Nysted in Chicago, Illinois. It was originally prepared by reacting dibromomethane and activated zinc in THF.[1] A proposed mechanism of the methenylation reaction can be seen at the bottom right.

A proposed mechanism for the Nysted olefination

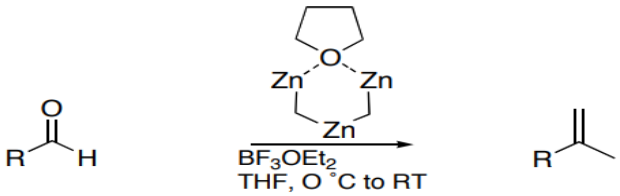
A similar reagent is Tebbe's reagent.[2] In the Nysted olefination, the Nysted reagent reacts with $TiCl_4$ to methylenate a carbonyl group. The biggest problem with these reagents are that the reactivity has not been well documented. It is believed that the $TiCl_4$ acts as a mediator in the reaction. Nysted reagent can methylenate different carbonyl groups in the presence of different mediators. For example, in the presence of BF_3•OEt_2, the reagent will methylenate aldehydes. On the other hand, in the presence of $TiCl_4$, $TiCl_3$ or $TiCl_2$ and

BF_3•OEt_2, the reagent can methylenate ketones. Most commonly, it is used to methylenate ketones because of their general difficulty to methylenate due to crowding around the carbonyl group. The Nysted reagent is able to overcome the additional steric hindrance found in ketones, and more easily methylenate the carbonyl group.

There is little research on Nysted reagent because of the hazards and high reactivity and the difficulty of keeping the reagent stable while it is in use. More specifically, it can form explosive peroxides when exposed to air and is extremely flammable. Also, it reacts violently with water. These make this reagent very dangerous to work with.



Nysted Reagent/Reaction

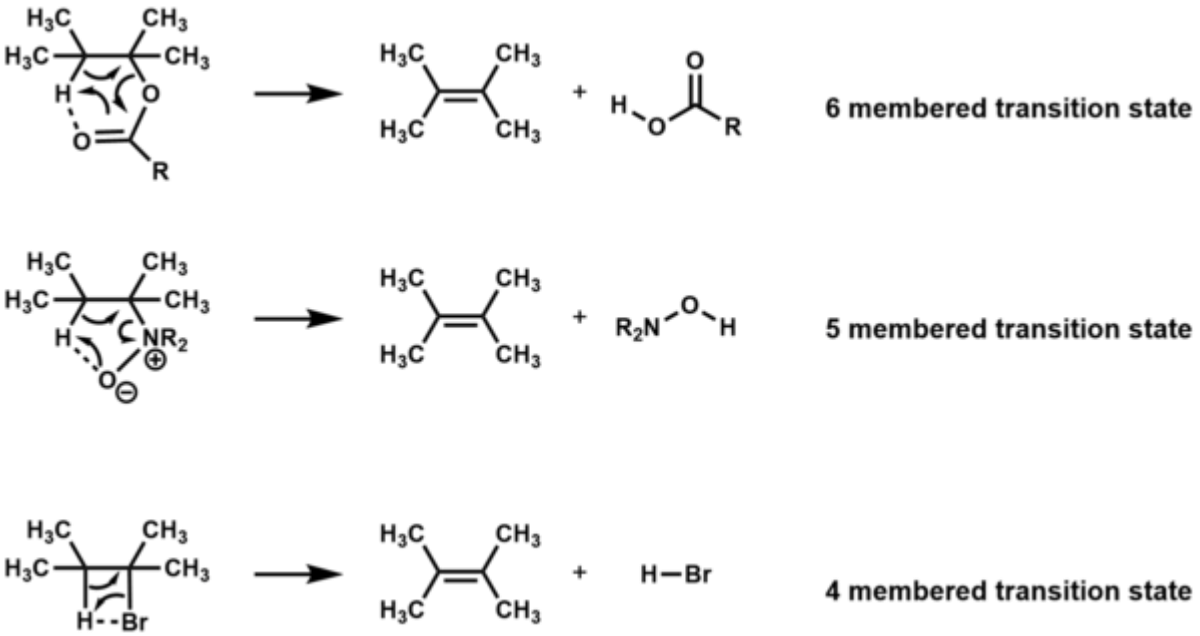


ELIMINATION REACTIONS

The **E_i mechanism** (Elimination Internal/Intramolecular), also known as a **thermal syn elimination** or a **pericyclic syn elimination**, in organic chemistry is a special type of elimination reaction in which two vicinal substituents on an alkane framework leave simultaneously via a cyclic transition state to form an alkene in a *syn* elimination.[1] This type of elimination is unique because it is thermally activated and does not require additional reagents unlike regular eliminations which require an acid or base, or would in many cases involve charged intermediates. This reaction mechanism is often found in pyrolysis.

General Features

Compounds that undergo elimination through cyclic transition states upon heating, with no other reagents present, are given the designation as E_i reactions. Depending on the compound, elimination takes place through a four, five, or six-membered transition state.[1][2]

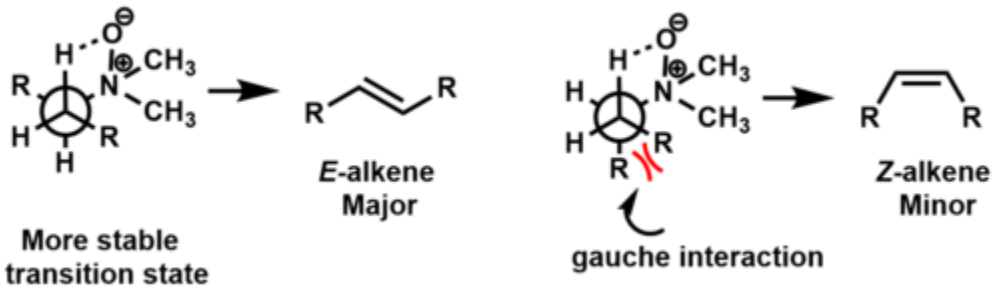


The elimination must be *syn* and the atoms coplanar for four and five-membered transition states,[3] but coplanarity is not required for six-membered transition states.[1]

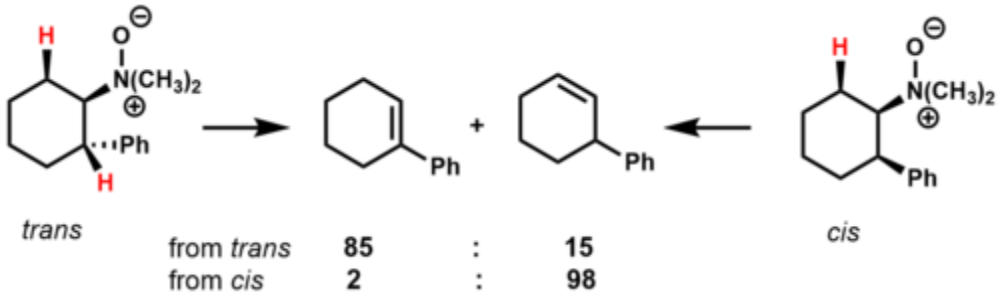
There is a substantial amount of evidence to support the existence of the E_i mechanism such as: 1) the kinetics of the reactions were found to be first order,[4] 2) the use of free-radical inhibitors did not affect the rate of the reactions, indicating no free-radical mechanisms are involved [5][6] 3) isotope studies for the Cope elimination indicate the C-H and C-N bonds are partially broken in the transition state,[7] this is also supported by computations that show bond lengthening in the transition state [8] and 4) without the intervention of other mechanisms, the E_i mechanism gives exclusively syn elimination products.

There are many factors that affect the product composition of E_i reactions, but typically they follow Hofmann's rule and lose a β-hydrogen from the least substituted position, giving the alkene that is less substituted (the opposite of Zaitsev's rule).[1] Some factors affecting product composition include steric effects, conjugation, and stability of the forming alkene.

For acyclic substrates, the *Z*-isomer is typically the minor product due to the destabilizing gauche interaction in the transition state, but the selectivity is not usually high.[2]



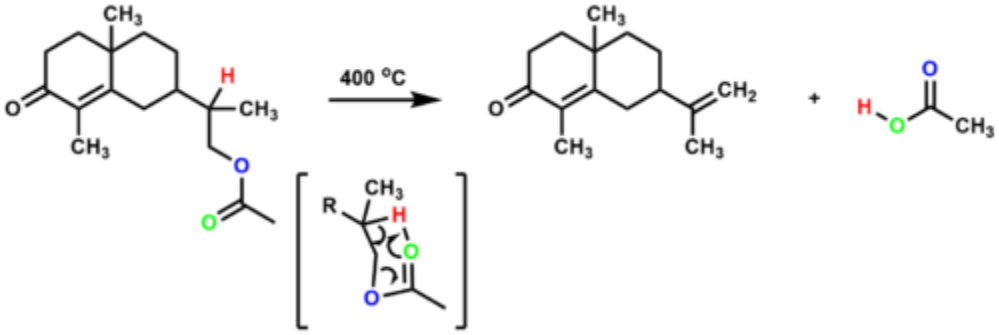
The pyrolysis of *N*,*N*-dimethyl-2-phenylcyclohexylamine-N-oxide shows how conformational effects and the stability of the transition state affect product composition for cyclic substrates.[2]



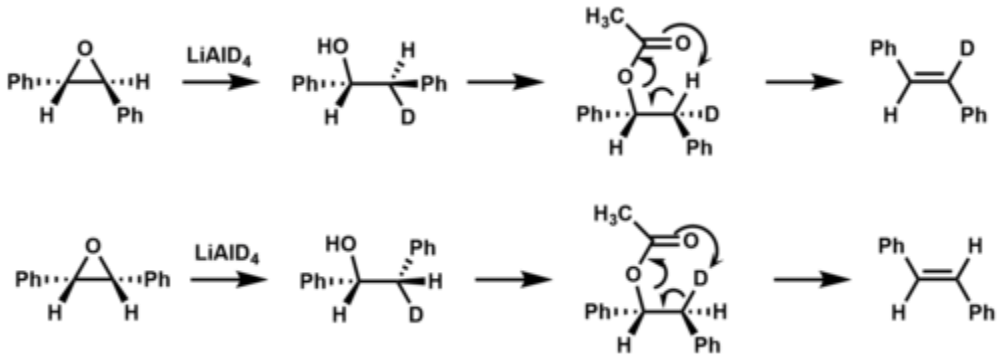
In the *trans* isomer, there are two *cis*-β-hydrogens that can eliminate. The major product is the alkene that is in conjugation with the phenyl ring, presumably due to the stabilizing effect on the transition state. In the *cis* isomer, there is only one *cis*-*B*-hydrogen that can eliminate, giving the nonconjugated regioisomer as the major product.

Ester (Acetate) Pyrolysis

The pyrolytic decomposition of esters is an example of a thermal *syn* elimination. When subjected to temperatures above 400 °C, esters containing β-hydrogens can eliminate a carboxylic acid through a 6-membered transition state, resulting in an alkene.[2][6]

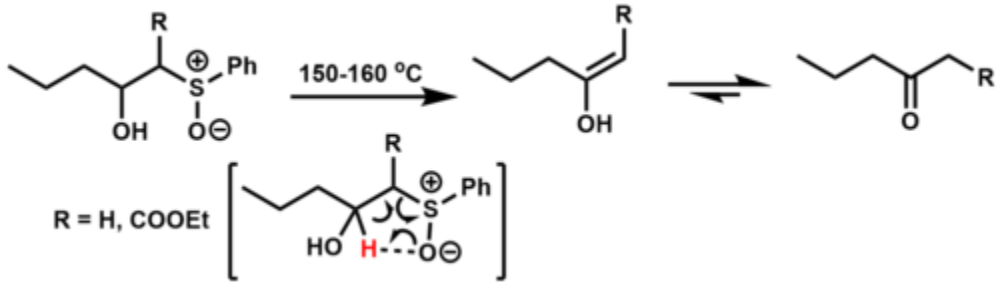


Isotopic labeling was used to confirm that *syn* elimination occurs during ester pyrolysis in the formation of stilbene.[9]

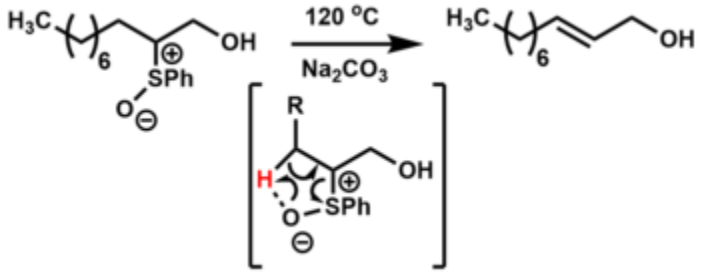


Sulfoxide Elimination

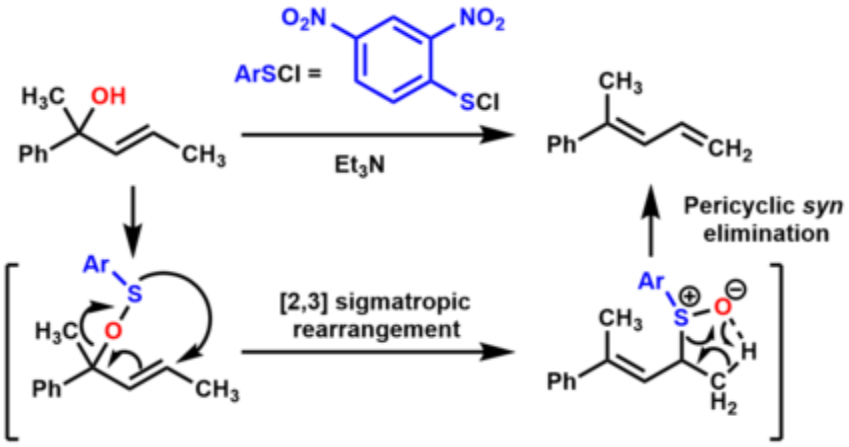
β-hydroxy phenyl sulfoxides were found to undergo thermal elimination through a 5-membered cyclic transition state, yielding β-keto esters and methyl ketones after tautomerization.[10]



Allylic alcohols can be formed from β-hydroxy phenyl sulfoxides that contain a β'-hydrogen through an E_i mechanism, tending to give the β,γ-unsaturation.[11]

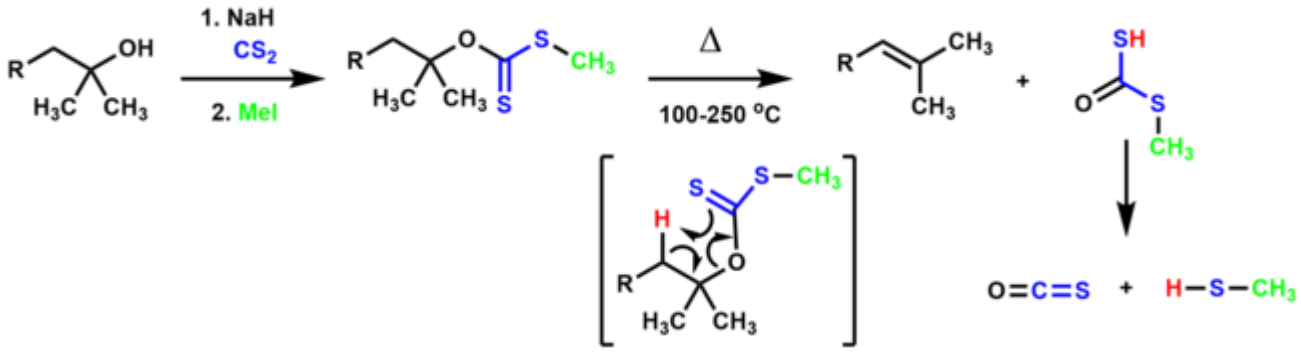


1,3-Dienes were found to be formed upon the treatment of an allylic alcohol with an aryl sulfide in the presence of triethylamine.[12] Initially, a sulfenate ester is formed followed by a [2,3]-sigmatropic rearrangement to afford an allylic sulfoxide which undergoes thermal *syn* elimination to yield the 1,3-diene.



Chugaev Elimination

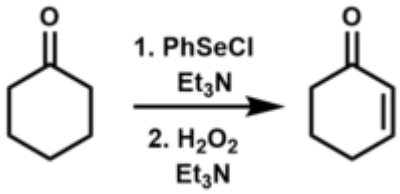
The Chugaev elimination is the pyrolysis of a xanthate ester, resulting in an olefin.[1][13] To form the xanthate ester, an alcohol reacts with carbon disulfide in the presence of a base, resulting in a metal xanthate which is trapped with an alkylating agent (typically methyl iodide). The olefin is formed through the thermal *syn* elimination of the β-hydrogen and xanthate ester. The reaction is irreversible because the resulting by-products, carbonyl sulfide and methanethiol, are very stable.



The Chugaev elimination is very similar to the ester pyrolysis, but requires significantly lower temperatures to achieve the elimination, thus making it valuable for rearrangement-prone substrates.

Selenoxide Elimination

The selenoxide elimination has been used in converting ketones, esters, and aldehydes to their α,β-unsaturated derivatives.[1][17]

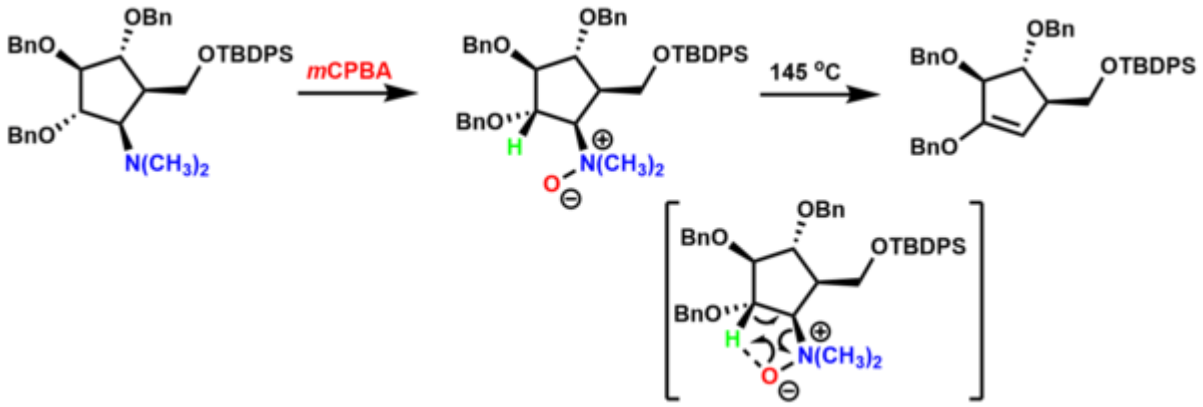


The mechanism for this reaction is analogous to the sulfoxide elimination, which is a thermal *syn* elimination through a 5-membered cyclic transition state. Selenoxides are preferred for this type of transformation over sulfoxides due to their increased reactivity toward β-elimination, in some cases allowing the elimination to take place at room temperature.[2]

The areneselenic acid generated after the elimination step is in equilibrium with the diphenyl diselenide which can react with olefins to yield β-hydroxy selenides under acidic or neutral conditions. Under basic conditions, this side reaction is suppressed.[18]

Cope Elimination

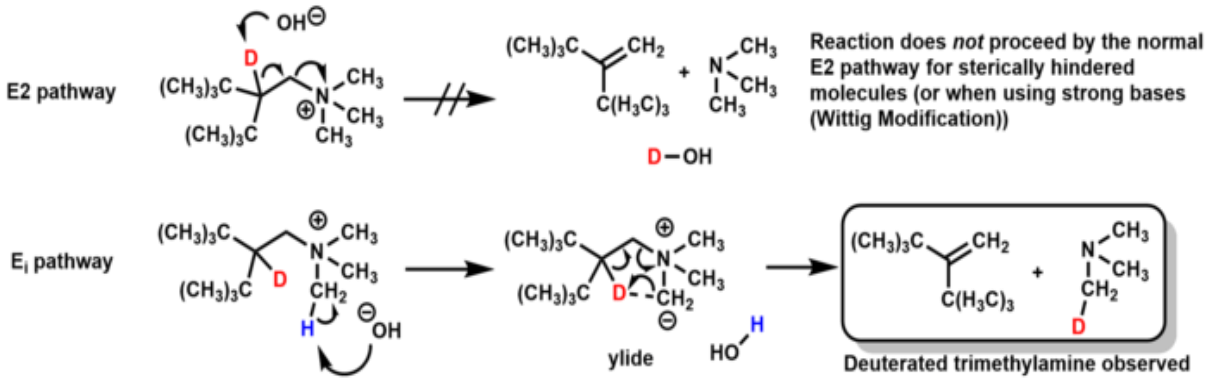
The Cope elimination (Cope reaction) is the elimination of a tertiary amine oxide to yield an alkene and a hydroxylamine through an E_i mechanism.[13][21] The Cope elimination was used in the synthesis of a mannopyranosylamine mimic.[22] The tertiary amine was oxidized to the amine oxide using *m*-chloroperoxybenzoic acid (*m*CPBA) and subjected to high temperatures for thermal *syn* elimination of the β-hydrogen and amine oxide through a cyclic transition state, yielding the alkene. It is worth noting that the indicated hydrogen (in green) is the only hydrogen available for *syn* elimination.



Cyclic amine oxides (5, 7-10-membered nitrogen containing rings) can also undergo internal *syn* elimination to yield acyclic hydroxylamines containing terminal alkenes.[13]

Special Cases for the Hofmann Elimination

The mechanism for the Hofmann elimination is generally E2, but can go through an E_i pathway under certain circumstances. For some sterically hindered molecules the base deprotonates a methyl group on the amine instead of the β-hydrogen directly, forming an ylide intermediate which eliminates trimethylamine through a 5-membered transition state, forming the alkene. Deuterium labeling studies confirmed this mechanism by observing the formation of deuterated trimethylamine (and no deuterated water, which would form from the E2 mechanism).[23]

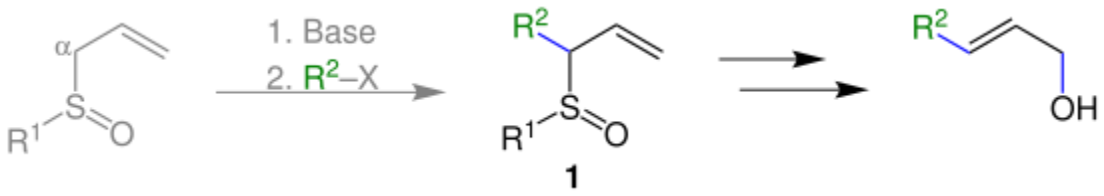


The Wittig modified Hofmann elimination goes through the same E_i mechanism, but instead of using silver oxide and water as base, the Wittig modification uses strong bases like alkylithiums or KNH2/liquid NH3.

Mislow–Evans rearrangement

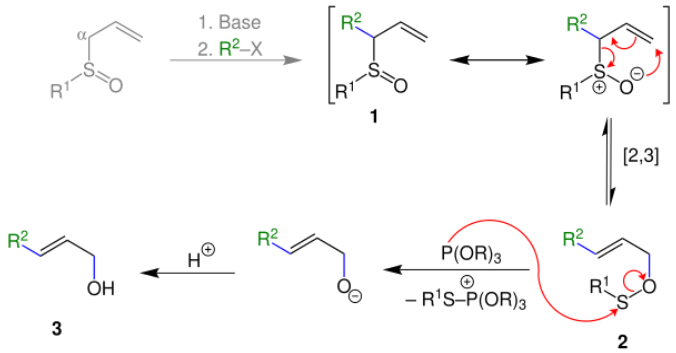
The **Mislow–Evans rearrangement** is a name reaction in organic chemistry. It is named after Kurt Mislow and David A. Evans who discovered this reaction in 1971. The reaction allows the formation of allylic alcohols from allylic sulfoxides in a 2,3-sigmatropic rearrangement.[1]

The reaction is a powerful way to create particular stereoisomers of the alcohol since it is highly diastereoselective and the chirality at the sulphur atom can be transmitted to the carbon next to the oxygen in the product.



The sulfoxide **1** reagent can be generated easily and enantioselectively from the corresponding sulfide by an oxidation reaction.[2] In this reaction various organic groups can be used, R^1 = alkyl, allyl and R^2 = alkyl, aryl or benzyl

Mechanism

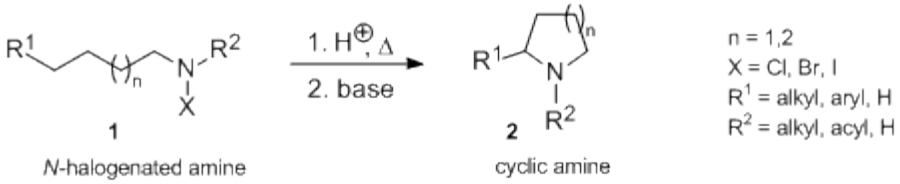


The mechanism starts with an allylic sulfoxide **1** which rearranges under heat to a sulfenate ester **2**. This can be cleaved using a thiophile, which leaves the allylic alcohol **3** as the product.

UNIT-III UN-ACTIVATED C-H BONDS & ORGANO BORANES

Hofmann–Löffler reaction

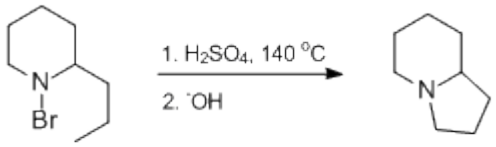
The **Hofmann–Löffler reaction** (also referred to as **Hofmann–Löffler–Freytag reaction**, **Löffler–Freytag reaction**, **Löffler–Hofmann reaction**, as well as **Löffler's method**) is an organic reaction in which a cyclic amine 2 (pyrrolidine or, in some cases, piperidine) is generated by thermal or photochemical decomposition of *N*-halogenated amine 1 in the presence of a strong acid (concentrated sulfuric acid or concentrated CF_3CO_2H). The Hofmann–Löffler–Freytag reaction proceeds via an intramolecular hydrogen atom transfer to a nitrogen-centered radical and is an example of a remote intramolecular free radical C–H functionalization.[1]



1 *N*-halogenated amine — 2 cyclic amine

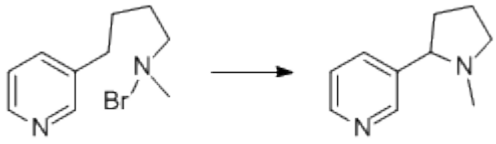
Historical perspective

In 1878, the structure of piperidine was still unknown, and A. W. Hofmann[2] made attempts to add hydrogen chloride or bromine to it in the belief that the compound possessed unsaturation (i.e. he performed standard alkene classification test reactions). In the course of his studies, A.W. Hofmann synthesized a number of *N*-haloamines and *N*-haloamides and investigated their reactions under acidic and basic conditions.[3][4] He reported that the treatment of 1-bromo-2-propylpiperidine 3 with hot sulfuric acid, followed by basic work-up, resulted in the formation of a tertiary amine,[5][6] which was later[7] shown to be δ-coneceine 4.



3 4

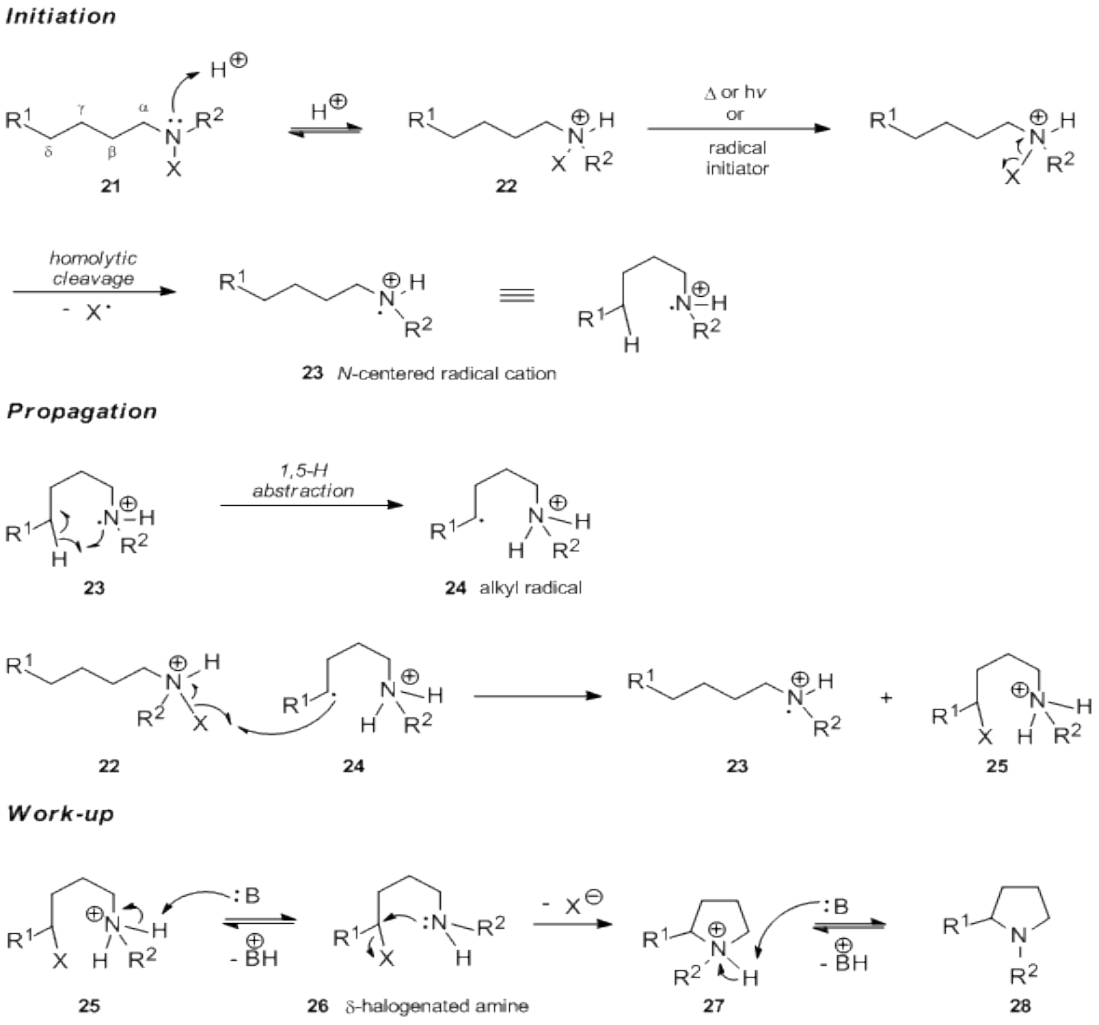
Although the Hofmann–Löffler–Freytag reaction was to become a general and expeditious process for the formation of pyrrolidines, it was not until about 25 years after Hofmann's work that further examples of the reaction were reported. In 1909, K. Löffler and C. Freytag extended the scope of this transformation to simple secondary amines and demonstrated the synthetic utility of the process as exemplified by their elegant synthesis of nicotine 6 from *N*-bromo-*N*-methyl-4-(pyridin-3-yl)butan-1-amine 5.[8][9][10]



5 6

Generally accepted mechanism

It is generally accepted that the first step in the Hofmann–Löffler–Freytag reaction conducted in acidic medium is the protonation of the *N*-halogenated amine 21 to form the corresponding *N*-halogenated ammonium salt 22. In case of thermal or chemical initiation of the free radical chain reaction, the *N*-halogenated ammonium salt 22 undergoes homolytic cleavage of the nitrogen-halogen bond to generate the nitrogen-centered radical cation 23. In contrast, it has been argued that the UV light-catalyzed initiation involves the free form of the *N*-haloamine and a rapid protonation of the newly generated neutral nitrogen radical (see the section devoted to mechanistic studies for arguments supporting this statement). Intramolecular 1,5-hydrogen atom transfer produces carbon-centered radical 24, which subsequently abstracts a halogen atom from the *N*-halogenated ammonium salt 22. This affords the protonated δ-halogenated amine 25 and regenerates the nitrogen-centered radical cation 23, the chain carrier of the reaction. Upon treatment with base, 25 undergoes deprotonation followed by an intramolecular S_N2 reaction to yield pyrrolidine 28 via intermediate 27.



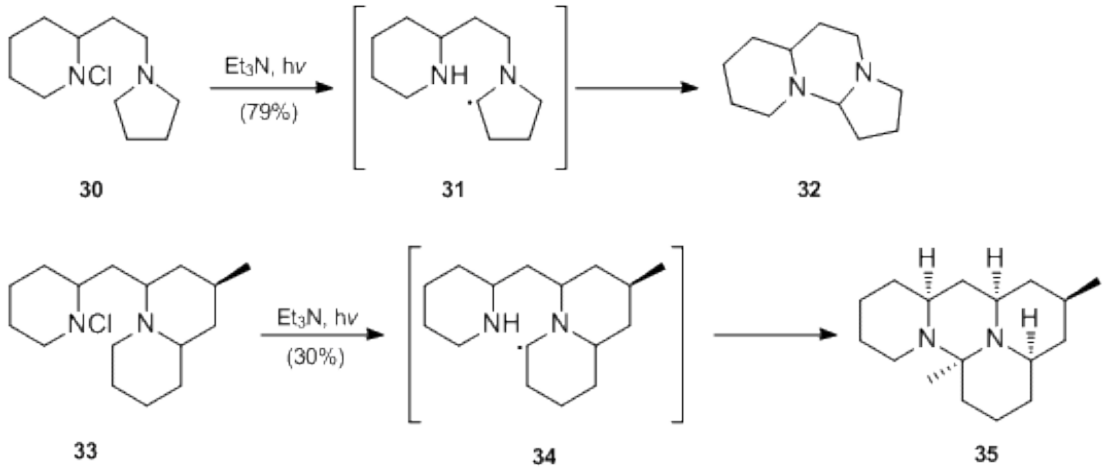
General features of the reaction

- The starting material for the Hofmann–Löffler–Freytag reaction could be *N*-chloro-, *N*-bromo-, and *N*-iodoamines. In case of thermal initiation, the *N*-chloroamines give better yields for pyrrolidines because *N*-bromoamines are less stable thermally than the corresponding *N*-chloroamines.[18] In contrast, when the initiation is carried out by irradiation, the *N*-bromoamines give higher yield for pyrrolidines.[11][*failed verification*]
- The Hofmann–Löffler–Freytag reaction was originally carried out under acidic conditions, but it has been demonstrated that neutral or even weakly basic conditions might also be successfully employed.[19][20]
- The initially formed nitrogen-centered radical abstracts a H-atom mostly from the δ-position and thus 5-membered rings are formed predominantly.
- Formation of 6-membered rings is also possible, but relatively rare, and in majority of cases is observed in rigid cyclic systems.[11]
- The reaction can be conducted under milder conditions provided that the alkyl radical experiences some form of extra stabilization, e.g. by an adjacent heteroatom.[20]
- The radical process may be initiated by heating, irradiation with light or with radical initiators (e.g. peroxides, metal salts).

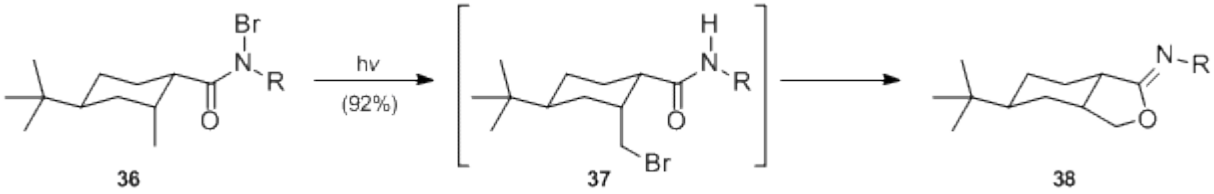
Modifications and improvements

Because the original strongly acidic reaction conditions are often not compatible with the sensitive functional and protecting groups of complex substrates, several modifications of the Hofmann–Löffler–Freytag reaction were introduced:

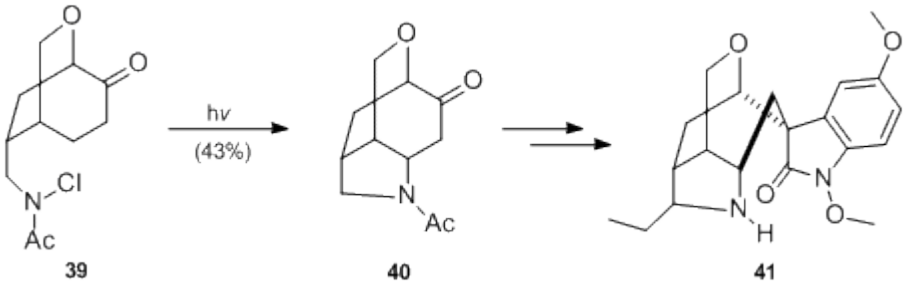
- M. Kimura and Y. Ban demonstrated that adjacent nitrogen atoms can stabilize radical species generated by H-atom abstraction and permit this step to take place under weakly basic conditions[20][21] They reported that far better yields are obtained on photoirradiation in the presence of triethylamine, which neutralizes the hydrogen chloride generated by cyclization. M. Kimura and Y. Ban employed the modified conditions of the Hofmann–Löffler–Freytag reaction to the synthesis of dihydrodeoxyepiallocernuine 35.[20]



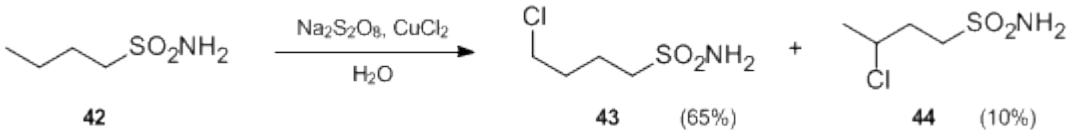
- It has been demonstrated that photolysis of *N*-haloamides proceeds efficiently under neutral conditions. Irradiation of *N*-bromoamide 36 (R=^{t}Bu) gave rise to bromomethyl-cyclohexane-amide 37 which, upon treatment with base *in situ* afforded iminolactone 38 in 92% yield.[22]



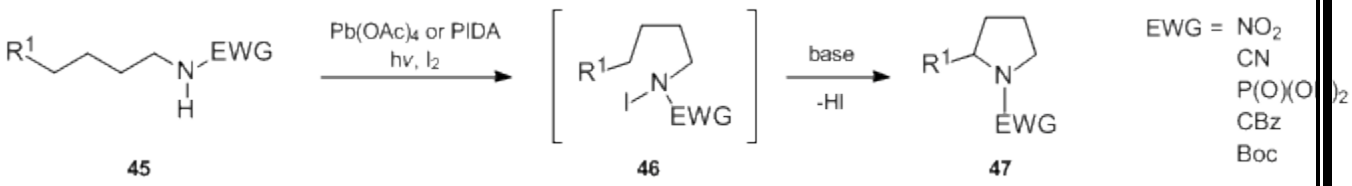
Similarly, S. W. Baldwin and T. J. Doll examined a modification of the Hofmann–Löffler–Freytag reaction during their studies towards the synthesis of the alkaloid gelsemicine 41. The formation of the pyrrolidine ring of 40 was accomplished by irradiation of *N*-chloroamide 39.[19]



- Another variation of the Hofmann–Löffler–Freytag reaction involves sulfonamides in place of *N*-haloamines. In the presence of persulphates and metal salts, sulfonamides can undergo intramolecular free-radical funcionalization to produce γ- and δ-chloroalkenylsulfonamides under neutral conditions. For instance, upon treatment with $Na_2S_2O_8$ and $CuCl_2$, butylsulfonamide 42 was transformed to 4-chlorobutylsulfonamide 43 and 3- chlorobutylsulfonamide 44 in the absence of acid.[23]



- The most important variation of the Hofmann–Löffler–Freytag reaction is the *Suárez modification*. In 1980, Suárez *et al.*[24] reported a process using neutral conditions for the Hofmann–Löffler–Freytag reaction of *N*-nitroamides. Further developments of this transformation have led to the expansion of the substrate scope to *N*-cyanamides, *N*-phosphoramidates and carbamates.[25][26][27][28][29] All these species react with hypervalent iodine reagents in the presence of iodine (I_2) to generate nitrogen-centered radical via homolytic fragmentation of a hypothetical iodoamide intermediate. Thus formed *N*-radicals might participate in an intramolecular 1,5-hydrogen abstraction reaction from unactivated carbons, the result being the formation of pyrrolidines.



DSVvery mild neutral conditions compatible with the stability of the protective groups most frequently used in synthetic organic chemistry. Consequently, it permits the use of the Hofmann–Löffler–Freytag reaction with more sensitive molecules. Other notable features of this methodology are the following: (1) the unstable iodoamide intermediates are generated in situ; (2) the iodoamide homolysis proceeds thermally at low temperature (20–40 °C) or by

irradiation with visible light, which obviates the need for a UV lamp. The *Suárez modification* has found numerous applications in synthesis (vide infra).

- Nagib and co-workers have employed a triiodide strategy that expands the scope of the Hofmann–Löffler–Freytag reaction via the *Suárez modification* to enable the amination of secondary C-H bonds.[30] This approach employs NaI, instead of I_2, as a radical precursor to prevent undesired I_2-mediated decomposition pathways. Other halide salts (e.g. NaCl and NaBr) afford the postulated intermediates of the interrupted Hofmann–Löffler–Freytag mechanism.

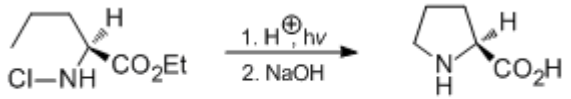
Applications in synthesis[edit]

The most prevalent synthetic utility of the Hofmann–Löffler–Freytag reaction is the assembly of the pyrrolidine ring.

The Hofmann–Löffler–Freytag reaction under standard conditions

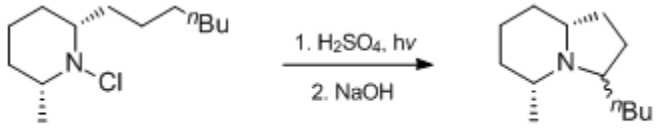
The procedure for the Hofmann–Löffler–Freytag reaction traditionally requires strongly acidic conditions, which limits its appeal. Nonetheless, it has been successfully applied to functionalization of a wide variety of structurally diverse molecules as exemplified below.

In 1980, J. P. Lavergne. *et al.*[31] used this methodology to prepare L-proline 49.



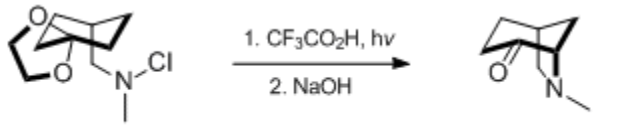
48 **49** (85%)

P. E. Sonnet and J. E. Oliver[32] employed classic Hofmann–Löffler–Freytag reaction conditions in the synthesis of potential ant sex pheromone precursors (i.e. octahydroindolizine 51).



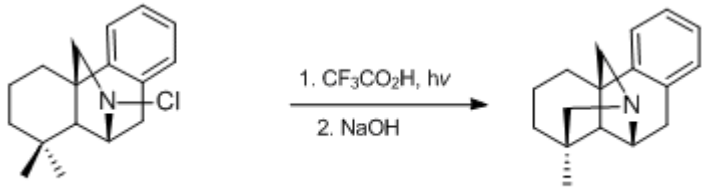
50 **51** (25%)

Another example of the construction of a bicyclic amine through the standard Hofmann–Löffler–Freytag methodology is the Waegell's synthesis[33] of azabicyclo[3.2.1]octane derivative 53.



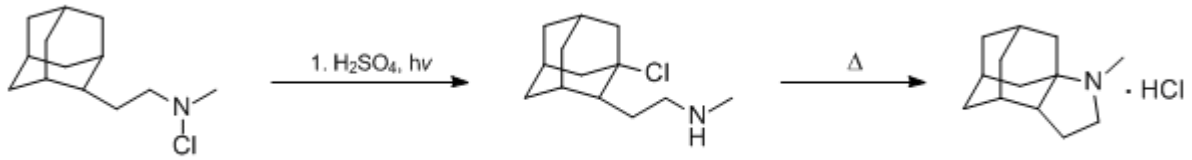
52 **53** (26%)

The Hofmann–Löffler–Freytag reaction was employed to synthesize the bridged nitrogen structure of (±)-6,15,16-iminopodocarpane-8,11,13-triene 55, an intermediate useful for the preparation of the kobusine-type alkaloids, from a bicyclic chloroamine 54.[34] Irradiation of 54 with a 400 W high-pressure mercury lamp in trifluoroacetic acid under a nitrogen atmosphere at room temperature for 5 h afforded a moderate yield of the product.



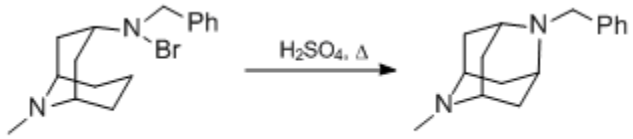
54 55 (39%)

Derivatives of adamantane have also been prepared using the Hofmann–Löffler–Freytag reaction.[35] When *N*-chloroamine 56 was treated with sulfuric acid and heat, 2-adamantanone was formed, but photolysis of 56 in the sulfuric acid-acetic acid mixture, using a low-pressure mercury lamp at 25 °C for 1-hour gave a good yield (85%) of the desired product 57. The cyclization of 57 presented considerable difficulties, but it was finally achieved in 34% yield under forcing conditions (heating at 290 °C for 10 min).



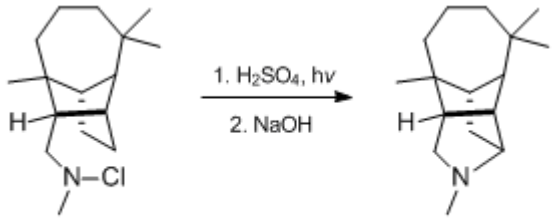
56 57 (85%) 58 (34%)

Similarly, it has been demonstrated[36] that derivatives of diaza-2,6 adamantane such as 60 might be formed under standard Hofmann–Löffler–Freytag reaction conditions; however, the yields are only moderate.



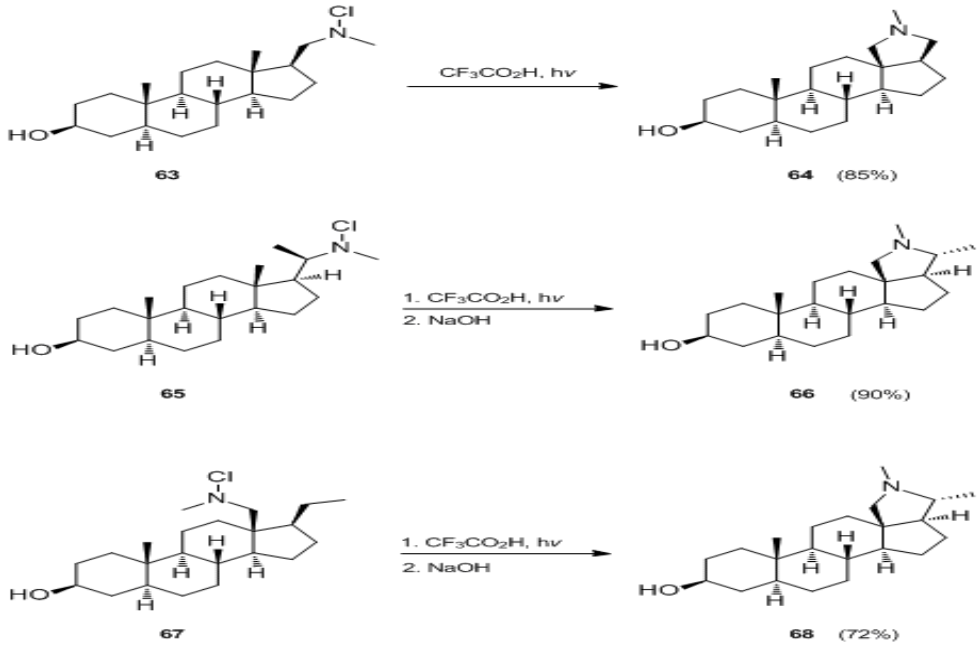
59 60 (25%)

R. P. Deshpande and U. R. Nayak[37] reported that the Hofmann–Löffler–Freytag reaction is applicable to the synthesis of pyrrolidines containing a longifolene nucleus, e.g. 62.

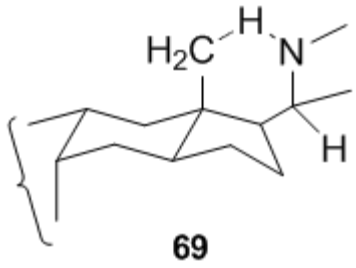


61 62 (10%)

An outstanding application of the Hofmann–Löffler–Freytag reaction is found in the preparation of the steroidal alkaloid derivatives. J. Hora[38] and G. van de Woude[39][40][41] used this procedure in their syntheses of conessine derivatives shown below.



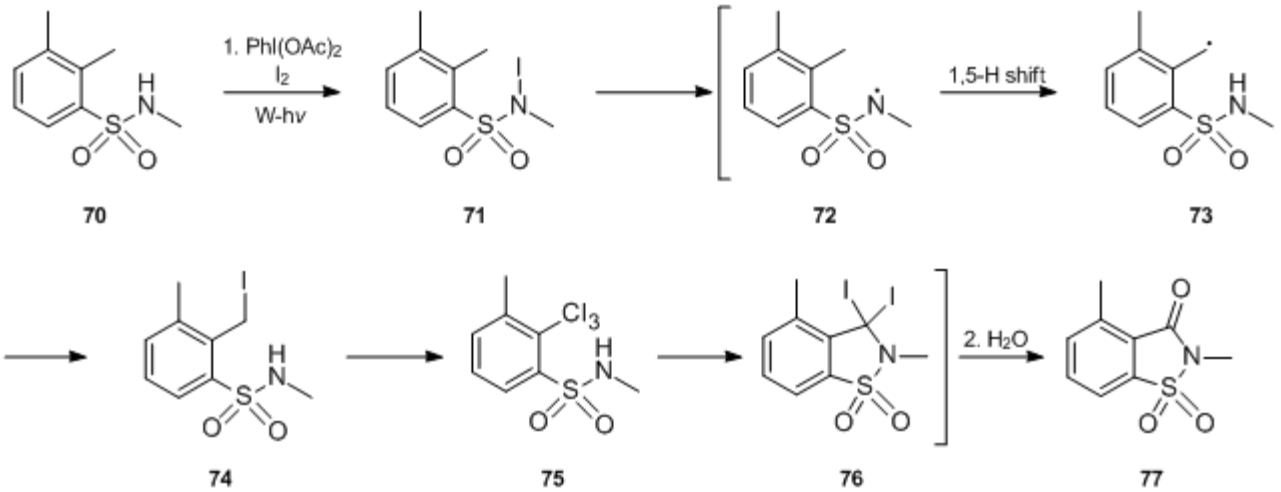
In case of 64 and 66, the five-membered nitrogen ring is formed by attack on the unactivated C-18 methyl group of the precursor (63 or 65, respectively) by a suitably placed nitrogen-centered radical at C-20. The ease of this reaction is due to the fact that in the rigid steroid framework the β-C-18 methyl group and the β-C-20 side chain carrying the nitrogen radical are suitably arranged in space in order to allow the 1,5-hydrogen abstraction to proceed via the six-membered transition state.



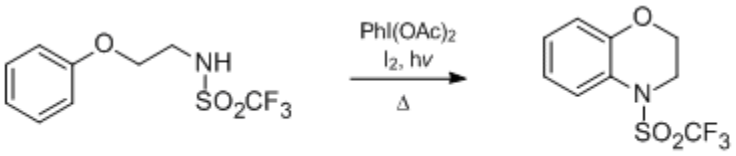
The Hofmann–Löffler–Freytag reaction under mild conditions[edit]

A number of examples of the Hofmann–Löffler–Freytag reaction under neutral conditions have been presented in the section devoted to modifications and improvements of the original reaction conditions. Hence, the main focus of this section are the applications of the *Suárez modification* of the Hofmann–Löffler–Freytag reaction.

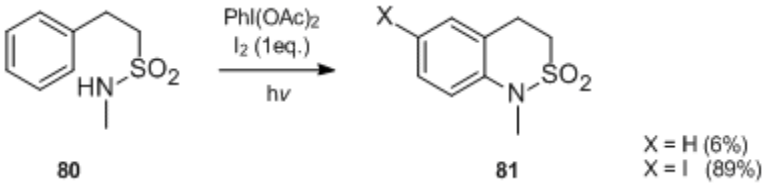
The *Suárez modification* of the Hofmann–Löffler–Freytag reaction was the basis of the new synthetic method developed by H. Togo *et al.*[42][43] The authors demonstrated that various *N*-alkylsaccharins (*N*-alkyl-1,2-benzisothiazoline-3-one-1,1,-dioxides) 77 are easily prepared in moderate to good yields by the reaction of *N*-alkyl(*o*-methyl)arenesulfonamides 70 with $PhI(OAc)_2$ in the presence of iodine under the irradiation of a tungsten lamp. 1,5 - Hydrogen abstraction/iodination of the *o*-methyl group is repeated three times and is most likely followed by cyclization to diiodo intermediate 76, which then undergoes hydrolysis.



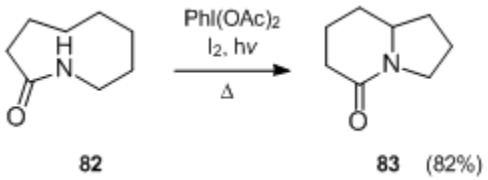
A very interesting transformation is observed when sulfonamides of primary amides bearing an aromatic ring at the γ-position are treated with various iodanes and iodine under the irradiation with a tungsten lamp.[44] The reaction leads to 1,2,3,4-tetrahydroquinoline derivatives and is a good preparative method of six-membered cyclic aromatic amines. For instance, sulfonamide 78 undergoes an intramolecular radical cyclization to afford 79 in relatively good yield.



By the same procedure, 3,4-dihydro-2,1-benzothiazine-2,2-dioxides 81 are obtained from the *N*-alkyl 2-(aryl)ethanesulfonamides via the sulfonamidyl radical.[45]

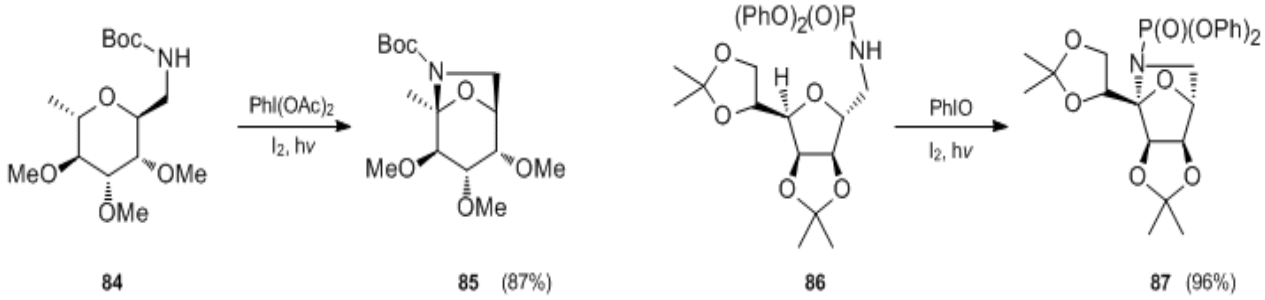


E. Suárez *et al.*[46] reported that the amidyl radical intermediates, produced by photolysis of medium-sized lactams, e.g. 82 in the presence of $PhI(OAc)_2$ and iodine, undergo transannular hydrogen abstraction to afford intramolecularly funcionalized compounds such as oxoindolizidines 83.



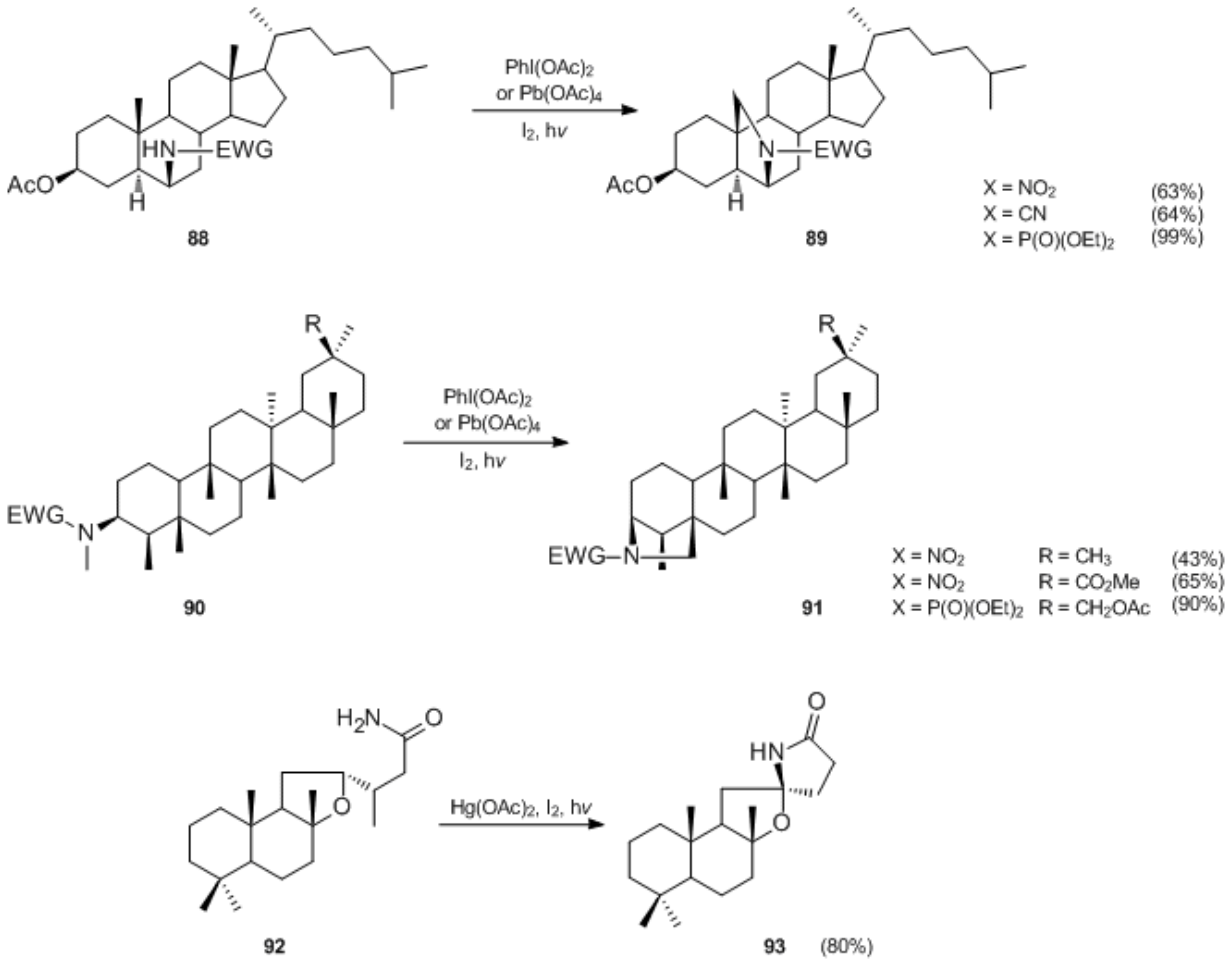
E. Suárez and co-workers[27] also applied their methodology in the synthesis of chiral 8-oxa-6-azabicyclo[3.2.1]-octane 85 and 7-oxa-2-azabicyclo[2.2.1]heptane 87 ring systems. This reaction can be considered to be an intramolecular *N*-glycosidation that goes through an intramolecular 1,5-hydrogen abstraction promoted by an *N*-amido radical followed by

oxidation of the transient C-radical intermediate to an oxycarbenium ion, which is subsequently trapped by an internal nucleophile.



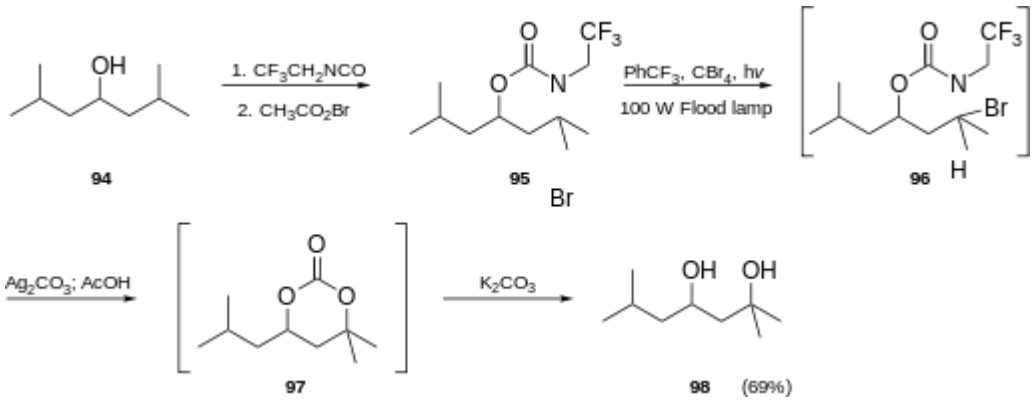
84 **85** (87%) **86** **87** (96%)

The utility of the *Suárez modification* of the Hofmann–Löffler–Freytag reaction was demonstrated by its application in synthesis of a number of steroid and triterpene compounds.[25][26][28][29][47] As illustrated below, the phosphoramidate-initiated funcionalizations generally proceed in higher yields than the reactions involving *N*-nitro or *N*-cyanamides.

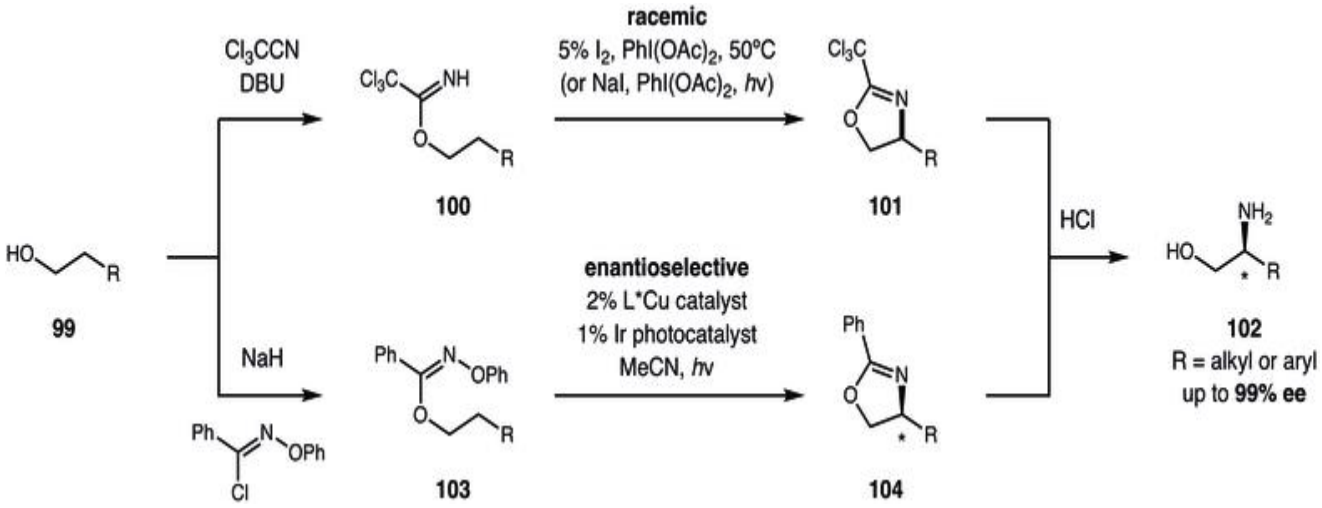


88 **89** **90** **91** **92** **93** (80%)

In 2008 Baran *et al.*[48] reported a new method for the synthesis of 1,3-diols using a variant of the Hofmann–Löffler–Freytag reaction.



In 2017, Nagib *et al.*[49][50] reported a new method for the synthesis of 1,2-amino-alcohols using a variant of the Hofmann–Löffler–Freytag reaction to promote β selective C-H amination of alcohols. In 2020, an asymmetric variant was disclosed by the same team.[51]



Barton reaction

The **Barton reaction**, also known as the **Barton nitrite ester reaction**, is a photochemical reaction that involves the photolysis of an alkyl nitrite to form a δ-nitroso alcohol.

Discovered in 1960, the reaction is named for its discoverer, Nobel Laureate Sir Derek Barton.[1] Barton's Nobel Prize in Chemistry in 1969 was awarded for his work on understanding conformations of organic molecules, work which was key to realizing the utility of the Barton Reaction.[2]

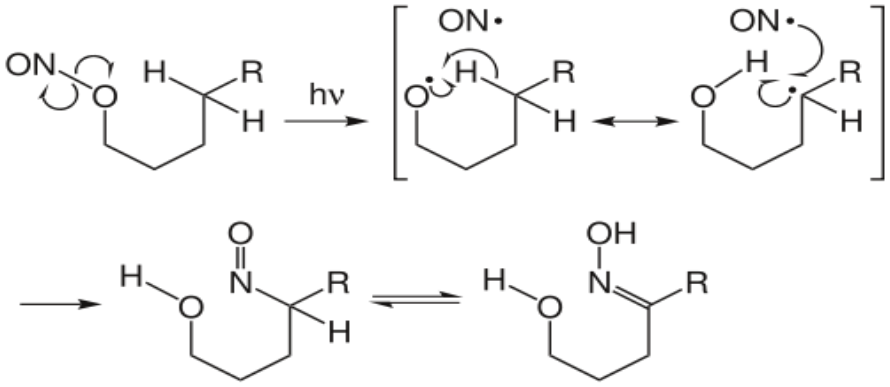
The Barton reaction involves a homolytic RO–NO cleavage, followed by δ-hydrogen abstraction, free radical recombination, and tautomerization to form an oxime.[3] Selectivity for the δ-hydrogen is a result of the conformation of the 6-membered radical intermediate. Often, the site of hydrogen atom abstraction can be easily predicted. This allows the regio- and stereo-selective introduction of functionality into complicated molecules with high yield. Due to its unique property at the time to change otherwise inert substrates, Barton used this reaction extensively in the 1960s to create a number of unnatural steroid analogues.[4]

While the Barton reaction has not enjoyed the popularity or widespread use of many other organic reactions, together with the mechanistically similar Hofmann–Löffler reaction it

represents one of the first examples of C-H activation chemistry, a field which is now the topic of much frontline research in industrial and academic chemistry circles.[5]

Reaction mechanism and regioselectivity

The Barton reaction commences with a photochemically induced cleavage of the nitrite O-N bond, typically using a high pressure mercury lamp.[8] This produces an alkyoxyl radical which immediately abstracts a hydrogen atom from the δ-carbon. In the absence of other radical sources or other proximal reactive groups, the alkyl radical recombines with the nitrosyl radical. The resultant nitroso compounds undergoes tautomerization to the isolated oxime product.



The carbon centered radical can be intercepted by other radical sources such as iodine or acrylonitrile. The first instance results in the δ-hydrogen being replaced with iodine, then subsequent cyclization to a tetrahydrofuran by an SN2 reaction.[9] The second example results in a chain elongation product with the oxime formed 2 carbon units further from the oxygen than normal.[10]

This mechanistic hypothesis is supported by kinetic isotope effect experiments.[11] Isotopic labeling of the nitrite with 15N has shown the mechanism non-'caged' and that the nitrosyl radical formed from a given nitrite recombines randomly with other alkyl radicals. However, recombination of the nitrosyl radical with the alkoxyl radical (a reversal of the homolytic cleavage) has been shown to proceed without scrambling of isotope labels.[12] This lack of tight radical pairing is also supported by the observation that alkyl radicals generated by Barton conditions can undergo radical cyclization while analogous intermediates generated by lead tetraacetate oxidation do not.[13]

In rare cases, it appears that the alkoxyl radical may epimerize before hydrogen atom abstraction.[14]

Most commonly, including steroidal systems, the hydrogen atom is abstracted from a methyl group that has a 1,3 diaxial relationship with the alkoxyl radical.[15] In the absence of a hydrogen on the δ-carbon, or when the particular conformation of the substrate orients the ε-carbon close together, 1,6-hydrogen atom transfer is the favored process. However, these reactions tend to be an order of magnitude slower than the corresponding 1,5-hydrogen atom transfer.

Computational studies have shown that this preference for 1,5-hydrogen atom transfer over 1,6-hydrogen atom transfer appears to be entropically favored rather than a result of a particular stable 'chair-like' transition state.[16] In fact, it has been calculated that the 1,6-

hydrogen atom transfer proceeds through a transition that is about 0.8 kcal/mol lower than that of the 1,5.

In acyclic systems, δ-hydrogen abstraction is still observed, however, alpha-hydrogen abstraction to form the corresponding ketone competes.[17]

In certain cases, particularly nitrites derived from cyclopentyl alcohols, the oxygen-centered radical prefers to react via C-C bond cleavage as opposed to H-atom abstraction.[9] For example, when subjected to Barton conditions, cyclopentyl nitrite forms glutaraldehyde monoxime. This is also observed in cases where the radical intermediate formed by fragmentation is particularly stable, such as the allylic radical formed by the fragmentation of isopulegol nitrite.[18]

In rigid systems such as aldosterone, the 1,5-hydrogen atom transfer is exceedingly fast, with a rate constant on the order of 10^7 s-1. Similar intermolecular H-atom transfer can be up to 100 times slower.[19] Furthermore, the hydrogen atom transfer benefits from the formation of a stronger O-H bond at the expense of a weaker C-H bond. For the formation of a primary, second, or tertiary alkyl radical from an alkoxyl radical, there is a driving force of 3 kcal/mol, 5 kcal/mol, and 9 kcal/mol, respectively.[15]

The alkyl radical formed after hydrogen atom transfer is susceptible to standard radical reactions when scavengers are present in sufficient excess to outcompete the nitrosyl radical. Soon after their initial disclosure, Barton and co-workers reported the trapping of the radical with I_2 and CCl_3Br (as Iodine and Bromine radical sources, respectively) to form the δ-halo-alcohol. These halohydrin species can be cyclized to the corresponding tetrahydropyran derivates under basic conditions.[20]

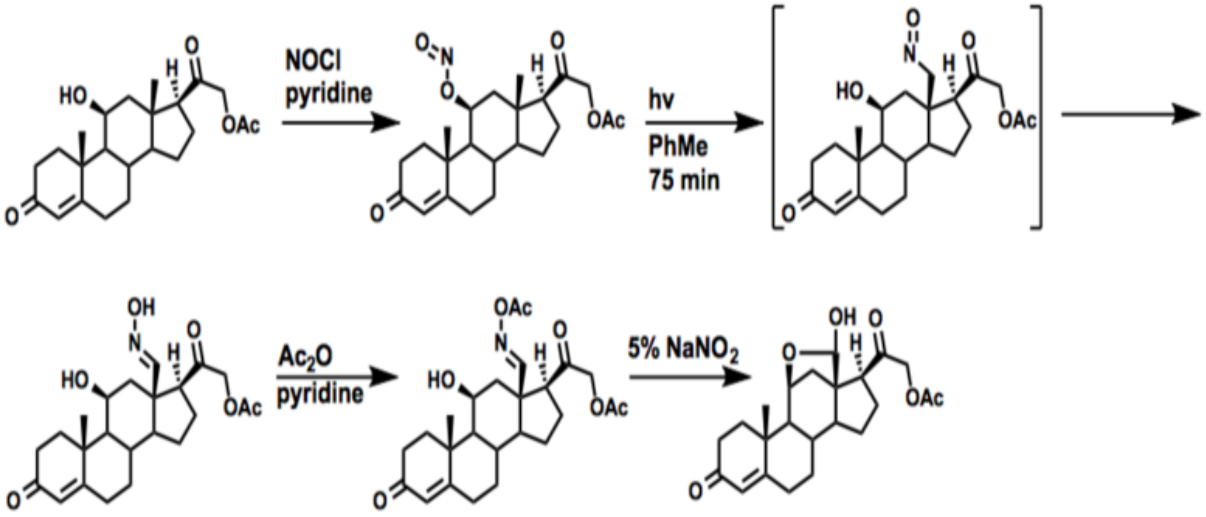
Large excesses of activated alkenes can be used to intercept the alkyl radical and results in formation of a C-C bond from an unactivated C-H bond.[21]

In the presence of oxygen, the alkyl radical is trapped and forms an organic peroxy radical. This intermediate is trapped by the nitrosyl radical and then isomerizes to give a δ-nitrate ester which, while both acid- and base-stable, can be reduced to the corresponding alcohol under mild conditions.[22]

Applications in complex molecule synthesissAS

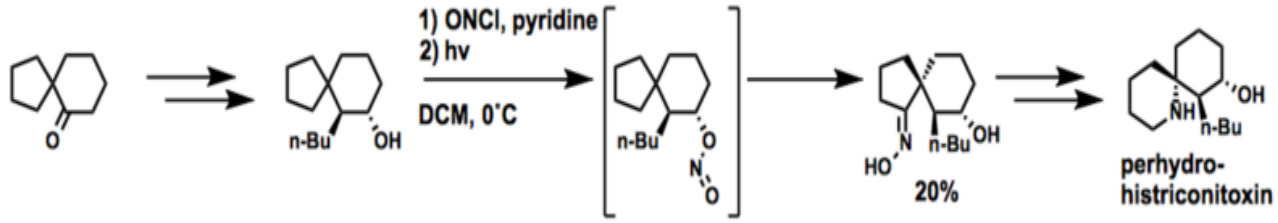
Aldosterone acetate

In a publication immediately proceeding Bartvon's initial disclosure of the methodology in the Journal of the American Chemical Society, a synthesis of aldosterone acetate is demonstrated.[23] Allowing corticosterone acetate to react with nitrosyl chloride in dry pyridine yields the nitrite. Subsequently, irradiation under inert atmosphere followed by treatment with aqueous sodium nitrite selectively gives the desired oxime. The oxime is then acetylated and hydrolyzed to yield the natural product hemiacetal.



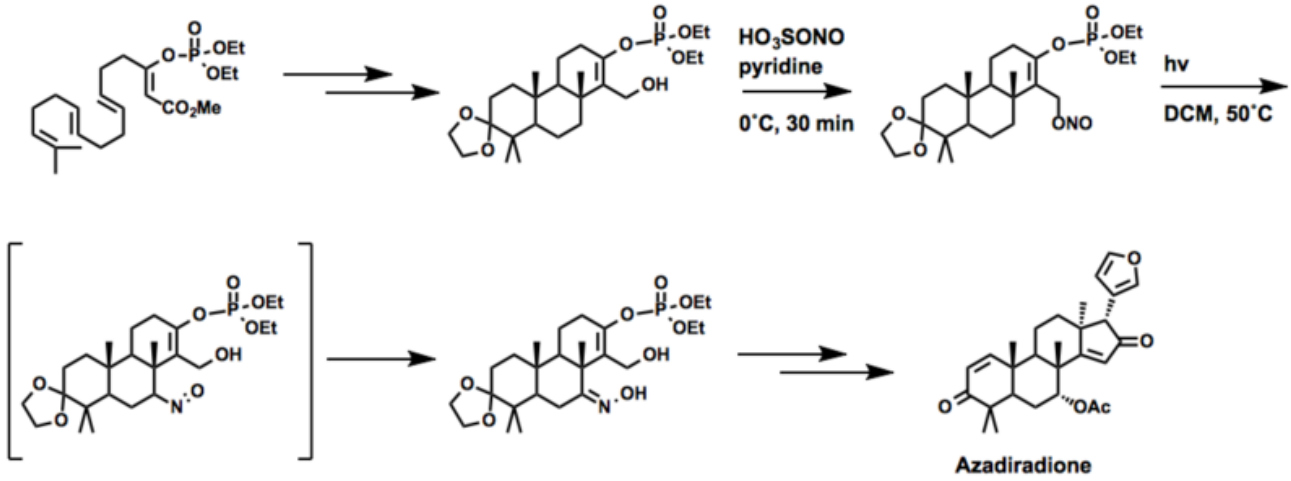
Perhydrohistrionicotoxin

After a short synthesis to obtain the desired spiro-[5.4] system, Nobel Laureaute E.J. Corey and co-workers employed a Barton reaction to selectively introduce an oxime in a 1,3-diaxial position to the nitrite ester. The oxime is converted to a lactam via a Beckmann rearrangement and then reduced to the natural product.[24]



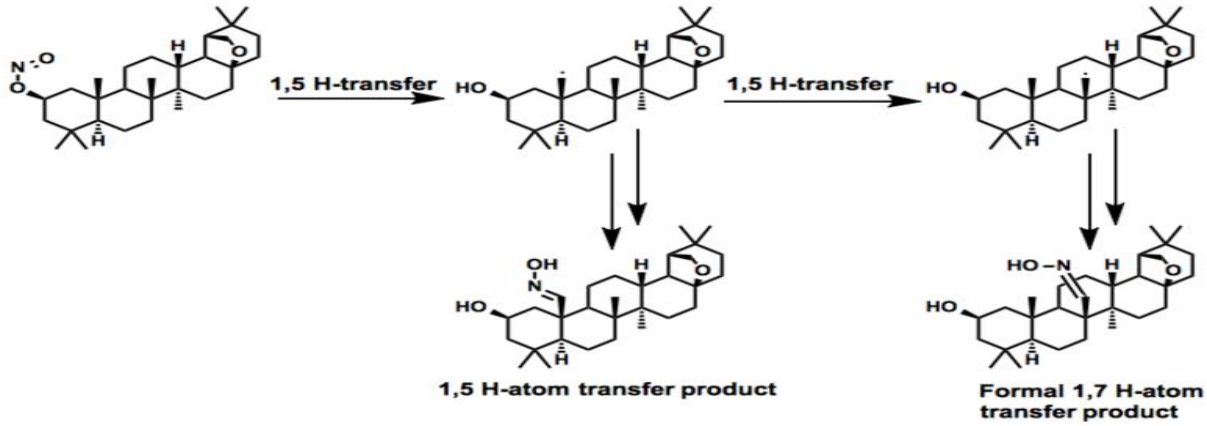
Azadiradione

Corey again employed the Barton reaction in the synthesis of Azadiradione, a member of the limonoid family of natural products. In this case, nitrosylsulfuric acid is used in place of nitrosyl chloride.[25]



Allobetulin derivatives

In the process of preparing a series of derivatives of the triterpenoid allobetulin, Dehan and coworkers observed a remarkable transformation resulting from two consecutive 1,5-hydrogen atom transfers. While the product of the single 1,5-hydrogen atom transfer was also observed, the former transformation represent a formal 1,7-hydrogen atom transfer across an enormous distance.[26]



Organoboron chemistry

Organoborane or **organoboron** compounds are chemical compounds of boron and carbon that are organic derivatives of BH_3, for example trialkyl boranes. **Organoboron chemistry** or **organoborane chemistry** is the chemistry of these compounds.

Organoboron compounds are important reagents in organic chemistry enabling many chemical transformations, the most important one called hydroboration.

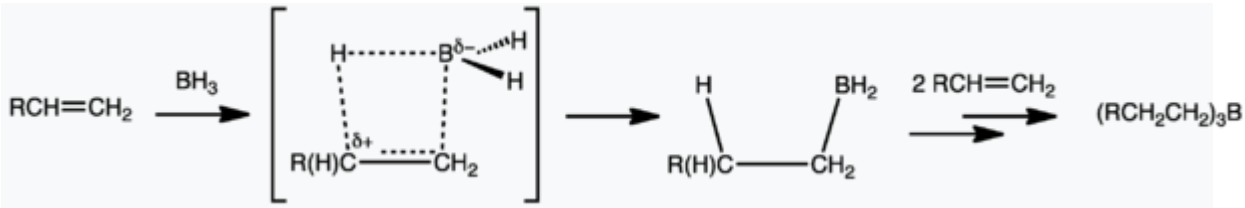
Hydroboration

In chemistry, **hydroboration** refers to the addition of a hydrogen-boron bond to C-C, C-N, and C-O double bonds, as well as C-C triple bonds. This chemical reaction is useful in the organic synthesis of organic compounds. The development of this technology and the underlying concepts were recognized by the Nobel Prize in Chemistry to Herbert C. Brown.[1] He shared the Nobel prize in chemistry with Georg Wittig in 1979[2] for his pioneering research on organoboranes as important synthetic intermediates.

Hydrogenation produces organoborane compounds that react with a variety of reagents to produce useful compounds, such as alcohols, amines, alkyl halides. The most widely known reaction of the organoboranes is oxidation to produce alcohols typically by hydrogen peroxide. This type of reaction has promoted research on hydroboration because of its mild condition and a wide scope of tolerated alkenes. Another research subtheme is metal-catalysed hydroboration.

Addition of a H-B bond to C-C double bonds

Hydroboration is typically anti-Markovnikov, i.e. the hydrogen adds to the most substituted carbon of the double bond. That the regiochemistry is reverse of a typical HX addition reflects the polarity of the $B^{\delta+}$-$H^{\delta-}$ bonds. Hydroboration proceeds via a four-membered transition state: the hydrogen and the boron atoms added on the same face of the double bond. Granted that the mechanism is concerted, the formation of the C-B bond proceeds slightly faster than the formation of the C-H bond. As a result, in the transition state, boron develops a partially negative charge while the more substituted carbon bears a partially positive charge. This partial positive charge is better supported by the more substituted carbon. Formally, the reaction is an example of a group transfer reaction. However, an analysis of the orbitals involved reveals that the reaction is 'pseudopericyclic' and not subject to the Woodward–Hoffmann rules for pericyclic reactivity.



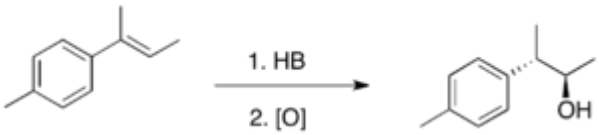
Hydroboration of a terminal alkene to a trialkylborane, showing idealized image of the cyclic transition state.

If BH_3 is used as the hydroborating reagent, reactions typically proceed beyond the monoalkyl borane compounds, especially for less sterically hindered small olefins. Trisubstituted olefins can rapidly produce dialkyl boranes, but further alkylation of the organoboranes is slowed because of steric hindrance. This significant rate difference in producing di- and tri-alkyl boranes is useful in the synthesis of bulky boranes that can enhance regioselectivity

Reactions of Organoboranes

Main article: Hydroboration–oxidation reaction

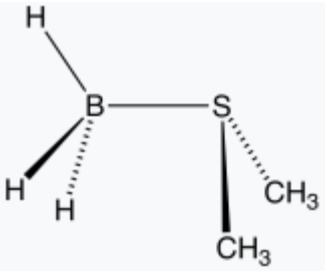
The C-B bonds generated by hydroboration are reactive with various reagents, the most common one being hydrogen peroxide. Because the addition of H-B to olefins is stereospecific, this oxidation reaction will be diastereoselective when the alkene is tri-substituted.[4] Hydroboration-oxidation is thus an excellent way of producing alcohols in a stereospecific and anti-Markovnikov fashion.



Hydroboration can also lead to amines by treating the intermediate organoboranes with monochloramine or O-hydroxylaminesulfonic acid (HSA).[5]

Terminal olefins are converted to the corresponding alkyl bromides and alkyl iodides by treating the organoborane intermediates with bromine[6] or iodine.[7] Such reactions have not however proven very popular, because succinimide-based reagents such as NIS and NBS are more versatile and do not require rigorous conditions as do organoboranes. etc.

Borane adducts

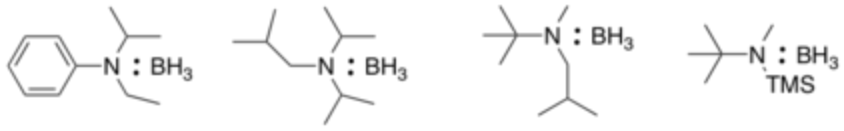


Borane dimethylsulfide (BMS) is a complexed borane reagent that is widely used for hydroborations.[8]

Diborane can be produced in situ by reduction BF_3 with $NaBH_4$ (see for Flavopiridol). Usually however, borane dimethylsulfide complex $BH_3S(CH_3)_2$ (BMS) is used as a source of BH_3.[9] It can be obtained in highly concentrated forms.[10]

The adduct BH_3(THF) is also commercially available as THF solutions wherein it exists as the 1:1 adduct. It degrades with time.[11]

Borane adducts with phosphines and amines are also available, but are not widely used.[12] Borane makes a strong adduct with triethylamine; using this adduct requires harsher conditions in hydroboration. This can be advantageous for cases such as hydroborating trienes to avoid polymerization. More sterically hindered tertiary and silyl amines can deliver borane to alkenes at room temperature.



Monosubstituted boranes

Monoalkyl boranes are relatively rare. They exist as dimers of the form $[RBH_2]_2$. One example is thexylborane ($ThxBH_2$), produced by the hydroboration of tetramethylethylene:[13]

$$B_2H_6 + 2\ Me_2C{=}CMe_2 \rightarrow [Me_2CHCMe_2BH_2]_2$$

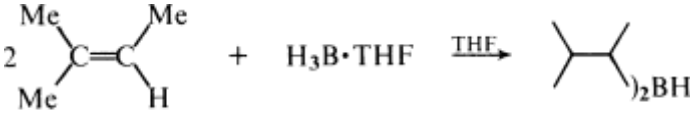
A chiral example is monoisopinocampheylborane. Although often written as $IpcBH_2$, it is a dimer $[IpcBH_2]_2$. It is obtained by hydroboration of (−)-α-pinene with borane-dimethyl sulfide.[14]

Species of the form RBH_2 are available for R = alkyl and halide. Monobromo- and monochloro-borane can be prepared from BMS and the corresponding boron trihalides. The stable complex of monochloroborane and 1,4-dioxane is a superior for selective hydroboration of terminal alkenes.[15]

Disubstituted boranes

Disubstituted boranes have the formula $(R_2BH)_2$, although they are often described as R_2BH, an example being dimesitylborane (Mes_2BH, or $(C_6H_2Me_3)_2BH$). Sterically bulky boranes are slow to undergo hydroboration. For example dimesitylborane react very slowly with simple terminal alkenes. On the other hand, alkynes undergo monohydroboration with Mes_2BH easily to produce alkenylboranes.[16]

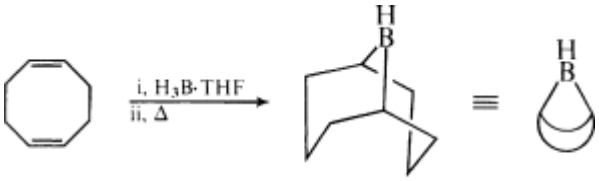
Disiamylborane



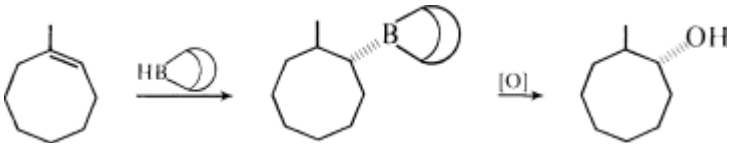
Sia_2BH

Among hindered dialkylboranes, disiamylborane (abbreviated Sia_2BH, but is a dimer $[Sia_2BH]_2$) is well known for selective hydroboration of less hindered, usually terminal alkenes in the presence of more substituted alkenes.[17] Disiamylborane must be freshly prepared as its solutions can only be stored at 0 °C for a few hours. Dicyclohexylborane Chx_2BH exhibits improved thermal stability than Sia_2BH.

9-BBN



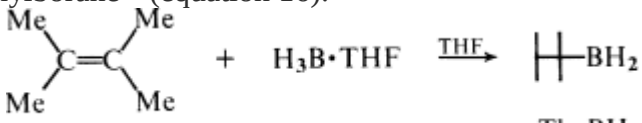
9-BBN



A versatile dialkylborane is 9-BBN (or "banana borane"). It exists as a dimer. It can be distilled without decomposition at 195 °C (12mm Hg). Reactions with 9-BBN typically occur at 60–80 °C, with most alkenes reacting within one hour. Tetrasubstituted alkenes add 9-BBN at elevated temperature. As mentioned above, hydroboration of alkenes with 9-BBN proceeds with excellent regioselectivity. It is more sensitive to subtle steric differences than Sia_2BH, perhaps because of the rigid backbone. 9-BBN is more reactive towards alkenes than alkynes.[18]

THEXYLBORANE

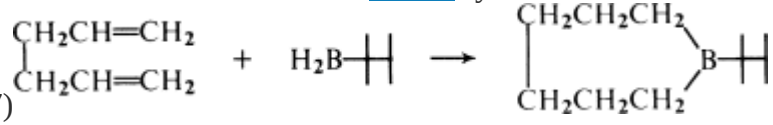
2,3-dimethyl-2-butene can be hydroborated to yield a monoalkylborane known as thexylborane[18] (equation 16).



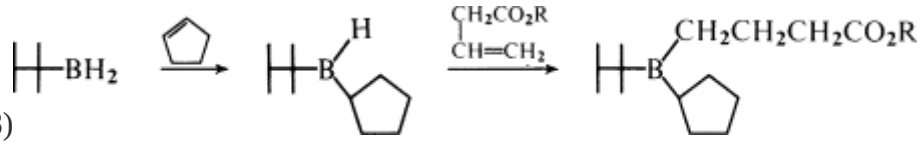
(16)

$ThxBH_2$

Thexylborane is valuable in achieving the cyclic hydroboration of dienes[19] (equation 17). It is also valuable in achieving the union of two different alkenes to boron[19–21] (equation 18). (One serious limitation should be noted. The first alkene introduced must be more hindered than a simple terminal alkene, $RCH{=}CH_2$.) Such thexyl derivatives provide the basis for a valuable ketone synthesis.



(17)



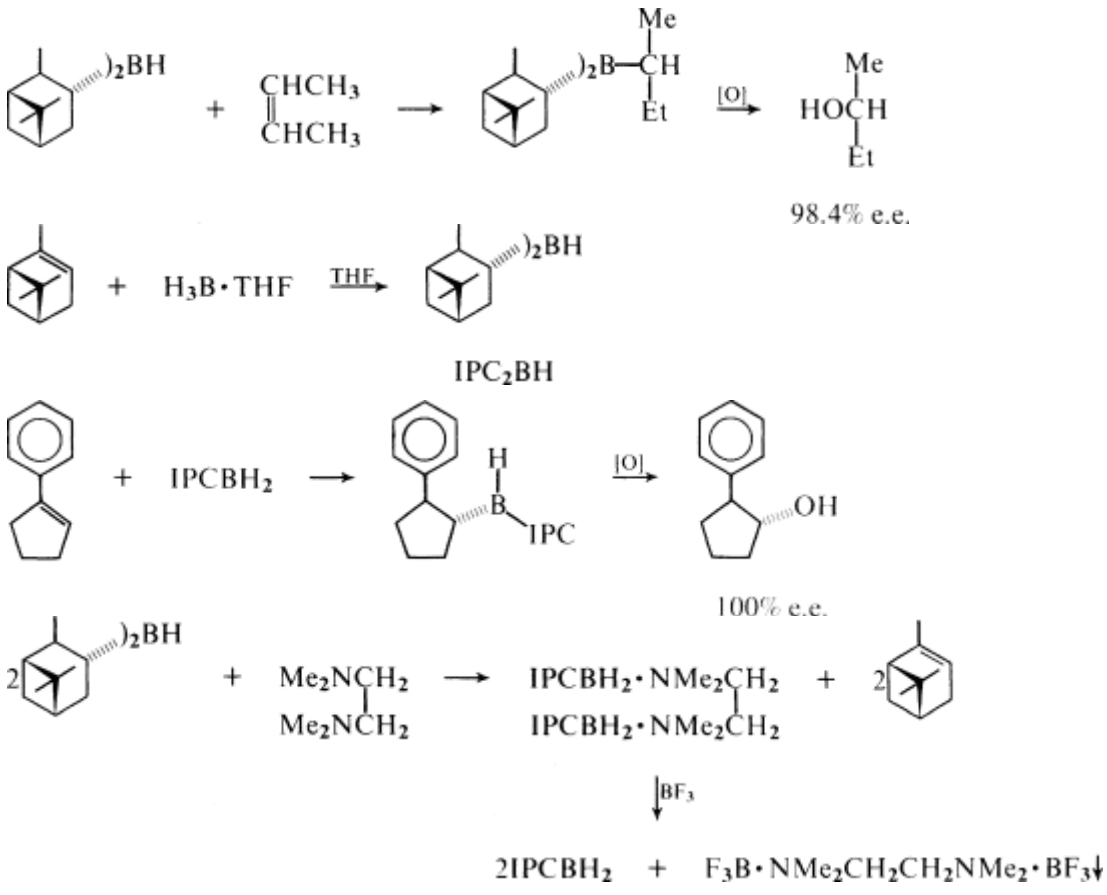
(18)

Other secondary boranes

Simple, unhindered dialkylboranes are reactive at room temperature towards most alkenes and terminal alkynes but are difficult to prepare in high purity, since they exist in equilibrium with mono- and trialkylboranes. One common way of preparing them is the reduction of dialkylhalogenoboranes with metal hydrides.[19] An important synthetic application using such dialkylboranes, such as diethylborane, is the transmetallation of the organoboron compounds to form organozinc compounds.[20][21]

Pinacolborane and catecholborane

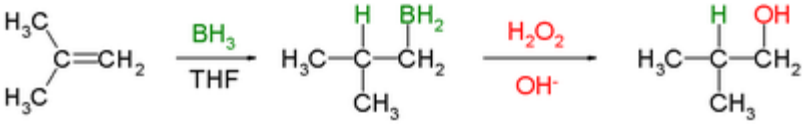
For catalytic hydroboration, pinacolborane and catecholborane are widely used. They also exhibit higher reactivity toward alkynes.[22] Pinacolborane is also widely used in a catalyst-free hydroborations.



Hydroboration–oxidation reaction

In organic chemistry, the **hydroboration–oxidation reaction** is a two-step hydration reaction that converts an alkene into an alcohol.[1] The process results in the syn addition of a hydrogen and a hydroxyl group where the double bond had been. Hydroboration–oxidation is an anti-Markovnikov reaction, with the hydroxyl group attaching to the less-substituted carbon. The reaction thus provides a more stereospecific and complementary regiochemical alternative to other hydration reactions such as acid-catalyzed addition and the oxymercuration–reduction process. The reaction was first reported by Herbert C. Brown in the late 1950s[2] and it was recognized in his receiving the Nobel Prize in Chemistry in 1979.

The general form of the reaction is as follows:



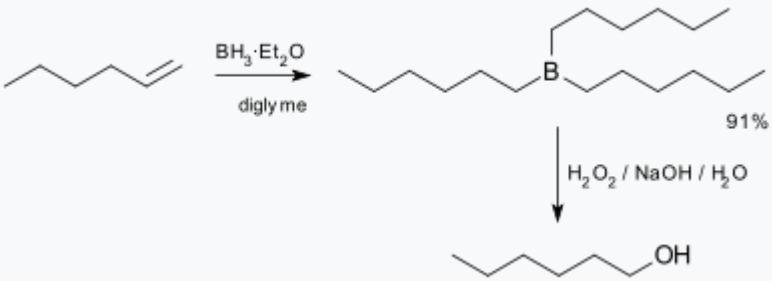
Tetrahydrofuran (THF) is the archetypal solvent used for hydroboration.

Mechanism and scope

Hydroboration step

Main article: hydroboration

In the first step, borane (BH_3) adds to the double bond, transferring one of the hydrogen atoms to the carbon adjacent to the one that becomes bonded to the boron. This hydroboration is repeated two additional times, successively reacting each B–H bond so that three alkenes add to each BH_3. The resulting trialkylborane is treated with hydrogen peroxide in the second step. This process replaces the B-C bonds with HO-C bonds. The boron reagent is converted to boric acid. The reaction was originally described by H.C. Brown in 1957 for the conversion of 1-hexene into 1-hexanol.[3]



Hexanol synthesis

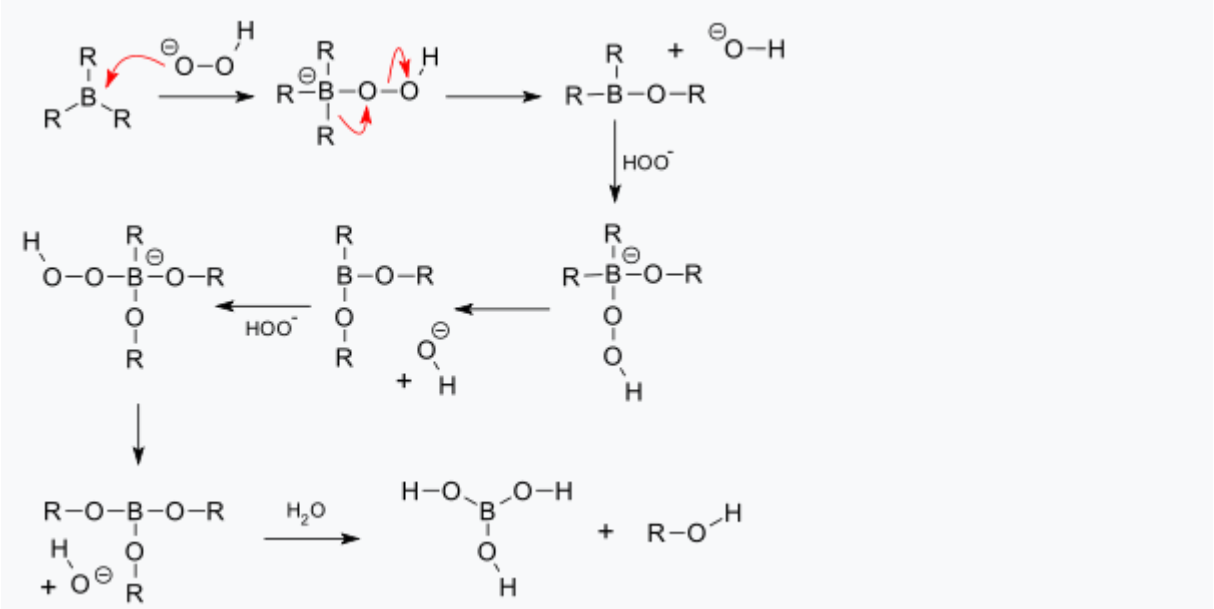
Knowing that the group containing the boron will be replaced by a hydroxyl group, it can be seen that the initial hydroboration step determines the regioselectivity. Hydroboration proceeds in an antimarkovnikov manner. The reaction sequence is also stereospecific, giving syn addition (on the same face of the alkene): the hydroboration is syn-selective and the oxidation replaces the boron with hydroxyl having the same geometric position. Thus 1-methylcyclopentene reacts with diborane predominantly to give *trans*-1-hydroxy-2-methylcyclopentane[4]—the newly added H and OH are *cis* to each other.

Until all hydrogens attached to boron have been transferred away, the boron group BH_2 will continue adding to more alkenes. This means that one mole of hydroborane will undergo the reaction with three moles of alkene. Furthermore, it is not necessary for the hydroborane to

have more than one hydrogen. For example, reagents of the type R_2BH are commonly used, where R can represents the remainder of the molecule. Such modified hydroboration reagents include 9-BBN, catecholborane, and disiamylborane.

Oxidation step

In the second step of the reaction sequence, the nucleophilic hydroperoxide anion attacks the boron atom. Alkyl migration to oxygen gives the alkyl borane with retention of stereochemistry (in reality, the reaction occurs via the trialkyl borate $B(OR)_3$, rather than the monoalkyl borinic ester BH_2OR).

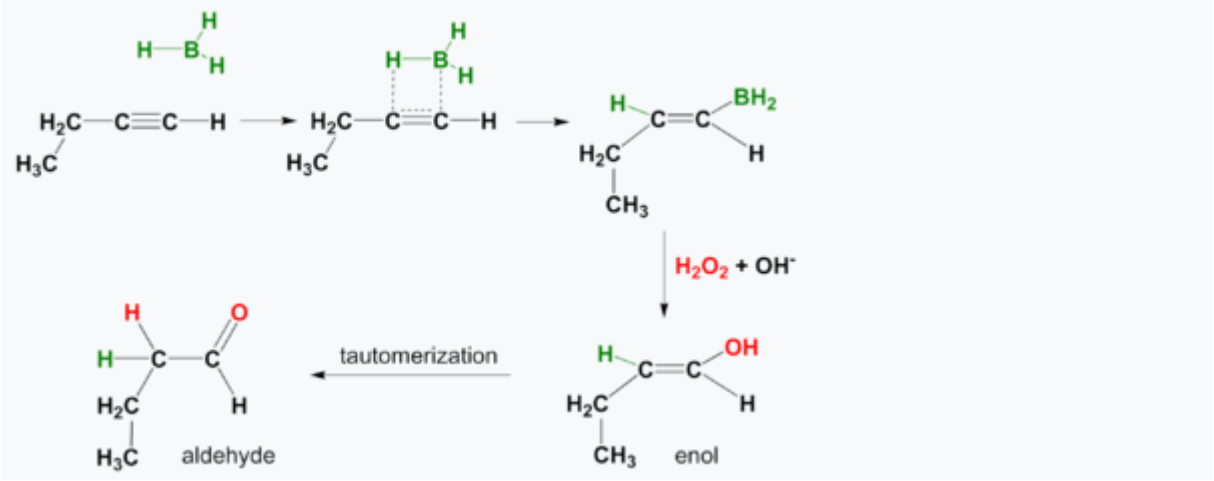


Hydroboration–oxidation mechanism

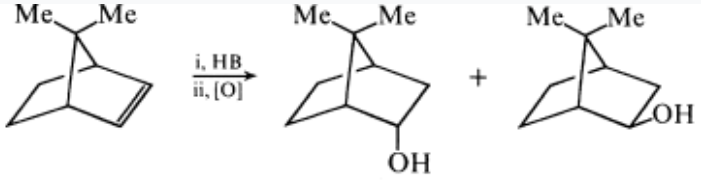
The 'H' atom in the reaction comes from B_2H_6, the 'O' atom comes from hydrogen peroxide (H_2O_2) whereas the O attached 'H' atom comes from the solvent (refer mechanism).

Alkyne hydroboration

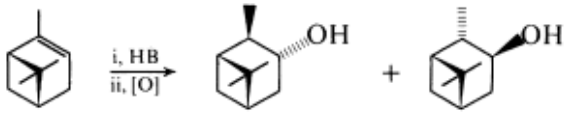
A hydroboration reaction also takes place on alkynes. Again the mode of action is *syn* and secondary reaction products are aldehydes from terminal alkynes and ketones from internal alkynes. In order to prevent hydroboration across both the pi-bonds, a bulky borane like disiamyl (di-sec-iso-amyl) borane is used.[5]



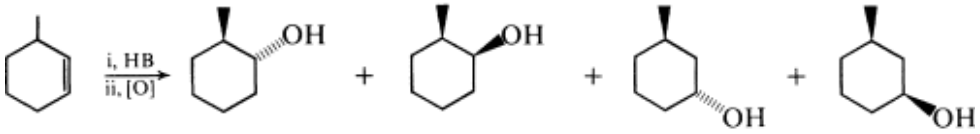
Applications of oxidation



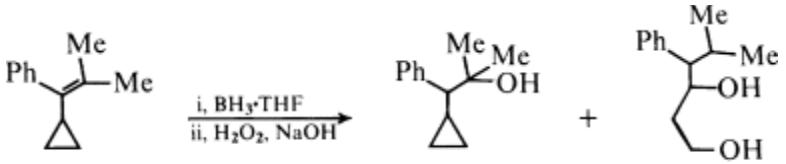
BH_3	79	21
9-BBN	97	3



BH_3	98	2
9-BBN	99.9	



9-BBN	20	0	40	40
Sia_2BH	30	18	25	27
BH_3	34	16	32	18



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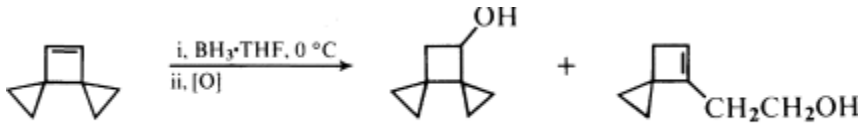

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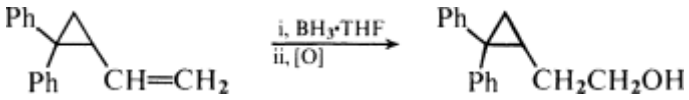
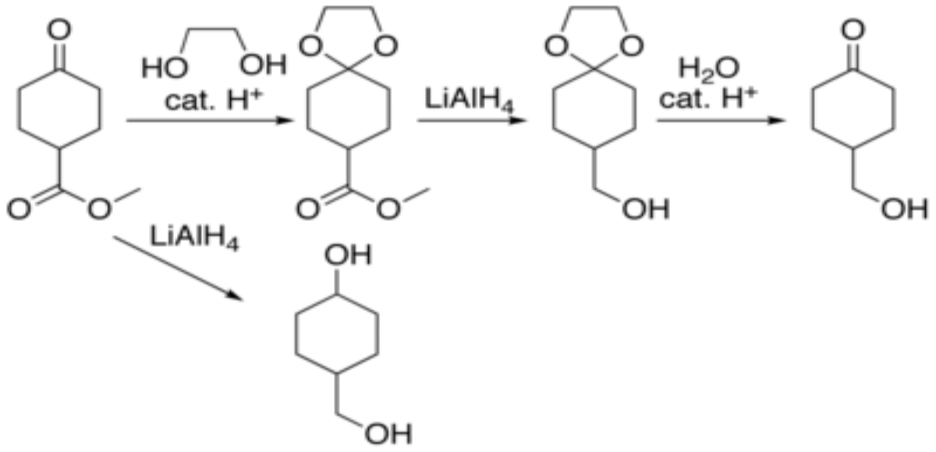


Protecting group

A protecting group or protective group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction. It plays an important role in multistep organic synthesis.[1]

In many preparations of delicate organic compounds, some specific parts of their molecules cannot survive the required reagents or chemical environments. Then, these parts, or groups, must be protected. For example, lithium aluminium hydride is a highly reactive but useful reagent capable of reducing esters to alcohols. It will always react with carbonyl groups, and this cannot be discouraged by any means. When a reduction of an ester is required in the presence of a carbonyl, the attack of the hydride on the carbonyl has to be prevented. For example, the carbonyl is converted into an acetal, which does not react with hydrides. The acetal is then called a protecting group for the carbonyl. After the step involving the hydride is complete, the acetal is removed (by reacting it with an aqueous acid), giving back the original carbonyl. This step is called deprotection.

Protecting groups are more commonly used in small-scale laboratory work and initial development than in industrial production processes because their use adds additional steps and material costs to the process. However, the availability of a cheap chiral building block can overcome these additional costs (e.g. shikimic acid for oseltamivir).



Acetal protection of a ketone with ethylene glycol during reduction of an ester, vs. reduction to a diol when unprotected.

Protection of Alcohols

Often during the synthesis of complex molecules on functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.

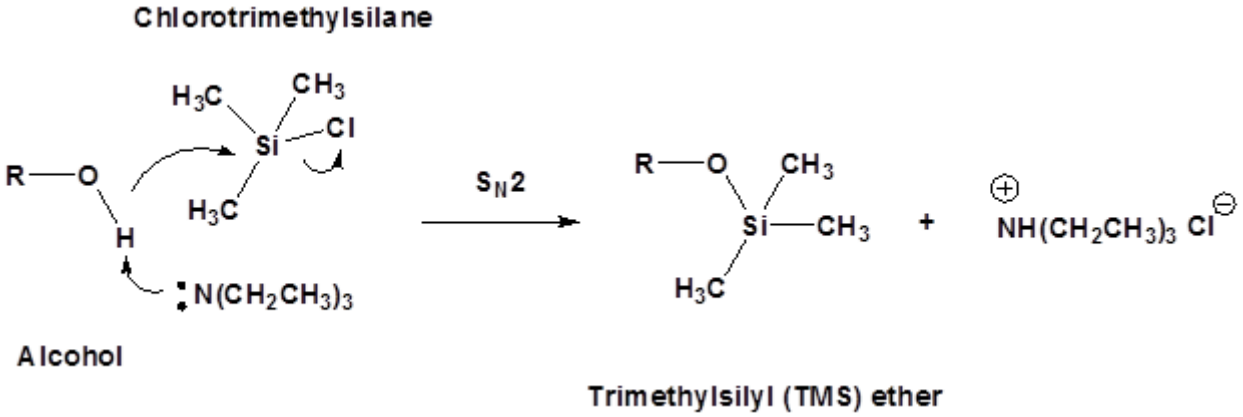
When situations like this occurs chemists circumvent the problem by protecting the interfering functional group. Functional group protection involves three steps:

1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

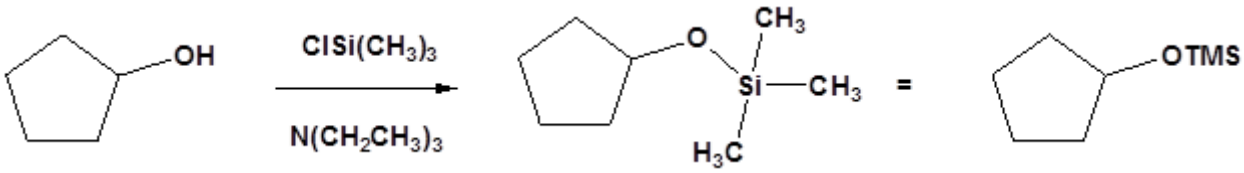
There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'-O-SiR_3. Chlorotrimethylsilane is often used in conjuction with a base, such as triethylamine, The base helps to form the alkoxide anion and remove the HCl produced by the reaction.

TRIMETHYLSILYL ETHERS(TMS)

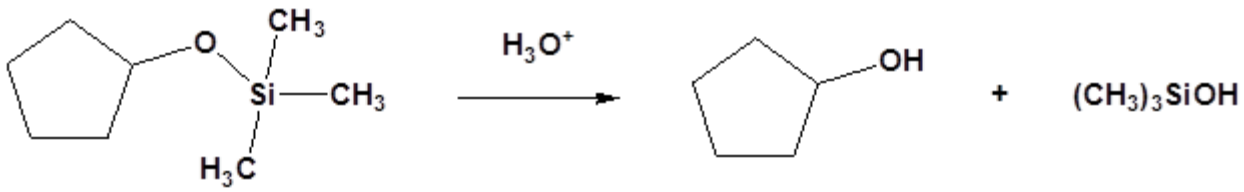
General Reaction



Example

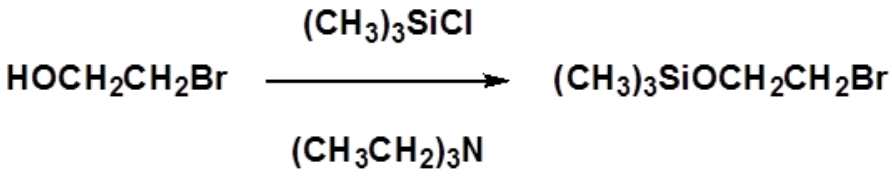


The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.

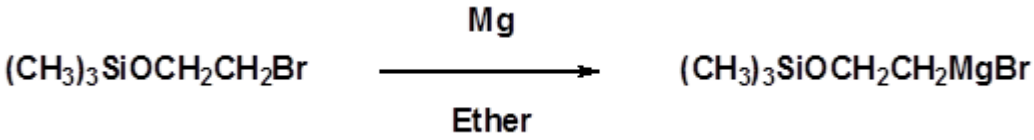


By utilizing a protecting group a Grignad reagent can be formed and reacted on a halo alcohol.

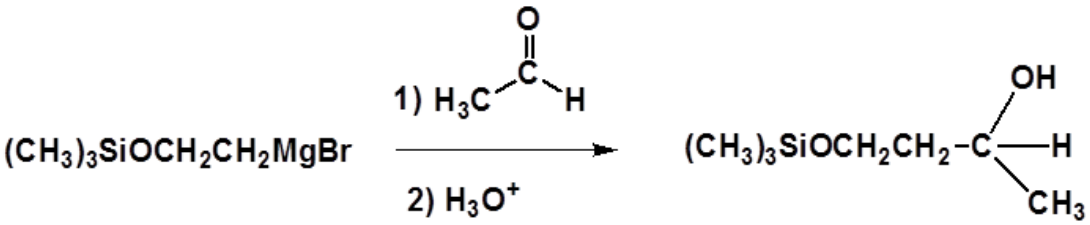
1) Protect the Alcohol



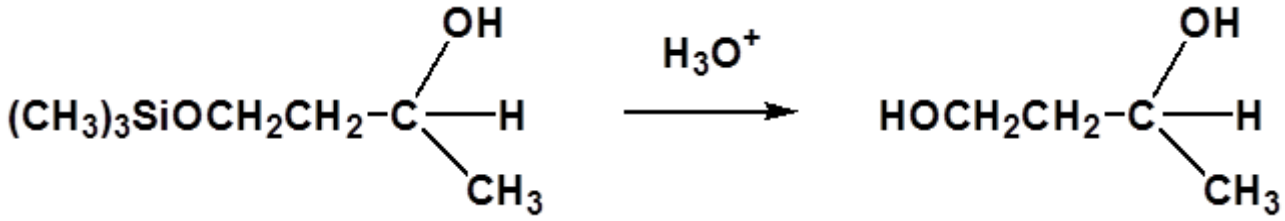
2) Form the Grignard Reagent



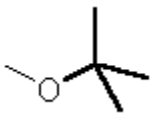
3) Perform the Grignard Reaction



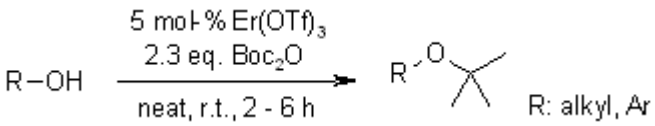
4) Deprotection



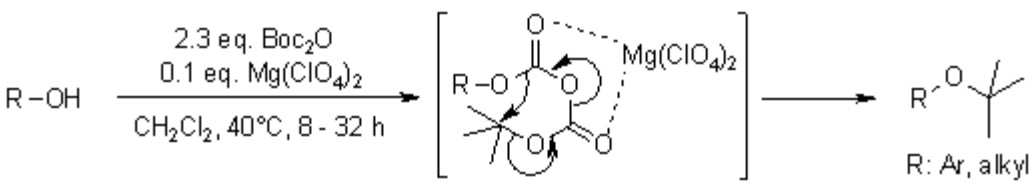
***tert*-Butyl ethers**



Protection

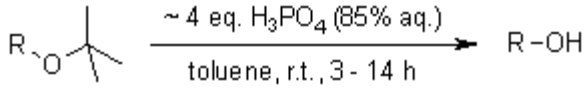


An eco-compatible method for the formation of *tert*-butyl ethers of alcohols and phenols is performed in solvent-free conditions at room temperature using catalytic amount of $Er(OTf)_3$. The catalyst is easily recovered and reused several times without loss of activity. In addition, the *tert*-butyl group is removed very quickly from alcohols and phenols in methanol in the presence of $Er(OTf)_3$ using MW irradiation.

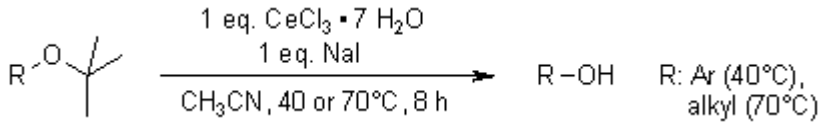


A mild reaction for the protection of alcohols as *t*-butyl ethers proceeds with $Mg(ClO_4)_2$ and Boc_2O and shows general applicability. In addition, preliminary results indicate that the $CeCl_3 \cdot 7H_2O$/NaI system is a very suitable catalyst for the deprotection of *t*-butyl ethers.

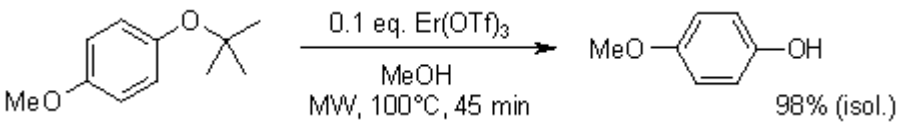
Deprotection



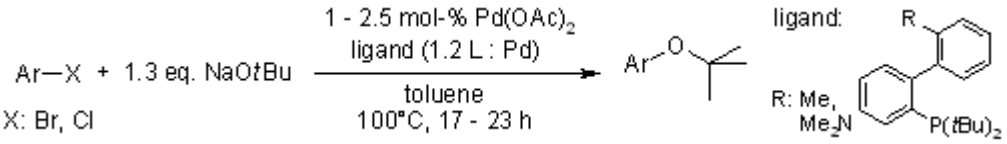
Aqueous phosphoric acid is an effective, environmentally benign, selective and mild reagent for the deprotection of *tert*-butyl carbamates, *tert*-butyl esters, and *tert*-butyl ethers. CBZ carbamates, azetidine, benzyl and methyl esters, TBDMS, and methyl phenyl ethers are tolerated. The reactions are high yielding, and the workup is convenient.



A mild reaction for the protection of alcohols as *t*-butyl ethers proceeds with $Mg(ClO_4)_2$ and Boc_2O and shows general applicability. In addition, preliminary results indicate that the $CeCl_3 \cdot 7H_2O$/NaI system is a very suitable catalyst for the deprotection of *t*-butyl ethers.



Other Syntheses of *t*-Butyl-protected Hydroxyl Groups



A palladium-catalyzed synthesis of aryl *tert*-butyl ethers from a variety of unactivated aryl bromides or chlorides is described. The ether products, which are precursors to phenols, are obtained in very good yield in the presence of air-stable dialkylphosphinobiphenyl ligands.

BENZYL ETHERS

Functionalization at the benzylic position[edit]

In a few cases, these benzylic transformations occur under conditions suitable for synthetic conditions. The Wohl-Ziegler reaction will brominate a benzylic C–H bond: ($ArCHR_2 \rightarrow ArCBrR_2$).[3] Any non-tertiary benzylic alkyl group will be oxidized to a carboxy group by aqueous potassium permanganate ($KMnO_4$) or concentrated nitric acid (HNO_3): ($ArCHR_2 \rightarrow ArCOOH$).[4] Finally, the complex of chromium trioxide and 3,5-

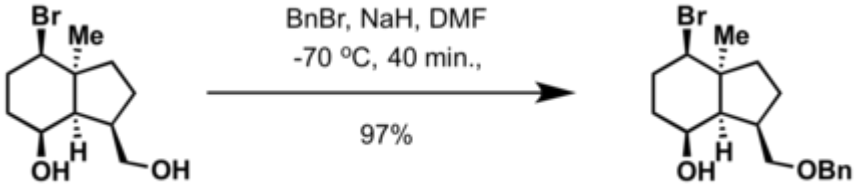
dimethylpyrazole (CrO_3–dmpyz) will selectively oxidize a benzylic methylene group to a carbonyl: ($ArCH_2R \rightarrow ArC(O)R$).[5] More recently, 2-iodoxybenzoic acid in DMSO has been reported to perform the same transformation.

Benzyl groups are occasionally employed as protecting groups in organic synthesis. Their installation and especially their removal require relatively harsh conditions, so benzyl is not typically preferred for protection.[7]

Alcohol protection

Benzyl is commonly used in organic synthesis as a robust protecting group for alcohols and carboxylic acids.

- Treatment of alcohol with a strong base such as powdered potassium hydroxide or sodium hydride and benzyl halide (BnCl or BnBr)[7][8]

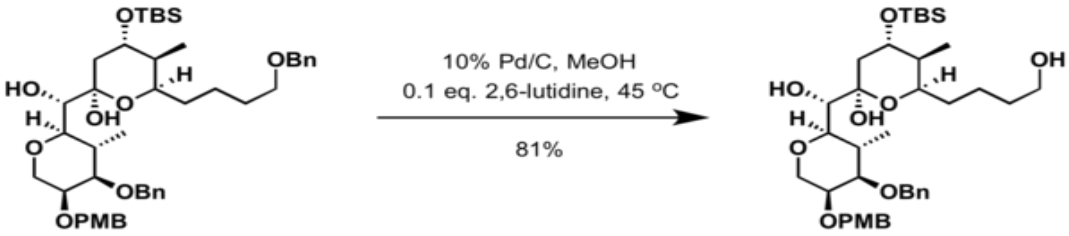


- Monobenzylation of diols can be achieved using Ag_2O in dimethylformamide (DMF) at ambient to elevated temperatures[9]
- Primary alcohols can be selectively benzylated in presence of phenol functional groups using $Cu(acac)_2$[10]

Deprotection methods

Benzyl ethers can be removed under *reductive conditions*, *oxidative conditions*, and the use of *Lewis Acids*.[7]

- Removed using hydrogenolysis[11]

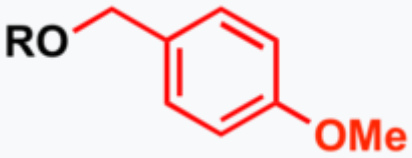


- Single electron process with Na/NH_3 or Li/NH_3
- Benzyl protecting groups can be removed using a wide range of oxidizing agents including:
  - CrO_3/acetic acid at ambient temperature
  - Ozone
  - *N*-Bromosuccinimide (NBS)
  - *N*-Iodosuccinimide (NIS)

Trimethylsilyl iodide (Me_3SiI) in dichloromethane at ambient temperature (selectivity can be achieved under specific conditions)

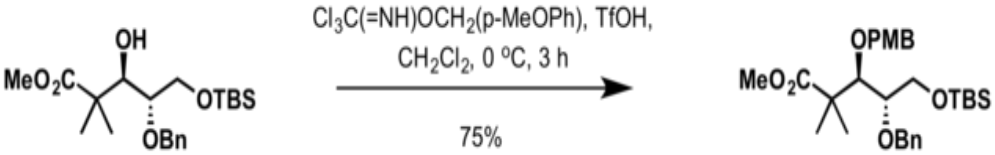
The *p*-methoxybenzyl protecting group

p-Methoxybenzyl (**PMB**) is used as a protecting group for alcohols in organic synthesis (4-Methoxybenzylthiol is used to protect thiols).



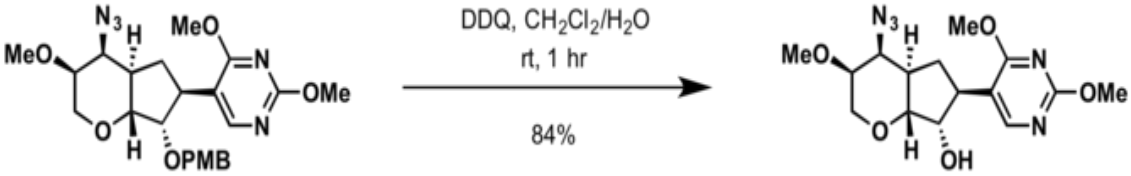
The *p*-methoxybenzyl group

- Strong base such as powdered potassium hydroxide or sodium hydride and *p*-methoxybenzyl halide (chloride or bromide)[12][13]
- 4-methoxybenzyl-2,2,2-trichloroacetimidate can be used to install the PMB group in presence of:
  - Scandium (III) triflate ($Sc(OTf)_3$) in toluene at 0 °C[14]
  - Trifluoromethanesulfonic acid (TfOH) in dichloromethane at 0 °C[15]



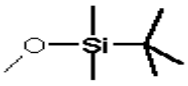
Deprotection methods[edit]

- 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[16]



- Conditions for deprotection of benzyl group are applicable for cleavage of the PMB protecting group
- , 6 M HCl and $NaBH_3CN$ in methanol[18]

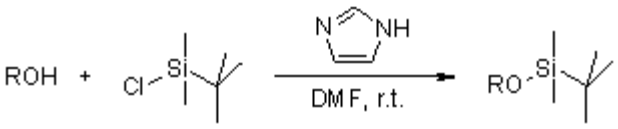
***tert*-Butyldimethylsilyl ethers**



TBDMS-OR, TBDMS ether, TBS-OR, TBS ether

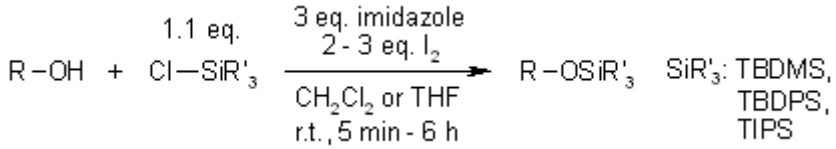
Trimethylsilyl ethers are too susceptible to solvolysis for them to have any utility as protecting groups. The *tert*-butyldimethylsilyloxy group is ca. 10^4 times more hydrolytically stable and holds more promise for such applications.

When the commercially available *tert*-butyldimethylsilyl chloride (TBDMS-Cl) was initially used as a silylation agent, it was found by E. J. Corey (*J. Am. Chem. Soc.* **1972**, *94*, 6192) to react very slowly and to give unsatisfactory yields with alcohols. Even forcing silylation techniques (excess silyl chloride, dry pyridine, elevated temperatures) were not successful. The use of 2.5 eq. imidazole with 1.2 eq. of TBDMS-Cl and dimethylformamide as solvent proved to be effective, and resulted in the mild conversion of various alcohols to *tert*-butyldimethylsilyl ethers in high yield.

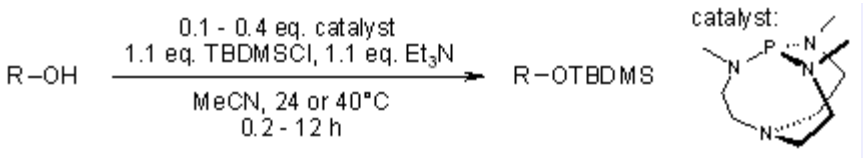


Corey assumed, that the reaction proceeds via *N*-tert-butyldimethylsilylimidazole as a very reactive silylating agent:

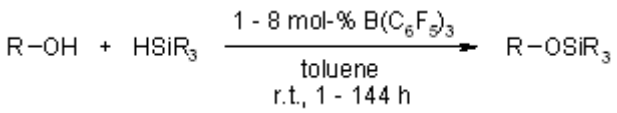
Protection of Hydroxyl Compounds



Reactions of alcohols with silyl chlorides in the presence of *N*-methylimidazole were significantly accelerated by addition of iodine. A general and high yielding method for efficient silylation of primary, secondary, and tertiary alcohols was developed.

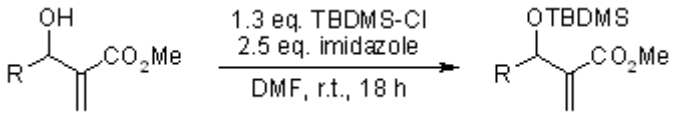


A commercially available proazaphosphatrane is an efficient and mild catalyst for the silylation of a wide variety of alcohols and phenols, including acid-sensitive, base-sensitive, and hindered substrates, using *tert*-butyldimethylsilyl chloride (TBDMSCl). The reactions are carried out in acetonitrile from 24 to 40°C and on rare occasions in DMF from 24 to 80°C. Although representative primary alcohols, secondary alcohols, and phenols were silylated using the more sterically hindered reagent *tert*-butyldiphenylsilyl chloride (TBDPSCl), tertiary alcohols were recovered unchanged.
B. A. D'Sa, D. McLeod, J. G. Verkade, *J. Org. Chem.*, **1997**, *62*, 5057-5061.

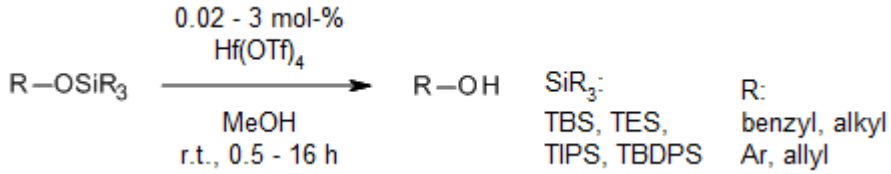


Tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, is an effective catalyst for a mild and efficient dehydrogenative silation of alcohols using a variety of silanes. Only the most bulky

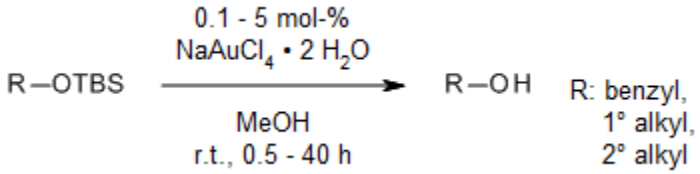
silanes (Bn_3SiH and iPr_3SiH) were not reactive under these conditions. Generally, the reactions are clean and high yielding, with dihydrogen as the only byproduct.



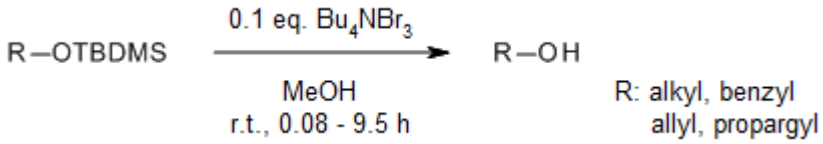
Deprotection



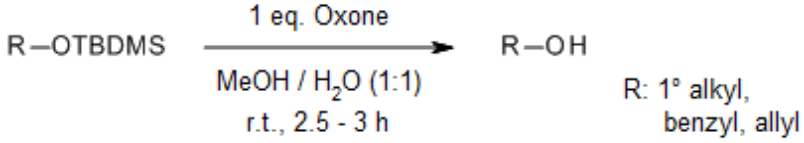
$Hf(OTf)_4$ exhibits exceptionally high potency in desilylations. Since the amounts of $Hf(OTf)_4$ required for the deprotection of 1°, 2°, 3° alkyl and aryl *tert*-butyldimethylsilyl (TBS) ethers range from 0.05 mol% to 3 mol%, a regioselective deprotection can be achieved. A chemoselective cleavage of different silyl ethers or removal of TBS in the presence of most hydroxyl protecting groups was also accomplished.



Sodium tetrachloroaurate(III) dihydrate as catalyst enables a simple and mild removal of *tert*-butyl(dimethyl)silyl (TBS) protecting groups. A selective deprotection of aliphatic TBS ethers is possible in the presence of aromatic TBS ethers, aliphatic triisopropylsilyl ethers, aliphatic *tert*-butyl(diphenyl)silyl ethers, or sterically hindered aliphatic TBS ethers. Additionally, TBS ethers can also be transformed into benzyl ethers in one pot.

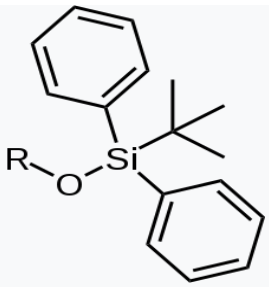


TBDMS ethers can be cleaved selectively in the presence of isopropylidine, Bn, Ac, Bz, THP, and TBDPS groups using tetrabutylammonium tribromide in methanol. This method is high yielding, fast, clean, safe, and cost-effective.



A 50% aqueous methanolic solution of Oxone selectively cleaves primary *tert*-butyldimethylsilyl ethers at room temperature. This method enables deprotection of TBDMS ethers of primary alcohols in the presence of TBDMS ethers of secondary and tertiary alcohols and phenols. The silyl ethers of phenols were deprotected at longer reaction times.

tert-Butyldiphenylsilyl



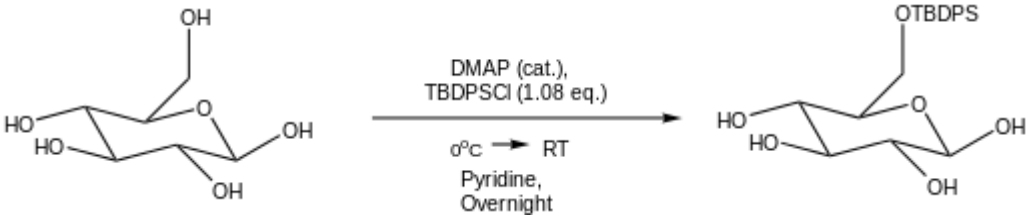
tert-Butyldiphenylsilyl protecting group attached to an alcohol.

***tert*-Butyldiphenylsilyl**, also known as **TBDPS**, is a protecting group for alcohols. Its formula is $C_{16}H_{19}Si$-.[1]

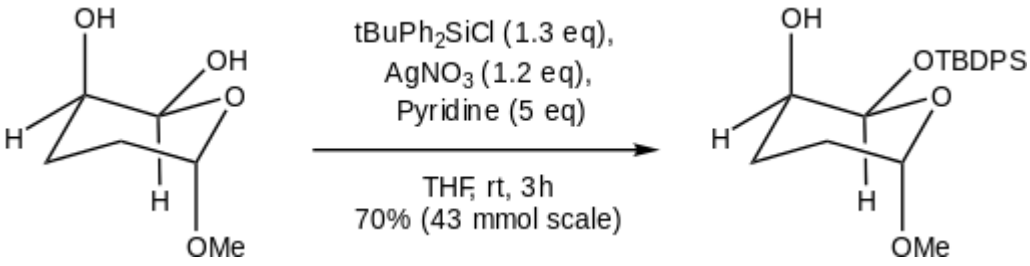
Applications in chemical synthesis

The TBDPS group is prized for its increased stability towards acidic conditions and nucleophilic species over the other silyl ether protecting groups. This can be thought of as arising from the extra steric bulk of the groups surrounding the silicon atom. The protecting group is easily introduced by using the latent nucleophilicity of the hydroxyl group and an electrophilic source of TBDPS. This might involve using the triflate or the less reactive chloride of TBDPS along with a mild base such as 2,6-lutidine or pyridine and potentially a catalyst such as DMAP or imidazole.[3]

The ease of installation of the protecting group follows the order: $1^o > 2^o > 3^o$, allowing the least hindered hydroxyl group to be protected in the presence of more hindered hydroxyls.

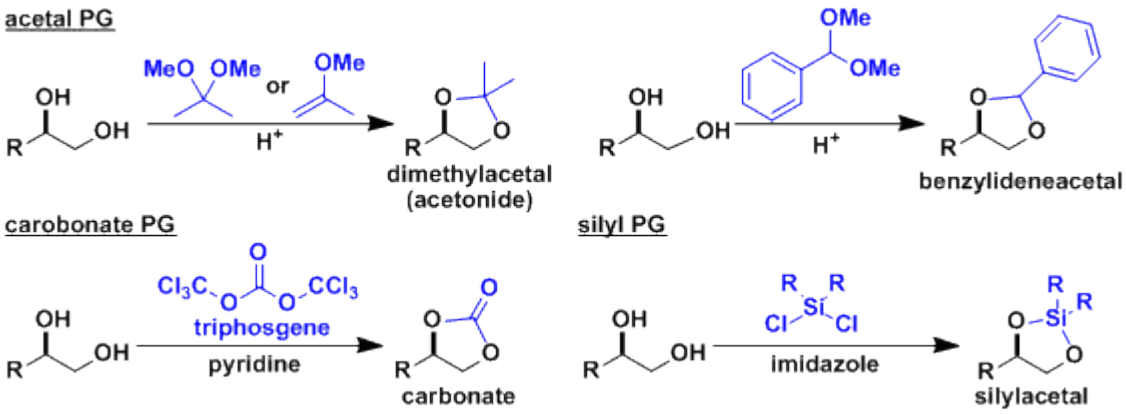


Protection of equatorial hydroxyl groups can be achieved over axial hydroxyl groups by the use of a cationic silyl species generated by *tert*-butyldiphenylsilyl chloride and a halogen abstractor, silver nitrate.



The increased stability towards acidic hydrolysis and nucleophilic species allows for the TBDPS groups in a substrate to be retained while other silyl ethers are removed. The TMS group may easily be removed in the presence of a TBDPS group by reaction with TsOH. The group is even more resistant to acid hydrolysis than the bulky TIPS. However, in the presence of a fluoride source such as TBAF or TAS-F, TIPS groups are more stable than TBDPS groups. The TBDPS group is of similar stability to the TBDMS group and is more stable in the presence of fluoride than all other simple alkyl silyl ethers.[5] It is possible to remove the TBDPS group selectively, leaving a TBDMS group intact, using NaH in HMPA at 0 °C for five minutes.[6]

Protection of 1,2-diols by acetal,ketal and carbonate formation



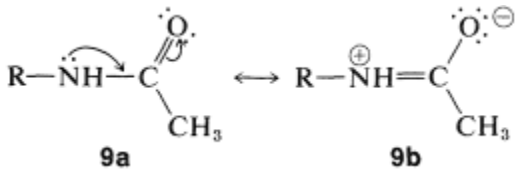
Protection of Amino Groups

Acylation

One useful way of reducing the basicity and nucleophilicity of an amine nitrogen is to convert it to an amide by treatment with an acid chloride or acid anhydride:

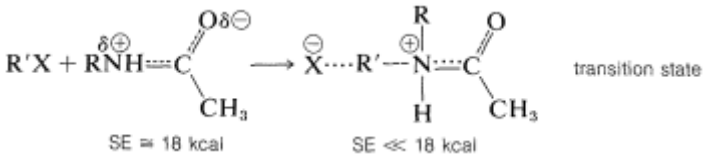
RNH2+CH3COClRNH2+(CH3CO)2O→RNHCOCH3+HCl→RNHCOCH3+CH3CO2H(23.13.2)(23.13.3)(23.13.2)RNH2+CH3COCl→RNHCOCH3+HCl(23.13.3)RNH2+(CH3CO)2O→RNHCOCH3+CH3CO2H

The reduced reactivity is associated with the stabilization produced by the attached carbonyl group because of its ability to accept electrons from the nitrogen atom. This can be seen clearly in valence-bond structures 9a9a and 9b9b, which show electron delocalization of the unshared pair of the amide function:



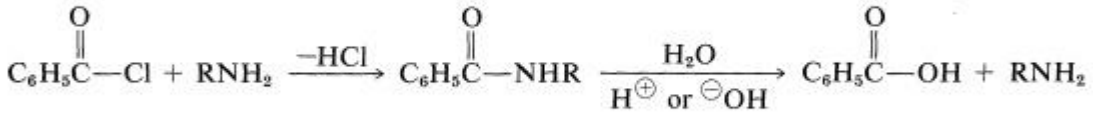
The stabilization energy (SE) of a simple amide grouping is about 18kcal mol−118kcal mol−1, and if a reaction occurs in which the amide nitrogen acts as an electron-

pair donor, almost all of the electron delocalization of the amide group is lost in the transition state:

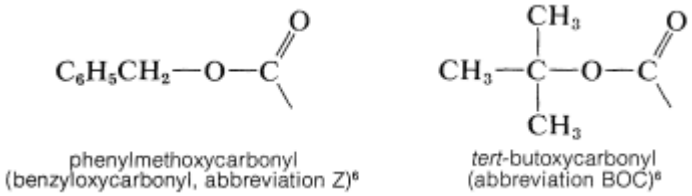


This loss in stabilization energy at the transition state makes an amide far less nucleophilic than an amine.

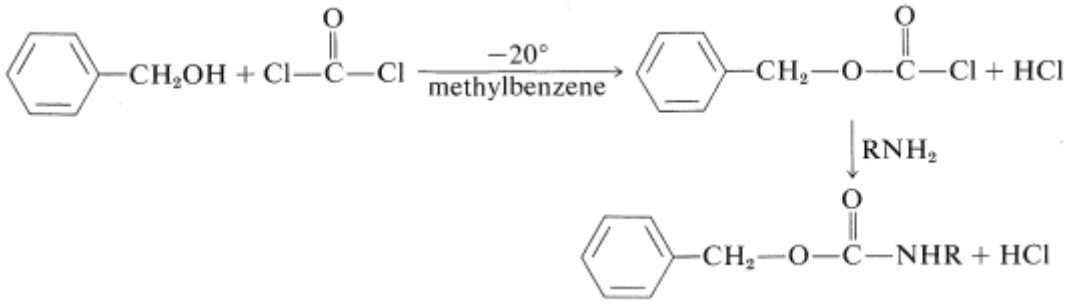
The most common acylating agents are the acyl chlorides and acid anhydrides of ethanoic acid and benzoic acid. The amine can be recovered from the amide by acid- or base-catalyzed hydrolysis:



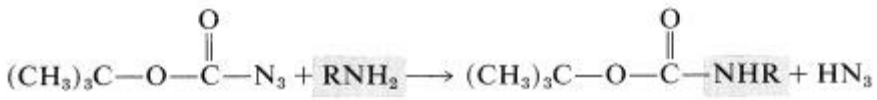
Another useful protecting group for amines has the structure R−O−CO−R−O−CO−. It differs from the common acyl groups of the type R−CO−R−CO− in that it has the *alkoxy*carbonyl structure rather than an *alkyl*carbonyl structure. The most used examples are:



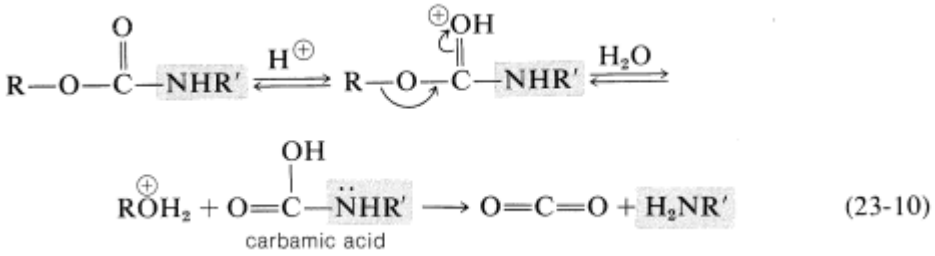
The phenylmethoxycarbonyl (benzyloxycarbonyl) group can be introduced by way of the corresponding acyl chloride, which is prepared from phenylmethanol (benzyl alcohol) and carbonyl dichloride:



The *tert*-butoxycarbonyl group cannot be introduced by way of the corresponding acyl chloride because (CH3)3COCOCl(CH3)3COCOCl is unstable. One of several alternative derivatives is the azide, ROCON3ROCON3:

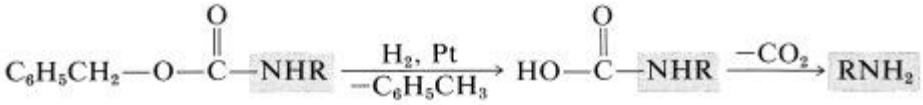


Although these protecting groups may seem bizarre, their value lies in the fact that they can be removed easily by acid-catalyzed hydrolysis under very mild conditions. The sequence of steps is shown in Equation 23-10 and involves proton transfer to the carbonyl oxygen and cleavage of the carbon-oxygen bond by an SN1SN1 process (R=R= *tert*-butyl) or SN2SN2 process (R=R= phenylmethyl). The product of this step is a carbamic acid. Acids of this type are unstable and readily eliminate carbon dioxide, leaving only the free amine (also see Section 23-12E):

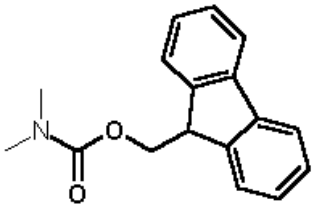


(23-10)

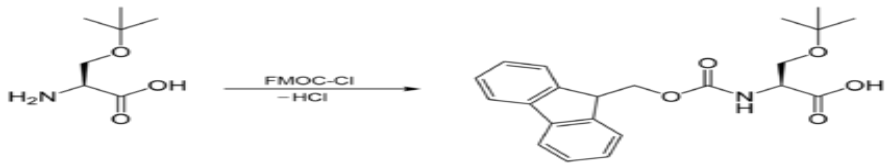
The benzyloxycarbonyl group, but not the *tert*-butoxycarbonyl group, may be removed by catalytic hydrogenation. Again a carbamic acid is formed, which readily loses CO2CO2:



9-fluorenylmethylsuccinimidyl carbonate

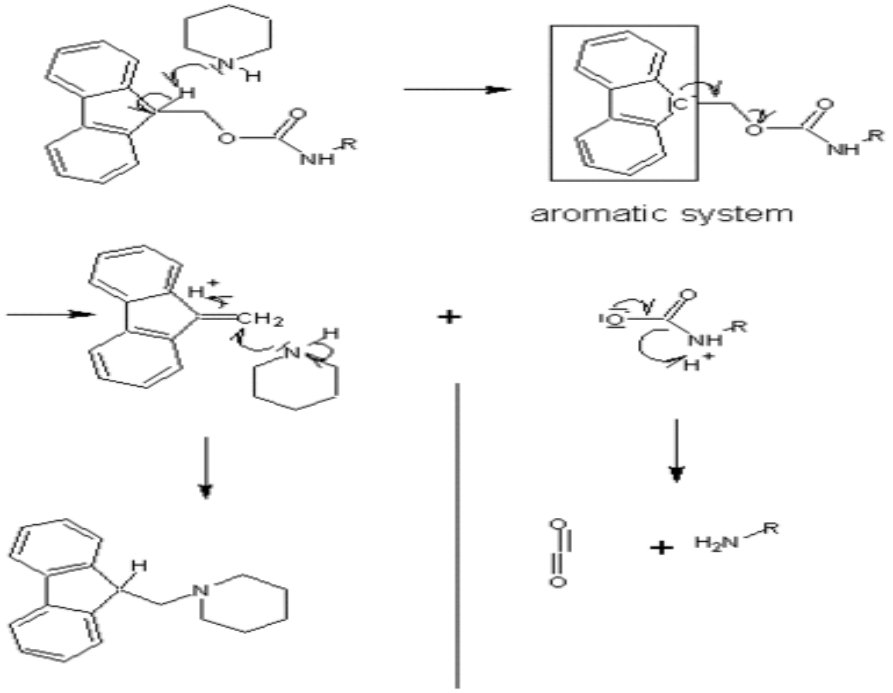


Fmoc carbamate is frequently used as a protecting group for amines, where the Fmoc group can be introduced by reacting the amine with fluorenylmethyloxycarbonyl chloride (Fmoc-Cl),



The other common method for introducing the Fmoc group is through 9-fluorenylmethylsuccinimidyl carbonate (Fmoc-OSu), which may itself be obtained by the reaction of Fmoc-Cl with the dicyclohexylammonium salt of *N*-hydroxysuccinimide.[2]

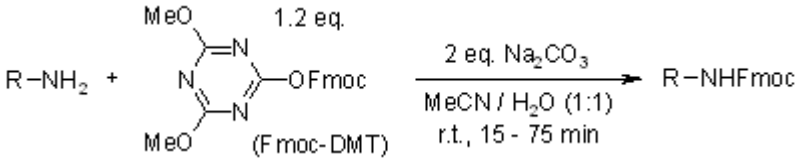
It may be cleaved by bases, typically a solution of piperidine:



Fmoc protection has found significant use in solid phase peptide synthesis because its removal with piperidine solution does not disturb the acid labile linker between the peptide and the resin.[3]

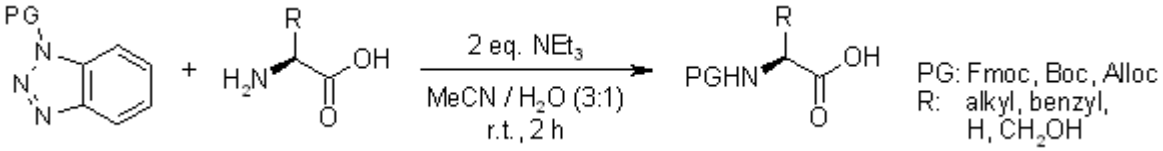
Because the fluorenyl group is highly fluorescent, certain UV-inactive compounds may be reacted to give the Fmoc derivatives, suitable for analysis by reversed phase HPLC. Analytical uses of Fmoc-Cl that do not use chromatography may be limited by the requirement that excess Fmoc-Cl be removed before an analysis of fluorescence.

Protection of Amino Groups

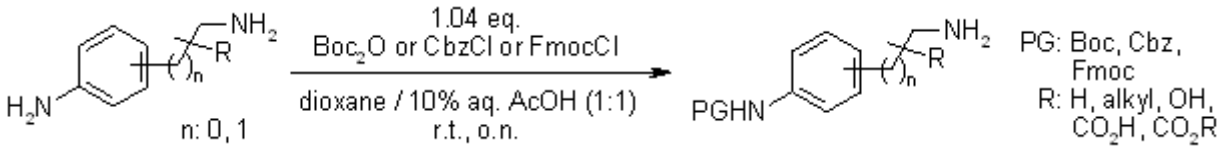


New, stable amino-protecting reagents, Boc-DMT and Fmoc-DMT, were prepared,

and found to be useful for the introduction of Boc and Fmoc groups into amines. Both the reagents can protect various amines including amino acids in good yield in aqueous media..

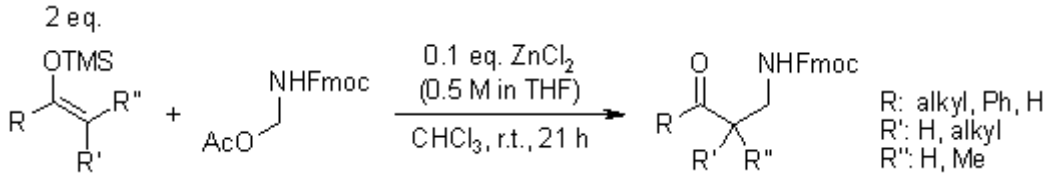


Stable Fmoc-, Boc-, and Alloc-benzotriazoles react with various amino acids including unprotected serine and glutamic acid, in the presence of triethylamine at 20˚C to afford Fmoc-, Boc-, and Alloc-protected amino acids in very good yields free of dipeptide and tripeptide impurities. Fmoc-, and Alloc-Gly-Gly-OH dipeptides were prepared in excellent yields by N-acylation of glycylglycine..



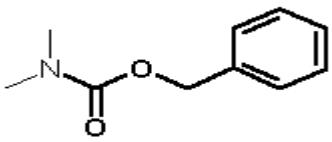
A simple and efficient protection procedure is general and regioselective for the preparation of mono-*N*-Boc, *N*-Cbz, *N*-Fmoc or *N*-Alloc aromatic amines in high yield without affecting aliphatic amino groups and other functionalities.

Other Syntheses of Fmoc-Protected Amino Groups

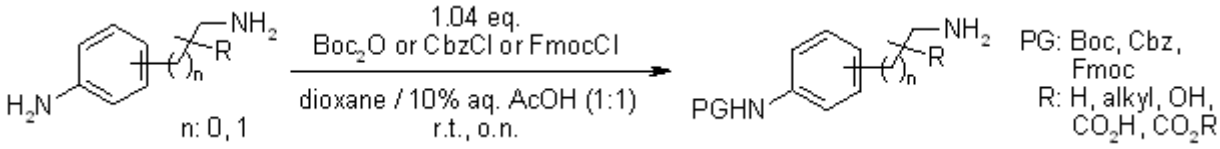


Weakly basic carbon nucleophiles add efficiently to a Fmoc-protected *N,O*-acetal. The new reactions shows the compatibility of the Fmoc protecting group with moderately basic reaction conditions and should serve as a model for the development of more efficient syntheses of Fmoc-protected amino acids.

Benzyl carbamates

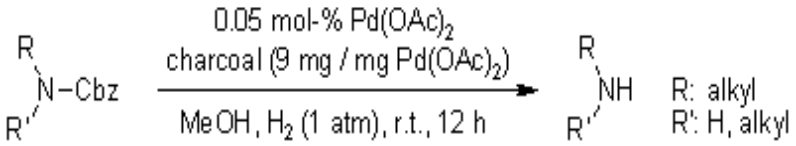


Protection of Amino Groups

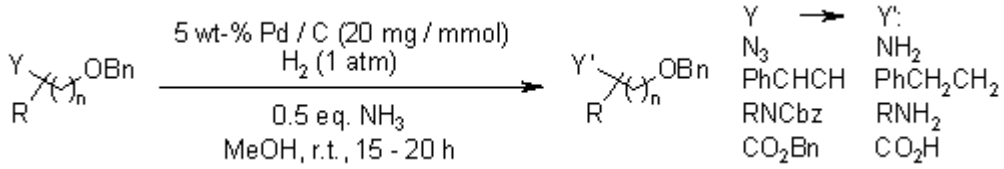


A simple and efficient protection procedure is general and regioselective for the preparation of mono-*N*-Boc, *N*-Cbz, *N*-Fmoc or *N*-Alloc aromatic amines in high yield without affecting aliphatic amino groups and other functionalities.

Deprotection

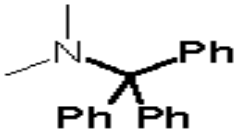


In situ preparation of an active Pd/C catalyst from $Pd(OAc)_2$ and charcoal in methanol enables a simple, highly reproducible protocol for the hydrogenation of alkenes and alkynes and for the hydrogenolysis of *O*-benzyl ethers. Mild reaction conditions and low catalyst loadings, as well as the absence of contamination of the product by palladium residues, make this a sustainable, useful process.



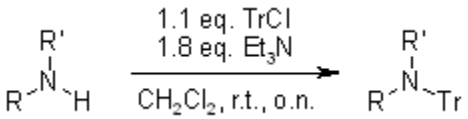
Ammonia, pyridine and ammonium acetate were extremely effective as inhibitors of Pd/C catalyzed benzyl ether hydrogenolysis. While olefin, Cbz, benzyl ester and azide functionalities were hydrogenated smoothly, benzyl ethers were not cleaved.

Triphenylmethylamines



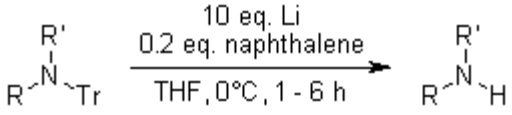
Tr-NR_2, Triphenylmethylamines

Protection of Amino Groups



The reaction of aliphatic and aromatic secondary and tertiary *N*-tritylamines with lithium powder and a catalytic amount of naphthalene led to reductive detritylation affording the corresponding amines in good yields. The trityl group could selectively be removed in the presence of an allyl or a benzyl group.

Deprotection



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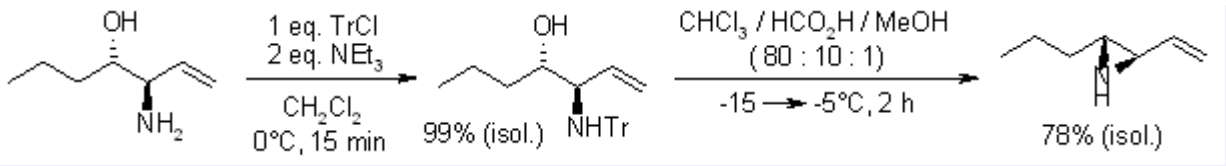
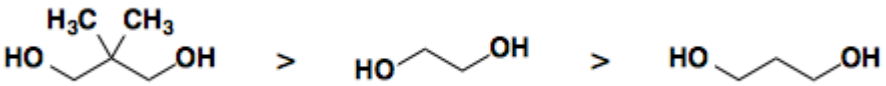
Trityl-protected Amino Groups in Multi-Step Syntheses



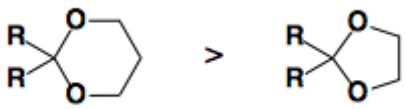
Carbonyl Protecting Group

Acetals and Ketals

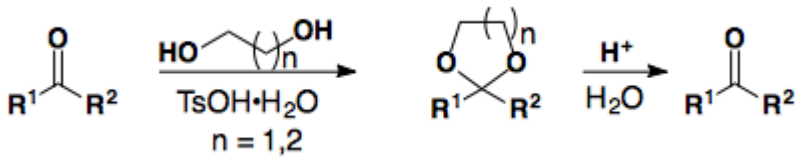
Cyclic acetals and ketals are the most useful carbonyl (aldehyde or ketone) protecting groups. Common diols used to form ketals are show below in order of their relative rate of formation.



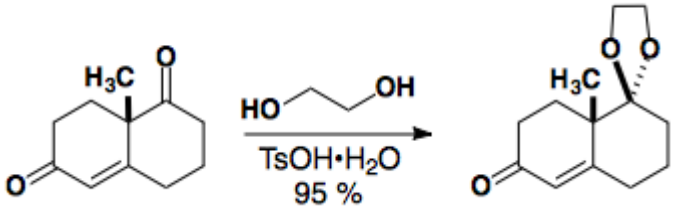
1,3-dioxanes cleave faster than 1,3-dioxolanes.



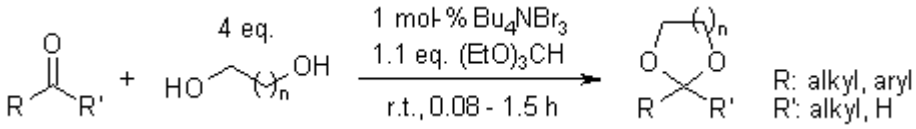
Acetals and ketals are easily formed and cleaved.



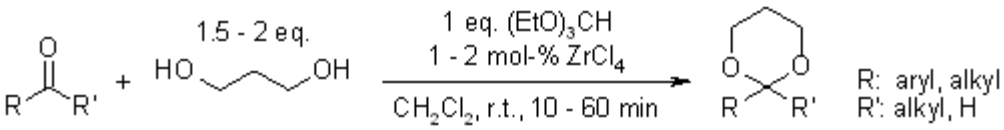
In general, saturated ketones can be selectively protected in the presence of a,b-unsaturated ketone



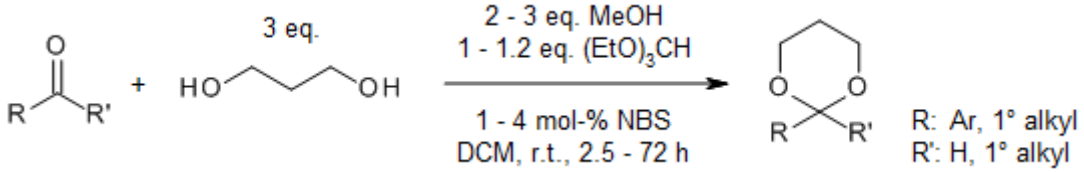
Protection of Carbonyl Compounds



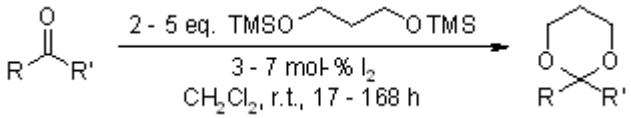
Acyclic and cyclic acetals of various carbonyl compounds were obtained in excellent yields in the presence of trialkyl orthoformate and a catalytic amount of tetrabutylammonium tribromide in absolute alcohol. This convenient, mild, chemoselective method allows acetalization of an aldehyde in the presence of ketone, unsymmetrical acetal formation, and tolerates acid-sensitive protecting groups



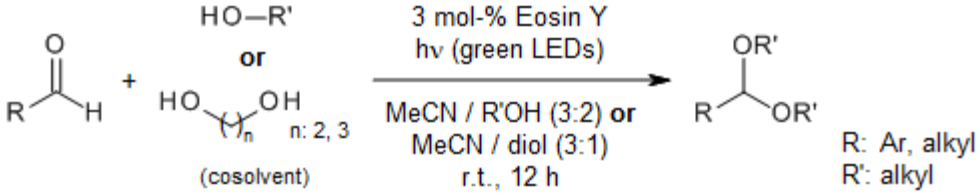
Zirconium tetrachloride ($ZrCl_4$) is a highly efficient and chemoselective catalyst for the acetalization, and *in situ* transacetalization of carbonyl compounds under mild reaction conditions.



Carbonyl compounds were converted to the corresponding 1,3-dioxanes in the presence of ethyl orthoformate, 1,3-propanediol, and a catalytic amount of NBS via an in situ acetal exchange process. The reaction tolerates acid-sensitive groups such as THP ethers and TBDMS ether.

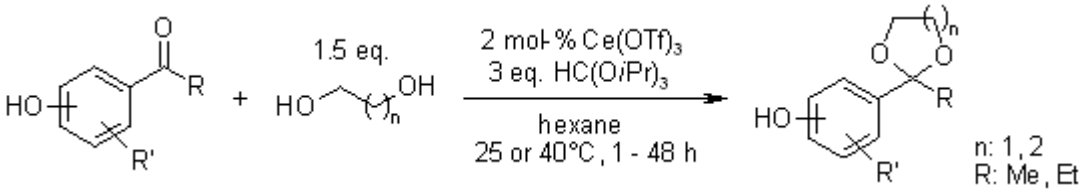


Various types of carbonyl compounds are efficiently converted to their 1,3-dioxanes by the use of 1,3-bis(trimethylsiloxy)propane (BTSP) and a catalytic amount of iodine under essentially neutral aprotic condition.

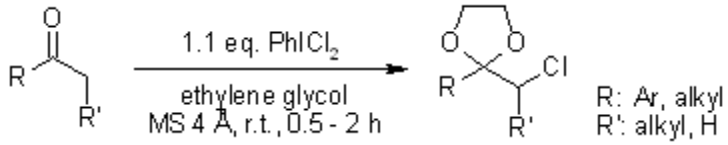


Using a photochemical method for acetalization of aldehydes under low-energy visible light irradiation, a broad range of aromatic, heteroaromatic, and aliphatic aldehydes have been protected under neutral conditions in good to excellent yields using a catalytic

amount of Eosin Y as the photocatalyst. Even challenging acid-sensitive aldehydes and sterically hindered aldehydes can be converted, while ketones remain intact.

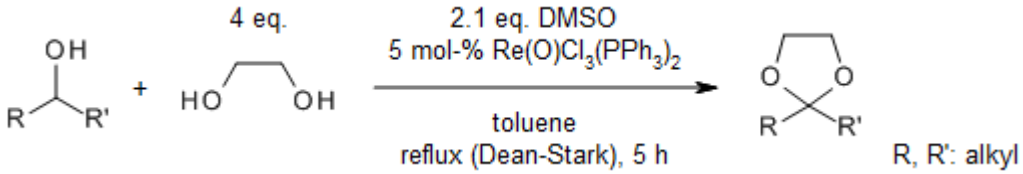


Various types of hydroxyacetophenones are efficiently converted into the corresponding cyclic acetals in the presence of a diol, triisopropyl orthoformate, and a catalytic amount of cerium(III) trifluoromethanesulfonate under mild reaction conditions.

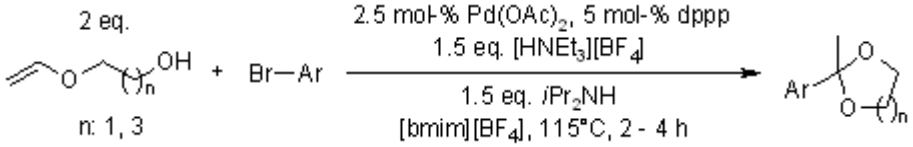


Aliphatic and aromatic ketones can be directly converted into their corresponding α-chloroketone acetals in very good yields using iodobenzene dichloride in ethylene glycol in the presence of 4 Å molecular sieves at room temperature.

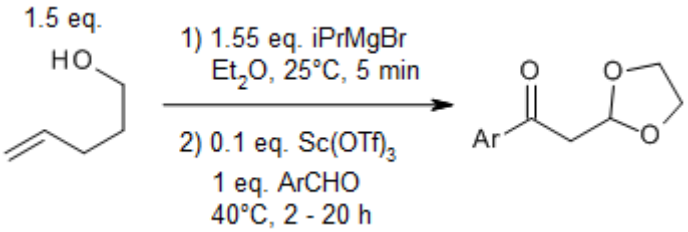
Other Syntheses of Cyclic Acetals



$ReOCl_3(PPh_3)_2$ catalyzes a rapid oxidation of secondary alcohols by DMSO in the presence of ethylene glycol and refluxing toluene to provide the corresponding ketals very good yields. Methyl sulfide and water as byproducts of the reaction are easily removed.

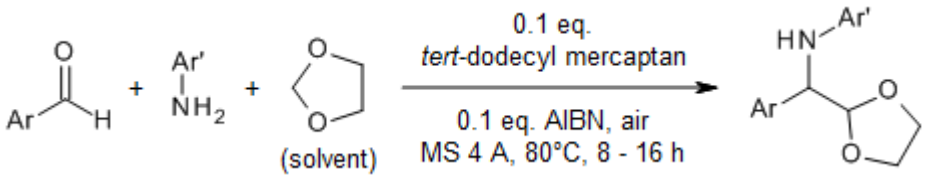


Ammonium salts that can act as hydrogen-bond donors exert a remarkable acceleration on the rates of the regioselective arylation of electron-rich olefins by aryl halides in ionic liquids and common solvents.

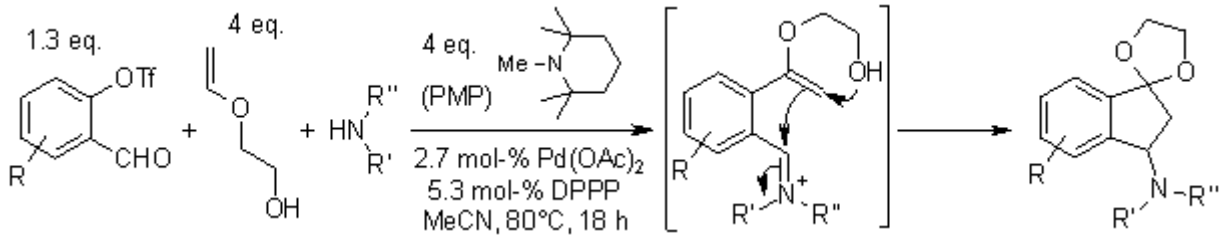


The addition of bromomagnesium 2-vinyloxy ethoxide to various aldehydes in the presence of 10 mol% $Sc(OTf)_3$ provides a broad range of functionalized protected aldol

compounds. A Swern oxidation-CBS reduction sequence enables the preparation of chiral protected aldol products.

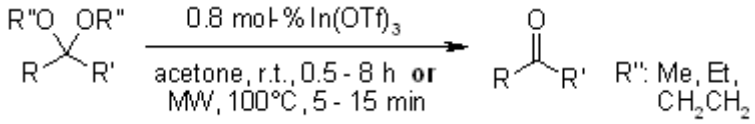


A thiol-promoted site-specific addition of 1,3-dioxolane to imines through a radical chain process enables a metal-free and redox-neutral conversion of inexpensive materials to a broad range of protected α-amino aldehydes in very good yields using only a catalytic amount of radical precursor. Both the thiol and a small amount of oxygen from air are indispensable to the success of this reaction.

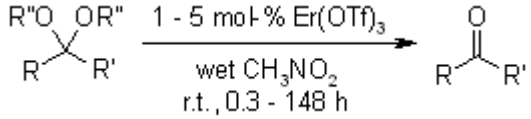


A new palladium(0)-catalyzed three-component reaction of salicylic aldehyde triflates, ethylene glycol vinyl ether, and various secondary nucleophilic amines involving an initial internal Heck arylation, iminium ion formation, and subsequent tandem cyclization gives tertiary 3-aminoindan acetals.

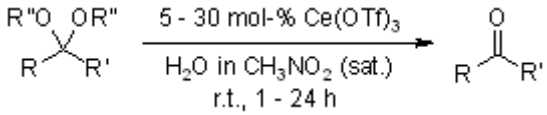
Deprotection



Acetals and ketals are readily deprotected under neutral conditions in the presence of acetone and indium(III) trifluoromethanesulfonate as catalyst at room temperature or mild microwave heating conditions to give the corresponding aldehydes and ketones in good to excellent yields.

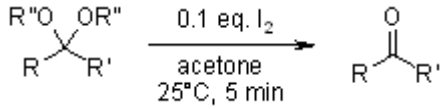


$Er(OTf)_3$ is a very gentle Lewis acid catalyst in the chemoselective cleavage of alkyl and cyclic acetals and ketals at room temperature in wet nitromethane. R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, A. Procopio, A. Tagarelli, *Synthesis*, **2004**, 496-498.

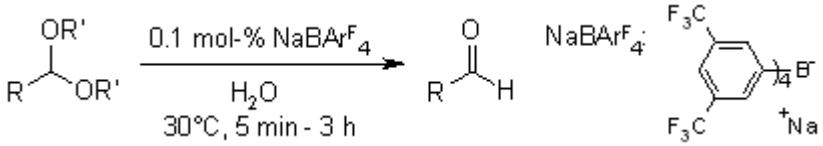


A chemoselective method for the cleavage of acetals and ketals at room

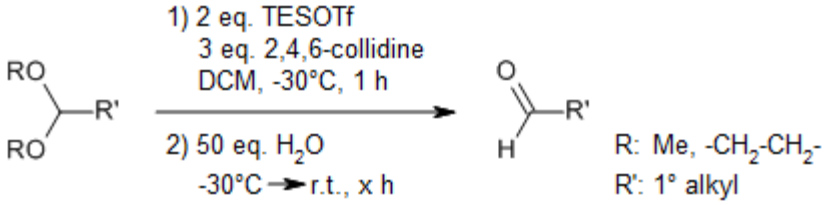
temperature in wet nitromethane by using catalytic cerium(III) triflate at almost neutral pH is presented. High yields and selectivity make this procedure particularly attractive for multistep synthesis.



A convenient deprotection of acyclic and cyclic *O,O*-acetals and *O,O*-ketals is achieved in excellent yields within minutes under neutral conditions in the presence of a catalytic amount of iodine. Double bonds, hydroxyl groups, acetate groups, and highly acid-sensitive groups such as furyl, *tert*-butyl ethers, and ketoximes are tolerated.

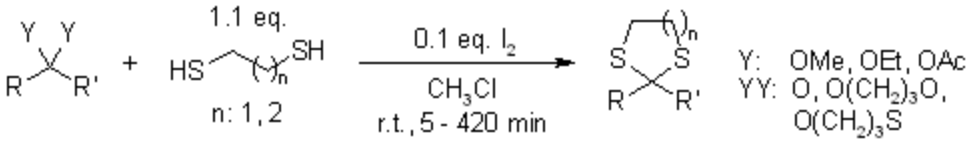


Deprotection of acetals and ketals can be achieved by using a catalytic amount of sodium tetrakis(3,5-trifluoromethylphenyl)borate ($NaBArF_4$) in water at 30 °C. For example, a quantitative conversion of 2-phenyl-1,3-dioxolane into benzaldehyde was accomplished within five minutes.

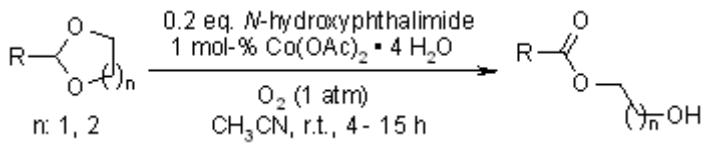


The combination of R_3SiOTf/2,4,6-collidine promotes a highly discriminative and chemoselective transformation of acetals bearing different substitution patterns, different types of acetals, as well as mixed acetals.

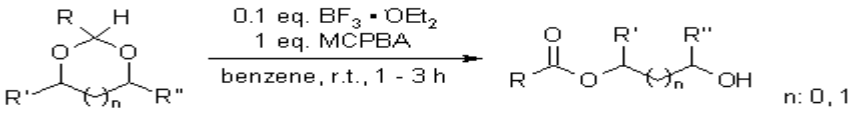
Conversion of Cyclic Acetals and Ketals to Other Functional Groups



Aldehydes and ketones were protected as their thioacetals in the presence of a catalytic amount of iodine. These mild reaction conditions were also applied in the transthioacetalization of *O,O*-acetals, *O,O*-ketals, *O,S*-acetals, and acylals.

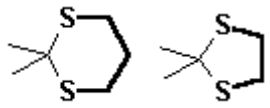


An efficient oxidation of various acetals, including open-chain acetals, 1,3-dioxanes and 1,3-dioxalanes, with molecular oxygen in the presence of catalytic amounts of *N*-hydroxy-phthalimide (NHPI) and $Co(OAc)_2$ as co-catalyst gave esters.

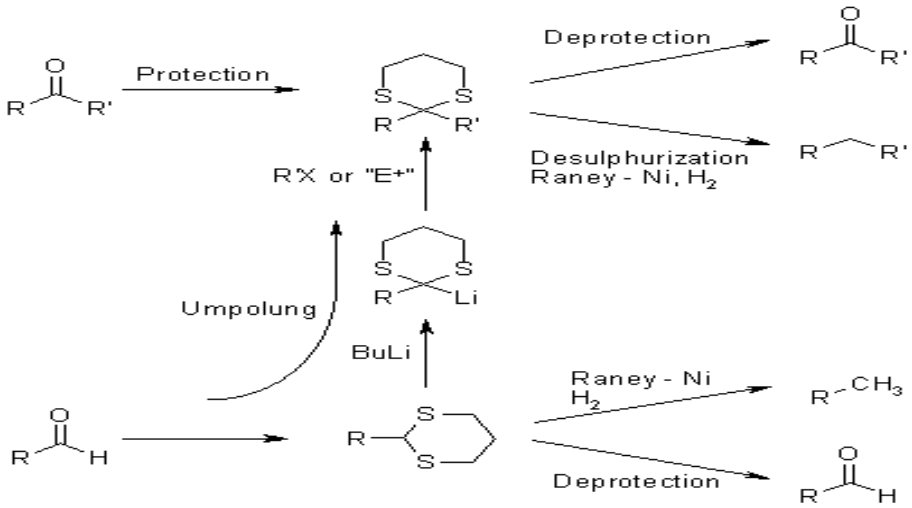


An efficient oxidation of cyclic acetals provided hydroxy alkyl esters in good yields in the presence of MCPBA.

1,3-Dithianes, 1,3-Dithiolanes

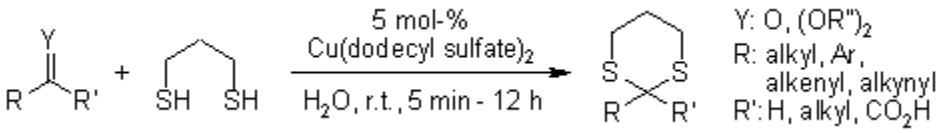


1,3-Dithianes and 1,3-dithiolanes can easily be prepared from carbonyl compounds with 1,3-propanedithiol or 1,2-ethanedithiol in the presence of a Brönsted or a Lewis acid catalyst. Removal of a dithiane protection group often requires harsh conditions and is usually performed in the late synthetic stage.

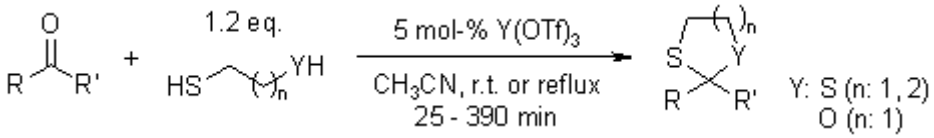


Summary of the use of 1,3-dithianes in synthesis

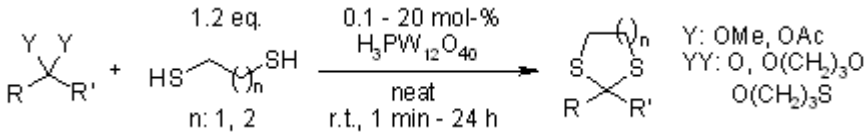
Protection of Carbonyl Compounds



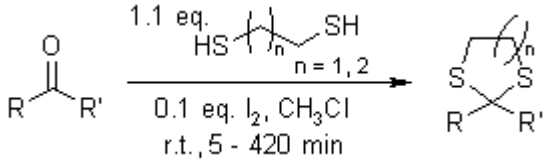
A Lewis acid-surfactant-combined copper bis(dodecyl sulfate) [$Cu(DS)_2$] catalyst served as an efficient and reusable catalyst for the thioacetalization and transthioacetalization of carbonyl compounds and *O,O*-acetals in water at room temperature. This procedure offers high chemoselectivity, ease of operation and purification without any organic solvent, and high yields.



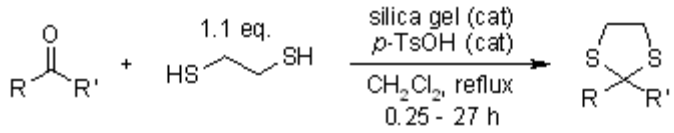
Carbonyl compounds have been successfully converted into their corresponding oxathiolane, dithiolane, and dithiane derivatives with 2-mercaptoethanol, 1,2-ethanedithiol, and 1,3-propanedithiol using a catalytic amount of yttrium triflate. In addition, by using this catalyst, highly chemoselective protection of aldehydes has been achieved.



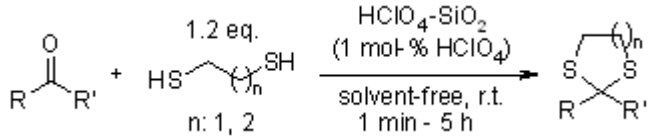
Tungstophosphoric acid ($H_3PW_{12}O_{40}$) was found to be an effective and highly selective catalyst for the thioacetalization of aldehydes, ketones, acetals, acylals and *O,S*-acetals in excellent yields in the absence of solvent. Chemoselective conversions of α- or β-diketones and a β-keto ester are described. Sterically hindered carbonyl compounds were converted to the corresponding thioacetals in refluxing petroleum ether in good yields.



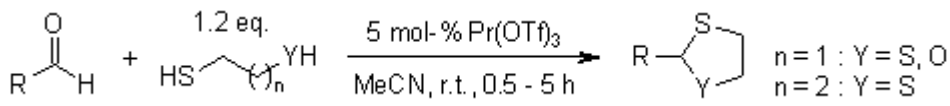
Aldehydes and ketones were protected as their thioacetals in the presence of a catalytic amount of iodine. These mild reaction conditions were also applied in the transthioacetalization of *O,O*-acetals, *O,O*-ketals and *O,S*-acetals and acylals.



A new procedure for the protection of aldehydes and ketones as thioacetals promoted by catalytic amount of *p*-toluenesulfonic acid and silica gel has been developed. This procedure offers versatility, short reaction time, excellent yield, and is easy to carry out. A simple filtration followed by removal of solvent in most cases produces pure product.

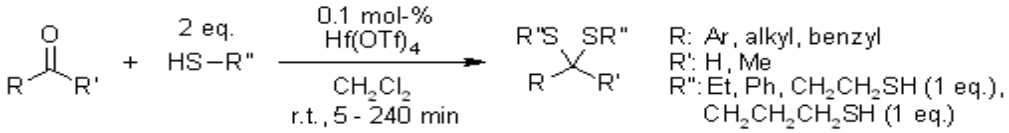


Perchloric acid adsorbed on silica gel ($HClO_4$-SiO_2) has been found to be an extremely efficient and reusable catalyst for 1,3-dithiolane and 1,3-dithiane formation under solvent-free conditions at room temperature.

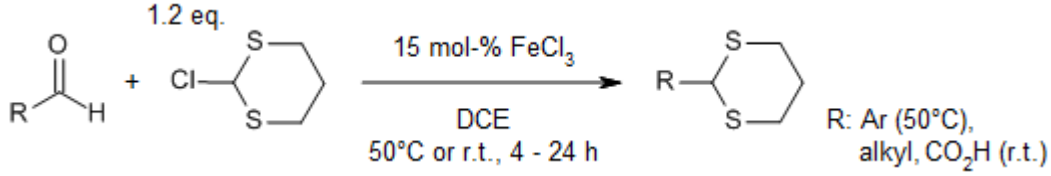


Praseodymium triflate is an efficient and recyclable catalyst for chemoselective protection of aldehydes.

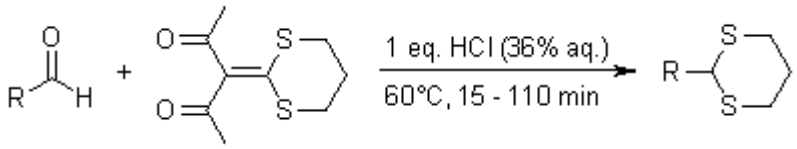
A catalytic amount of a water-stable Brønsted acidic ionic liquid with an alkane sulfonic acid catalyzed a mild and chemoselective thioacetalization of various aldehydes to afford 1,3-dithianes in very good yield and short reaction times.



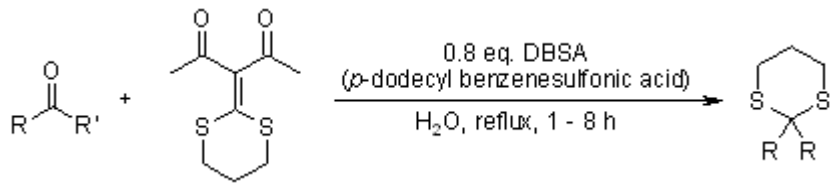
Various carbonyl compounds including aliphatic and aromatic aldehydes and ketones were converted to the corresponding thioacetals in high yields in the presence of a catalytic amount of hafnium trifluoromethanesulfonate. The mild conditions tolerated various sensitive functional and protecting groups and were racemization-free when applied to *R*-aminoaldehydes.



A catalytic dithioacetalization of aldehydes in the presence of iron catalyst provides access to 1,3-dithianes using 2-chloro-1,3-dithiane under mild conditions. This highly efficient dithioacetaliation process results in good to excellent yields.

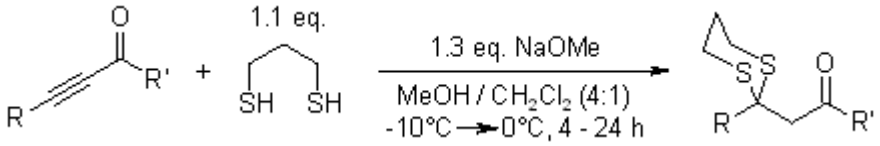


As a non-thiolic, odorless propane-1,3-dithiol equivalent, 3-(1,3-dithian-2-ylidene)pentane-2,4-dione has been investigated in acid-promoted thioacetalization under solvent-free conditions. A range of selected aldehydes and aliphatic ketones have been converted into the corresponding dithioacetals in high yields. The relatively slow reaction rate of aromatic ketones allows chemoselective protection.

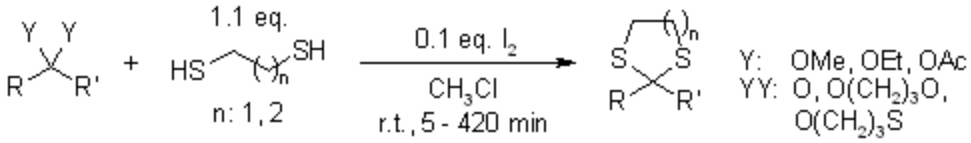


3-(1,3-dithian-2-ylidene)pentane-2,4-dione has been used as a nonthiolic, odorless 1,3-propanedithiol equivalent in the *p*-dodecylbenzenesulfonic acid-catalyzed thioacetalization of various aldehydes and ketones in water.

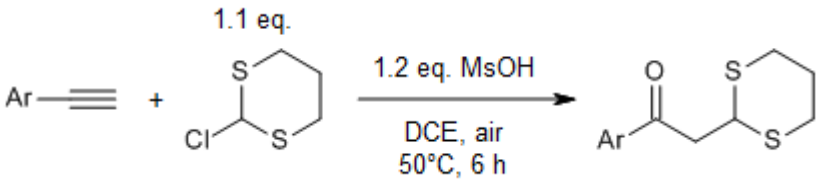
Other Syntheses of Dithianes



b-Keto 1,3-dithianes can be generated by the double conjugate addition of dithiols to propargylic ketones, esters and aldehydes in excellent yields. These masked 1,3-dicarbonyl systems can be converted to a range of functionalised oxygen-containing heterocycles that can be used in natural product synthesis.

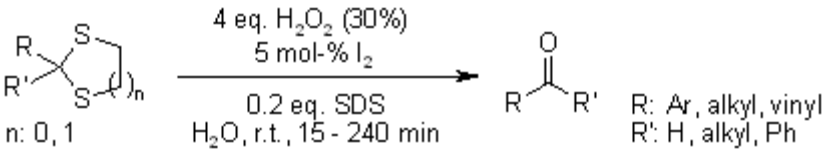


Aldehydes and ketones were protected as their thioacetals in the presence of a catalytic amount of iodine. These mild reaction conditions were also applied in the transthioacetalization of *O,O*-acetals, *O,O*-ketals, *O,S*-acetals, and acylals.

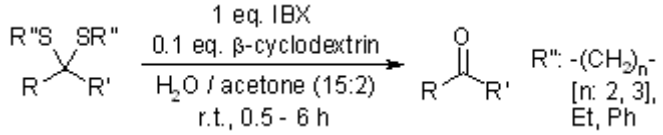


An oxidative coupling method for alkyne difunctionalization under metal-catalyst-free conditions affords various β-ketodithianes in very good yields with high regioselectivities. The reaction provides valuable dithianes with controlled formation of a new C-C bond and a C-O bond via a radical coupling pathway.

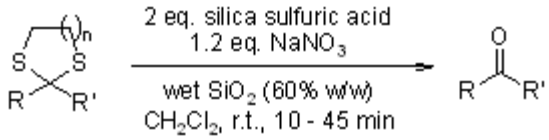
Deprotection



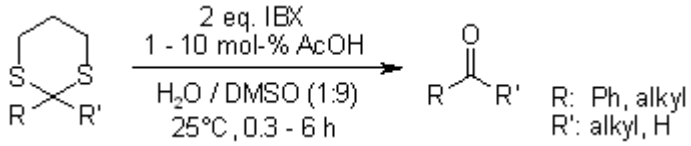
A simple protocol for the deprotection of 1,3-dithianes and 1,3-dithiolanes showed tolerance for a number of phenol and amino protecting groups using 30% aqueous hydrogen peroxide activated by iodine catalyst (5 mol%) in water in the presence of sodium dodecyl sulfate (SDS) under essentially neutral conditions without any detectable overoxidation.



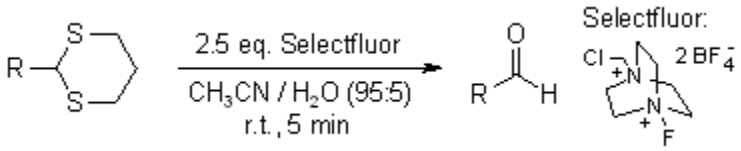
An efficient and convenient procedure has been developed for the hydrolysis of thioacetals/thioketals to the corresponding carbonyl compounds in excellent yields with *o*-iodoxybenzoic acid (IBX) in presence of β-cyclodextrin (β-CD) in water under neutral conditions at room temperature.



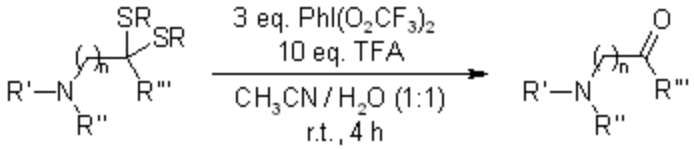
An efficient, mild and chemoselective method for the deprotection of *S,S*-acetals to the corresponding carbonyl compounds using silicasulfuric acid/$NaNO_3$ is reported.



A number of new reactions of IBX with heteroatom-containing substrates were discovered and their utility was demonstrated. IBX was used for the generation of imines from secondary amines in notably high yields, for the oxidative aromatization of nitrogen heterocycles and for the cleavage of dithianes.

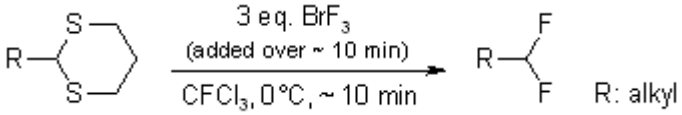


A new and efficient method for the cleavage of the PMP, THP and 1,3-dithiane protecting groups with Selectfluor™ has been developed.



Oxidative deprotection of several dithiane-containing alkaloids in the presence of bis(trifluoroacetoxy)iodobenzene and a nonchromatic purification cleanly generates the corresponding ketoamines. The described procedure is ideal for labile alkaloids.

Conversion of Dithianes to Other Functional Groups

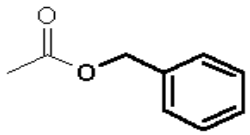


Easily prepared 2-alkyl-1,3-dithiane derivatives were reacted with BrF_3 to form the corresponding 1,1-difluoromethyl alkanes in good yield. The reaction proceeds well with primary alkyl halides. The limiting step for secondary alkyl halides is the relatively low yield.

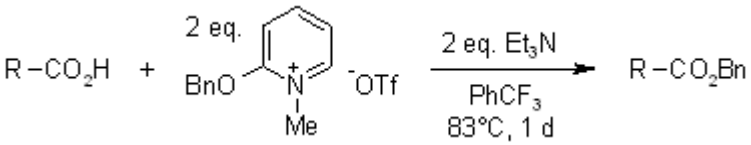
Protection of the Carboxyl Group

Protecting groups for carboxylic acids are used to avoid reaction of the acidic COOH hydrogen with bases and nucleophiles or to prevent nucleophilic additions at the carbonyl carbon.

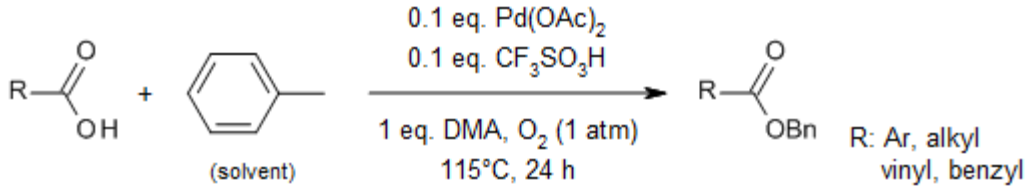
Benzyl esters



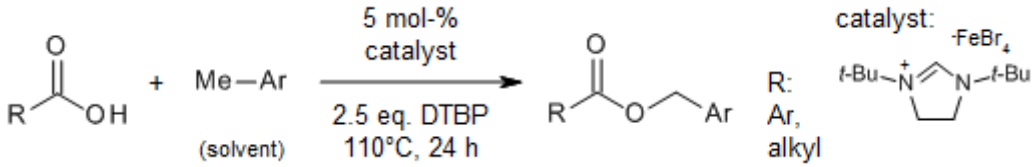
Protection of carboxylic acids



Triethylamine mediates esterification reactions between 2-benzyloxy-1-methylpyridinium triflate and carboxylic acids. Alcohols, phenols, amides, and other sensitive functionality are not affected; a dual role for triethylamine as a promoter and a scavenger is postulated.

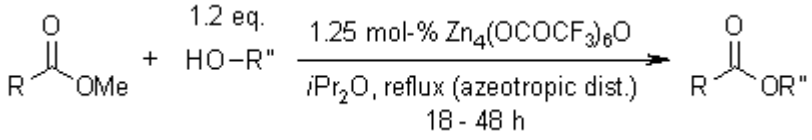


A direct benzylation of carboxylic acids with toluene via palladium-catalyzed C-H acyloxylation under 1 atm of oxygen demonstrates good functional group tolerance and high yields. The method provides a facile, atom-economic, and efficient synthesis of benzyl esters.

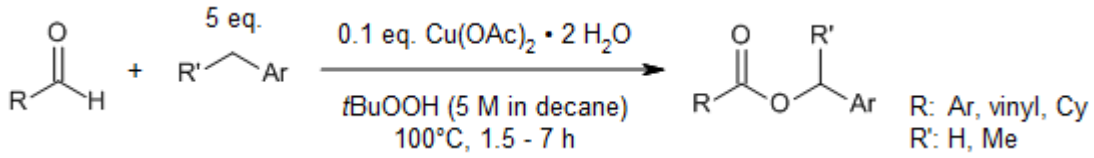


An esterification of primary benzylic C-H bonds with carboxylic acids using di-*tert*-butyl peroxide as an oxidant is catalyzed by novel ionic iron(III) complexes containing an imidazolinium cation. The reaction offers a broad generality and tolerates sterically hindered starting materials.

Other Syntheses of Benzyl esters

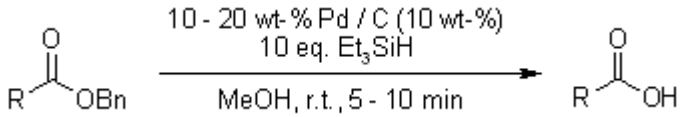


A catalytic transesterification is promoted by a tetranuclear zinc cluster. The mild reaction conditions enabled the reactions of various functionalized substrates to proceed in very good yield. A large-scale reaction under solvent-free conditions offers high environmental and economical advantages.

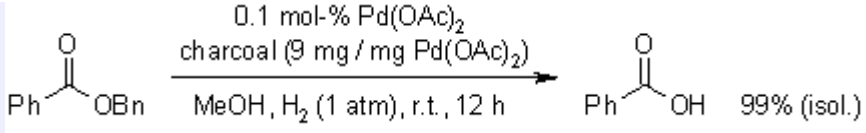


Copper(II) catalyzes a cross dehydrogenative coupling (CDC) reaction of aldehydes with alkylbenzenes in the presence of TBHP to yield benzylic esters.

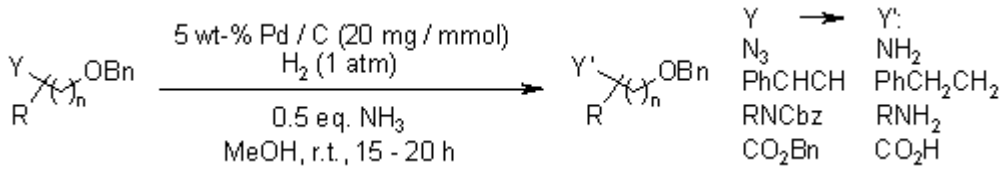
Deprotection



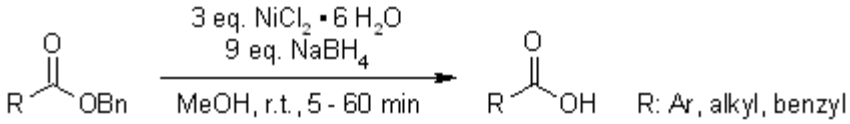
In situ generation of molecular hydrogen by addition of triethylsilane to palladium on charcoal results in rapid and efficient reduction of multiple bonds, azides, imines, and nitro groups, as well as deprotection of benzyl and allyl groups under mild, neutral conditions.



In situ preparation of an active Pd/C catalyst from $Pd(OAc)_2$ and charcoal in methanol enables a simple, highly reproducible protocol for the hydrogenation of alkenes and alkynes and for the hydrogenolysis of *O*-benzyl ethers. Mild reaction conditions and low catalyst loadings, as well as the absencef contamination of the product by palladium residues, make this a sustainable, useful process.



Ammonia, pyridine and ammonium acetate were extremely effective as inhibitors of Pd/C catalyzed benzyl ether hydrogenolysis. While olefin, Cbz, benzyl ester and azide functionalities were hydrogenated smoothly, benzyl ethers were not cleaved.



Benzyl esters of various acids can be chemoselectively cleaved on treatment with nickel boride in methanol at ambient temperature to give the parent carboxylic acids in high yields. Esters such as methyl, ethyl, *tert*-butyl, and trityl esters as well as benzyl ethers, *tert*-butyl ethers, and *N*-benzylamides remain unaffected under these conditions.

Phase-transfer catalyst

In chemistry, a **phase-transfer catalyst** or **PTC** is a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs. Phase-transfer catalysis is a special form of heterogeneous catalysis. Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase-transfer catalyst. The catalyst functions like a detergent for solubilizing the salts into the organic phase. Phase-transfer catalysis refers to the acceleration of the reaction upon the addition of the phase-transfer catalyst.

By using a PTC process, one can achieve faster reactions, obtain higher conversions or yields, make fewer byproducts, eliminate the need for expensive or dangerous solvents that will dissolve all the reactants in one phase, eliminate the need for expensive raw materials and/or minimize waste problems [1]. Phase-transfer catalysts are especially useful in green chemistry—by allowing the use of water, the need for organic solvents is reduced.[2][3]

Contrary to common perception, PTC is not limited to systems with hydrophilic and hydrophobic reactants. PTC is sometimes employed in liquid/solid and liquid/gas reactions. As the name implies, one or more of the reactants are transported into a second phase which contains both reactants.

Phase-transfer catalysts for anionic reactants are often quaternary ammonium salts. Commercially important catalysts include benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammonium chloride, and methyltrioctylammonium chloride. Organic phosphonium salts are also used, e.g., hexadecyltributylphosphonium bromide. The phosphonium salts tolerate higher temperatures, but are unstable toward base, degrading to phosphine oxide.[4]

For example, the nucleophilic substitution reaction of an aqueous sodium cyanide solution with an ethereal solution of 1-bromooctane does not readily occur. The 1-bromooctane is poorly soluble in the aqueous cyanide solution, and the sodium cyanide does not dissolve well in the ether. Upon the addition of small amounts of hexadecyltributylphosphonium bromide, a rapid reaction ensues to give nonyl nitrile:

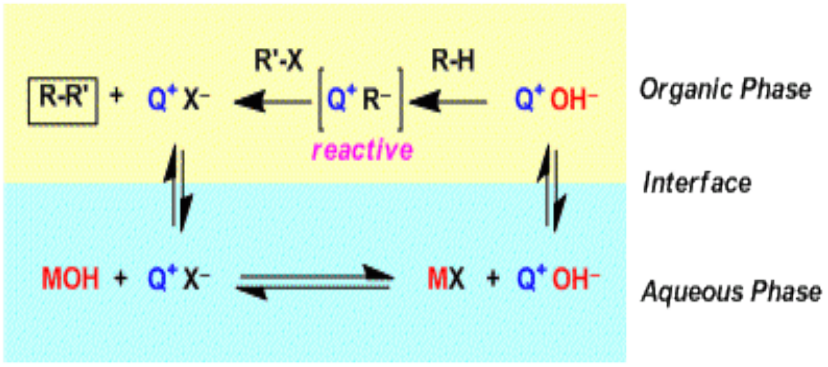
$$C_8H_{17}Br(org) + NaCN(aq) \rightarrow C_8H_{17}CN(org) + NaBr(aq)\ (\text{catalyzed by a } R_4P^+Br^-\ PTC)$$

By the quaternary phosphonium cation, cyanide ions are "ferried" from the aqueous phase into the organic phase.[5]

Subsequent work demonstrated that many such reactions can be performed rapidly at around room temperature using catalysts such as tetra-n-butylammonium bromide and methyltrioctylammonium chloride in benzene/water systems.[6]

An alternative to the use of "quat salts" is to convert alkali metal cations into hydrophobic cations. In the research lab, crown ethers are used for this purpose. Polyethylene glycols are more commonly used in practical applications. These ligands encapsulate alkali metal cations (typically Na^+ and K^+), affording large lipophilic cations. These polyethers have a hydrophilic "interiors" containing the ion and a hydrophobic exterior.

<Starks Extraction Mechanism>



Applications of PTC

PTC finds applications in a variety of reactions.

- Applications involving the use of a co-catalyst include co- catalysis by surfactants (Dolling, 1986), alcohols and other weak acids in hydroxide transfer reactions (Dehmlow et al., 1985, 1988), use of iodide (traditionally considered a catalyst poison, Hwu et al., 1992; Yeh et al., 1988), or reactions carried out with dual PIí catalysts (Szabo et al., 1987; Tsanov et al., 1995; Savelova and Vakhitova, 1995; Jagdale et al., 1996) have been also reported.

- In nucleophilic substitution reactions and in reactions in the presence of bases involving the deprotonation of moderately and weakly acidic organic compounds.

- PTC has made possible the use of cheaper and easily available alternative raw materials like potassium carbonate and aqueous NaOH solution, thereby obviating the need of severe anhydrous conditions, expensive solvents, and dangerous bases such as metal hydrides and organometallic reagents.

- When any kind of chemical reactions are carried out in the presence of a PT catalyst in biphasic systems, simple, cheap and mild bases like NaOH and K2CO3 can be used instead of toxic alkali metal alkoxides, amides, and hydrides.

- PTC can also be used for the synthesis process for fine chemicals manufacture. (agro-chemicals, pharmaceutical, dyes, paper, and so on) industries (Lindbloom and Elander, 1980; Reuben and Sjoberg, 1981; Freedman, 1986; Starks, 1990; Sharma, 1997).

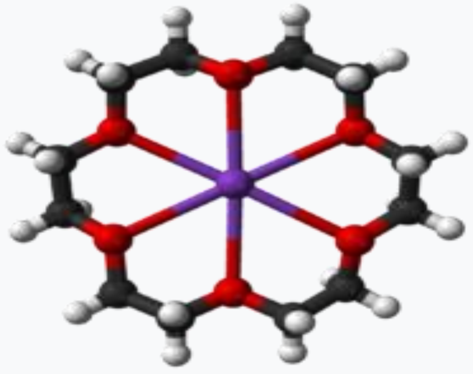
- Perfumery and Fragrance Industry like Synthesis of phenylacetic acid, an intermediate in the perfumery industry (Cassar et al. 1976).

- In the field of Pharmaceuticals like Synthesis of various drugs like dicyclonine, phenoperidine, oxaladine, ritaline, etc. (Lindbloom and Elander 1980).

- Polymeric bonded PTC for the determination of cyanide, iodide, nitrite, sulphide and thiocyanate, led to easy layer separation and PTC-free injection of the sample into the chromatograph[18-20].

- However, the main disadvantages of PTC, especially in commercial applications, are the need to separate the catalyst from the product organic phase.

Crown ether

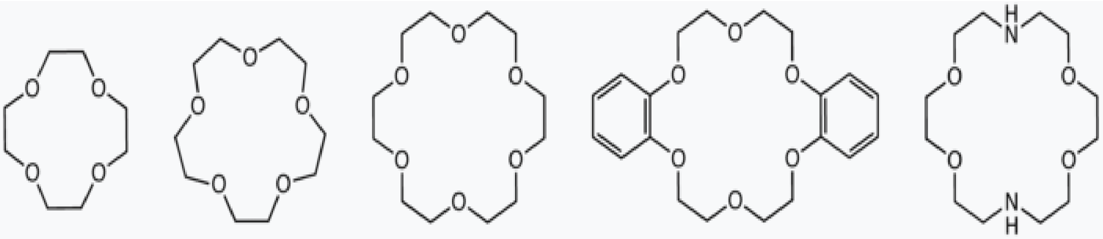


18-crown-6 coordinating a potassium ion

Crown ethers are cyclic chemical compounds that consist of a ring containing several ether groups. The most common crown ethers are cyclic oligomers of ethylene oxide, the repeating unit being ethyleneoxy, i.e., $–CH_2CH_2O–$. Important members of this series are the tetramer (*n* = 4), the pentamer (*n* = 5), and the hexamer (*n* = 6). The term "crown" refers to the resemblance between the structure of a crown ether bound to a cation, and a crown sitting on a person's head. The first number in a crown ether's name refers to the number of atoms in the cycle, and the second number refers to the number of those atoms that are oxygen. Crown ethers are much broader than the oligomers of ethylene oxide; an important group are derived from catechol.

Crown ethers strongly bind certain cations, forming complexes. The oxygen atoms are well situated to coordinate with a cation located at the interior of the ring, whereas the exterior of the ring is hydrophobic. The resulting cations often form salts that are soluble in nonpolar solvents, and for this reason crown ethers are useful in phase transfer catalysis. The denticity of the polyether influences the affinity of the crown ether for various cations. For example, 18-crown-6 has high affinity for potassium cation, 15-crown-5 for sodium cation, and 12-crown-4 for lithium cation. The high affinity of 18-crown-6 for potassium ions contributes to its toxicity. The smallest crown ether still capable of binding cations is 8-crown-4,[1] with the largest, experimentally confirmed crown ether being 81-crown-27.[2] Crown ethers are not the only macrocyclic ligands that have affinity for the potassium cation. Ionophores such as valinomycin also display a marked preference for the potassium cation over other cations.

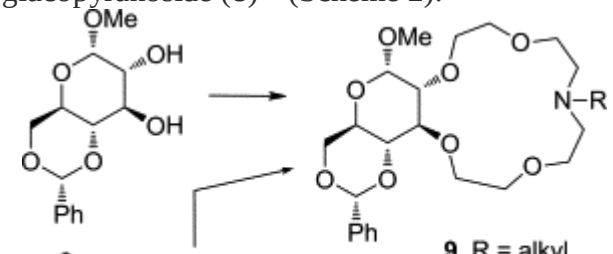
Crown ethers have been shown to coordinate to Lewis acids through electrostatic, σ-hole (see halogen bond) interactions, between the Lewis basic oxygen atoms of the crown ether and the electrophilic Lewis acid center.[3][4]



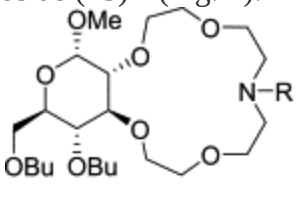
Structures of common crown ethers: 12-crown-4, 15-crown-5, 18-crown-6, dibenzo-18-crown-6, and diaza-18-crown-6

One of the most available and useful carbohydrate 1,2-diols is 1,2:5,6-di-*O*-isopropylidene-d-mannitol (**1**).[25,26] Alkylation of both hydroxyl groups at the C-3 and C-4 positions with bis(2-chloroethyl) ether (**2**) provided the bis-chloro podand **3**,[27] readily convertible into the more reactive di-iodide **4**, whose reaction with different primary amines (RNH_2) led to the macrocyclic 15-membered mono-aza-crown ethers **5** in 28–54% yields. The *N*-tosyl aza-macrocycle **6**, obtained by alkylation of **3** with tosylamine, is a convenient precursor of macrocycle **7**, having a secondary amine functionality.

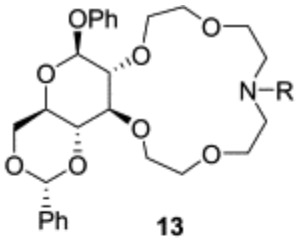
By a similar strategy, a number of aza-crown ethers were prepared from methyl 4,6-*O*-benzylidene-α-d-glucopyranoside (**8**)[29] (Scheme 2).[30–38]



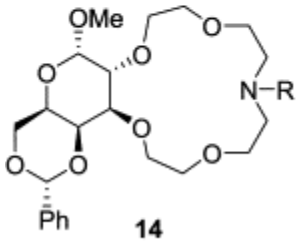
Macrocycles of type **12**, based on methyl 4,6-di-*O*-butyl-α-d-glucopyranoside, were prepared in an analogous way.[38] Bakó *et al.* also synthesized a series of aza-crown ethers based on phenyl β-d-glucopyranoside (**13**),[39,40] methyl α-d-galactopyranoside (**14**),[31] and methyl α-d-mannopyranoside (**15**)[41] (Fig. 1).



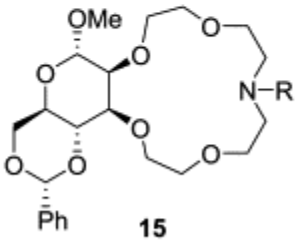
R = H, Ts, $(CH_2)_3CH_3$, $(CH_2)_9OCH_3$, Bn, $(CH_2)_2Ph$



R = *n*-Bu, $(CH_2)_5CH_3$, CH(*i*-Pr)$_2$, C_6H_{11}, $CH_2C_6H_{11}$, Bn, $(CH_2)_2Ph$, $(CH_2)_2$-C_6H_4-OMe, $(CH_2)_nOH$, *n* = 2,3; $(CH_2)_nOMe$, *n* = 2,3

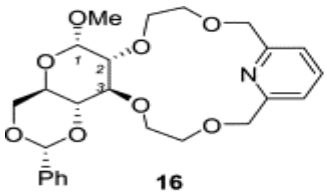


R = *n*-Bu, $(CH_2)_2C_6H_5$, $(CH_2)_nOH$, *n* = 2,3; $(CH_2)_3OMe$



R = H, Ts, $(CH_2)_nOH$, *n* = 2–4; $(CH_2)_4OMe$

More-complex aza-crowns, such as compound **16**,[42] as well as diaza-crown ethers, for instance **17**, **18**,[30] **19**, **20**,[43,44] were also prepared from simple sugars (Fig. 2). The latter (**20**) was used as synthetic receptor for substituted ammonium cations[45] and for chiral recognition of amino acids.[46]



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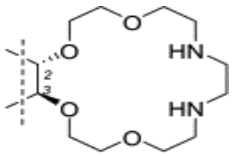
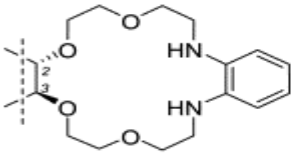


17



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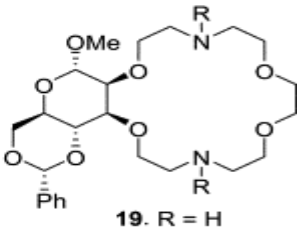

19. R = H
20. R = Me