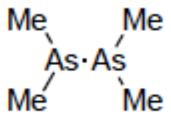
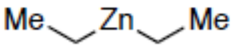
Organometallics

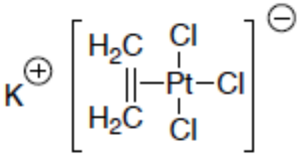
Organometallics: Compounds containing bonds between a **carbon atom** and a **metal**

Organometallics is the interface between *organic* and *inorganic* chemistry. It is a widely studied and applied field of chemistry with a long history.

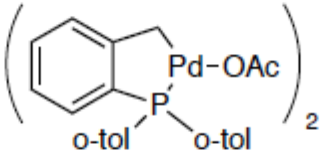
Some examples of organometallic compounds are shown here:


Cacodyl (As^{2+})
(Cadet, 1760)


Diethylzinc (Zn^{2+})
(Franklin, 1848)


Zeise's salt (Pt^{2+})
(1831/1868)

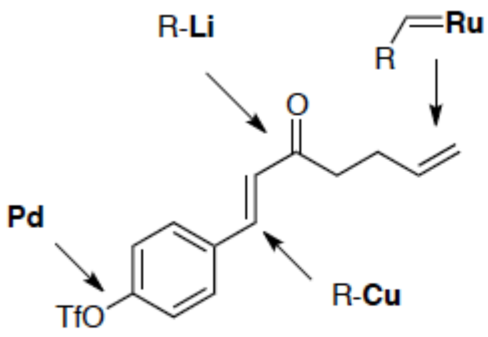

Ferrocene (Fe^{2+})
(1951/1952)


Herrmann's catalyst (Pd^{2+})
(1995)

The Nobel committee has recognized the field with numerous Chemistry prizes:

1912- Victor Grignard (organomagnesiums) and Paul Sabatier (metal-catalyzed hydrogenation)
1963- Karl Ziegler and Giulio Natta (Ti/Al catalysts for olefin polymerization)
1973- Ernst Otto Fischer and Geoffrey Wilkinson (pioneering work on sandwich complexes, i.e. ferrocene)
1979- Herbert C. Brown (development of boron-based reactions and reagents)
2001- Knowles, Noyori and Sharpless (asymmetric Rh-catalyzed hydrogenation and Ti/Os-catalyzed oxidations)
2005- Chauvin, Grubbs and Schrock (Mechanism and new catalysts for metal-catalyzed olefin metathesis)
2010- Heck, Negishi, Suzuki (Pd-catalyzed cross-couplings)

The power of organometallics lies in the ***ability to control their reactivity*** based on **the identity of the metal**. By the end of this section, you will see how a molecule with many different functional groups can be reacted selectivity through the choice of the organometallic reagent or catalyst.



Organolithiums and Organomagnesiums (Grignard Reagents)

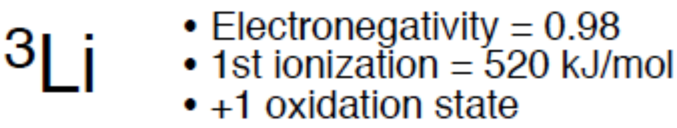
Properties and Preparation

Organolithiums and magnesiums are the “frontline” of synthetic organometallic chemistry – they are easy to prepare, highly reactive, commercially available, and serve as “high energy” precursors for the preparation of other organometallic species.

Most importantly, organometallic reagents are almost always strong bases and C-nucleophiles.
As we will see later, organic substitutents, can be transferred from one metal to another (“transmetallation”) but only in the direction from the more electropositive to the less electropositive metal (i.e. towards more noble metals). Therefore, Li and Mg organometal compounds serve as ideal starting points.
Al and Zn organometal compounds are also known and widely used.

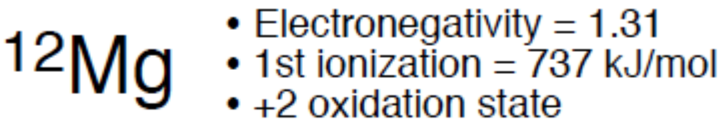
However, not all organic groups can be used for R. The more reactive the organometallic compound, the less functional groups on R are tolerated (as organometallics are both, strong bases and C-nucleophiles, they can easily react with themselves):

- Li: highly reactive, mostly unfunctionalized alkyl or aryl groups
- Mg: still highly reactive, a wider variety of alkyl and aryl groups is tolerated
- Zn: low reactivity, high functional group tolerance
- Al: highly reactive (highly Lewis acidic), mostly unfunctionalized alkyl groups



$^{3}\mathrm{Li}$

- Electronegativity = 0.98
- 1st ionization = 520 kJ/mol
- +1 oxidation state



$^{12}\mathrm{Mg}$

- Electronegativity = 1.31
- 1st ionization = 737 kJ/mol
- +2 oxidation state

As lithium is more easily oxidized and less electronegative than magnesium, we can predict organolithiums to be more reactive than organomagnesiums.

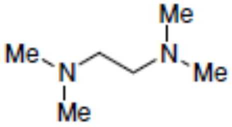
Structure of R-Li and R-MgX compounds, solvent and temperature dependence

The structure of R-Li and R-Mg compounds in solution is dependent on the solvent and the temperature.

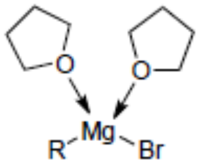
Whereas R-Li reagents in non-coordinating solvents (i.e. non-Lewis basic, such as hexane) form clusters (mostly hexameric or tetrameric), Grignard reagents tend to dimerize. These are dynamic structures, and equilibria exist between the various clusters (for R-MgX this is called “Schlenk-equilibrium”). The smaller the clusters, the higher the reactivity of the organometallic compound. Therefore, to maximize reactivity, one attempts to break the Li or Mg clusters to monomeric compounds. This can be done in a number of ways:

- adjusting temperature: For R-Li compounds (and only for those), the temperature is lowered (mostly to -78 °C), as this breaks up the clusters and favors monomeric compounds (entropy-favoured). For R-Mg compounds, temperature is generally raised to improve reactivity.
- using additiives or coordinating solvents: Additives such as TMEDA or coordinating solvents, mostly ethers such as THF, Et_2O or dioxane, are used or added.These coordinate the metal, break up the clusters and favor monomeric structures.

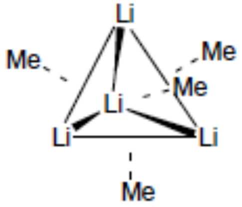
Note: The most reactive R-Li compound, tert-butyl lithium, is basic enough to deprotonate THF, so these two cannot be used in combination.



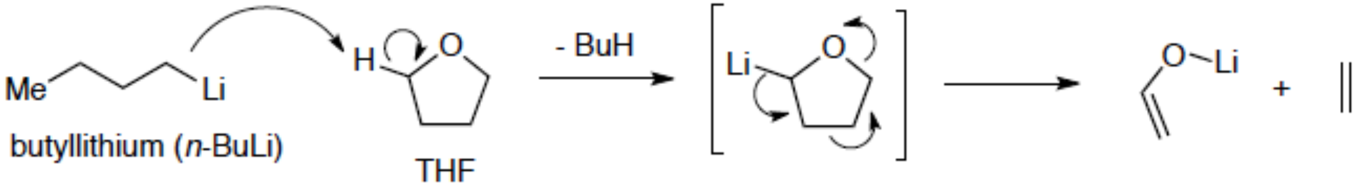
TMEDA
Tetramethyl-ethylene-diamine



THF coordinates a
Grignard reagent

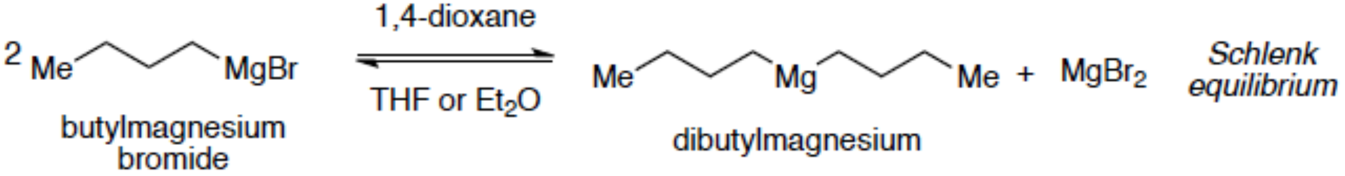


etrameric methyllithium cluster



butyllithium (*n*-BuLi)

THF



butylmagnesium bromide

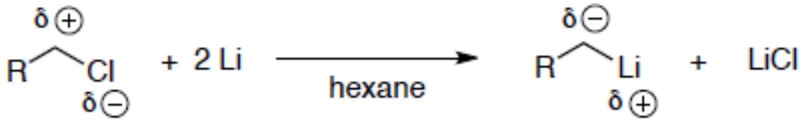
dibutylmagnesium

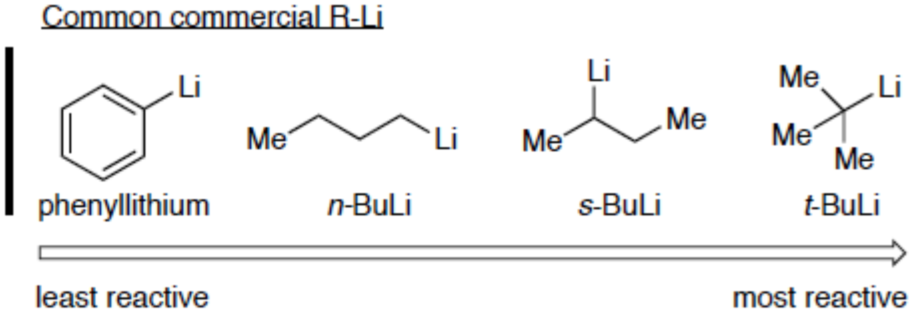
Schlenk equilibrium

A) Preparation of Li and Mg compounds

Organolithiums can be prepared by reaction of lithium metal with alkyl halides in an inert solvent (“oxidative insertion of Li into the R-X bond”); 2 equivalents of lithium are required to gain the two electrons needed to reverse the polarity of the carbon atom. However, this is rarely practiced as commercially available organolithiums provide a means of preparing most other R-Li without having to handle dangerous lithium metal.

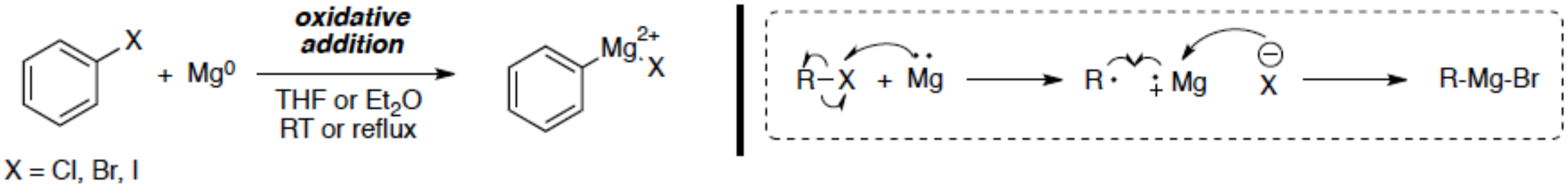
Reactivity of R-Li reagents is dependent on the pKa of the corresponding acid. The higher the pKa (i.e. less acidic) the corresponding acid, the higher the reactivity of R-Li. (For example, the corresponding acid of Me- Li is methane, pKa = ~56.)





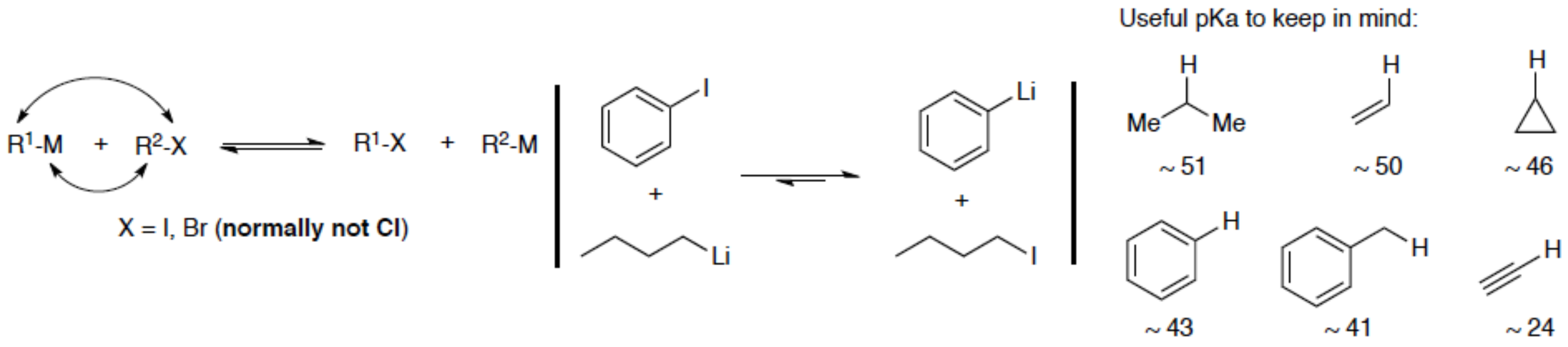
Grignard reagents are most commonly prepared by insertion of magnesium metal into the C-X bond of organohalides. This methods works very well to prepare alkyl, aryl, and alkenyl Grignard reagents.

Since the reaction transforms Mg0 into Mg2+, this is called ***oxidative addition***; in the reaction, Mg loses 2 electrons and the carbon bound to the halide gains them. Mg insertion is essentially irreversible (we will see ***oxidative additions*** a lot in the next sections, so keep the concept in mind). The mechanism of Grignard formation is most likely radical based, involving cleavage of the R-X bond by the *s*-electrons of Mg.

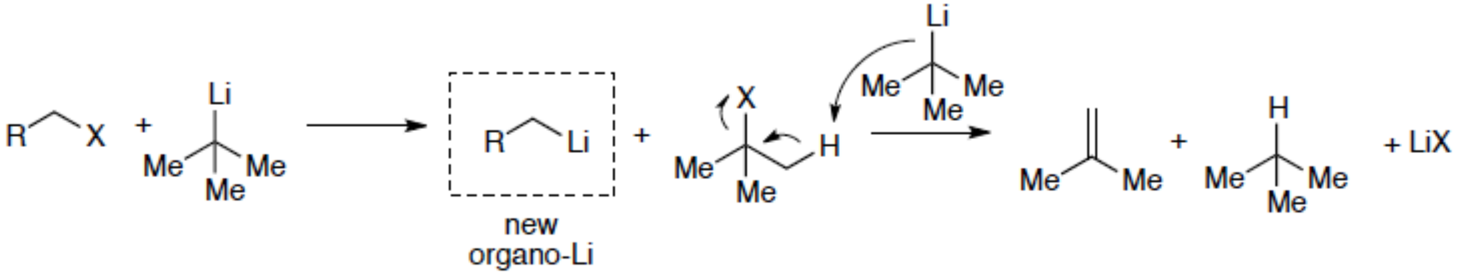


Metal-halogen exchange is another very useful and common method of preparing organolithiums and Grignard reagents. This reaction is an equilibrium, with the relative proportion correlating with the pKa of the two components. (In general, *alkyl*lithiums as BuLi and tert-BuLi (commercially available) are used to make *aryl*-lithiums by Li-halogen exchange. Aryl-C’s are more electronegative (more s-character at C) and can therefore better stabilize a negative charge. As Li-C bonds are very electron rich, the stabilization of the negative charge is the driving force for this reaction.

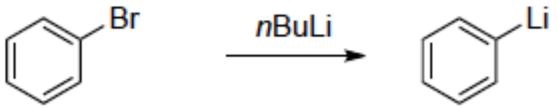
Metal-halogen exchange is a very useful synthetic procedure, as C-nucleophiles (generally difficult to prepare) can be generated from C-Hal bonds, which are easy to synthesize.

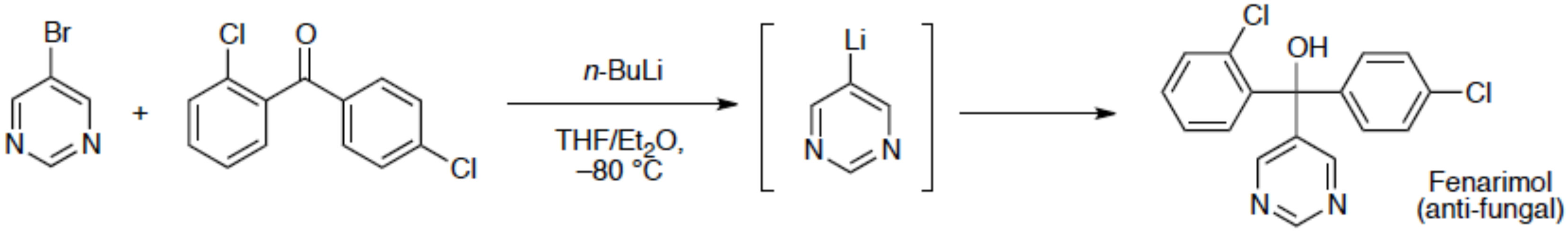


Example 1: Lithium halogen exchange is often performed using *n*-BuLi or *t*-BuLi (more reactive); reactions with *t*-BuLi generally require two equivalents. This prevents reaction of the new R-Li with the formed t-butyl halide, and drives the equilibrium forward based on LeChatelier's principle.

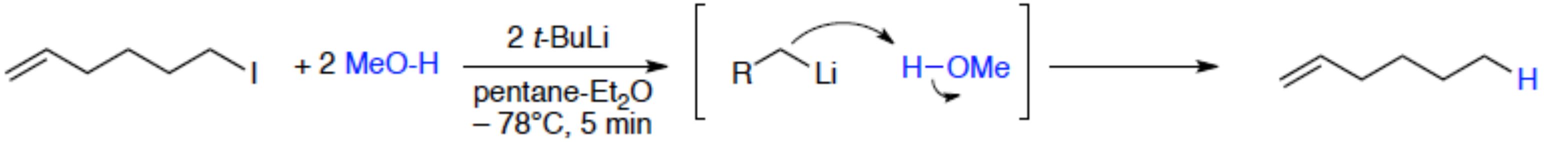


Lithium-halogen exchange is extremely rapid – this a useful characteristic that allows selective formation of reactive anions even in complex molecules. For example, a brominated aromatic can be lithiated in the presence of a ketone, two chlorides, and senstive pyrimidine ring. This reaction is used by Eli-Lilly to manufacture Fenarimol.





Lithium-halogen exchange can in some cases even out-compete deprotonation:

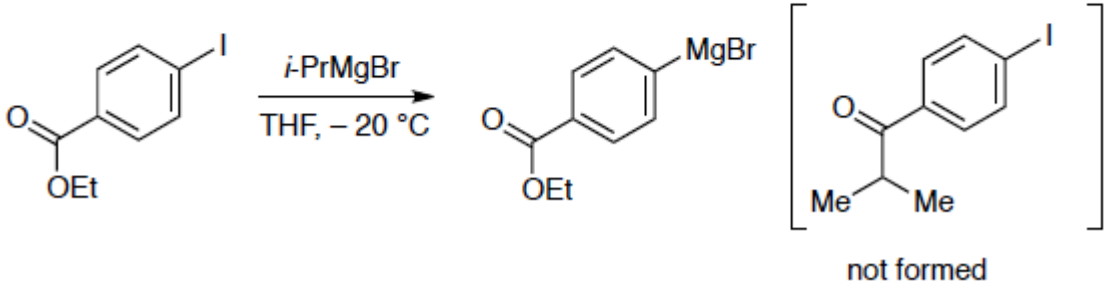


Example 2: Magnesium-halogen exchange was less developed than Li-X exchange until fairly recently.

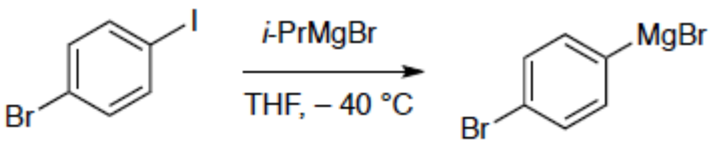
Paul Knochel (now professor at Ludwig-Maximilians-University, Münich) has rediscovered and popularized it.

Its advantages are low-temperature formation of Grignard reagents that are impossible to synthesize otherwise. The most common reagent used is *i*-PrMgX because it is reactive and commercially available.

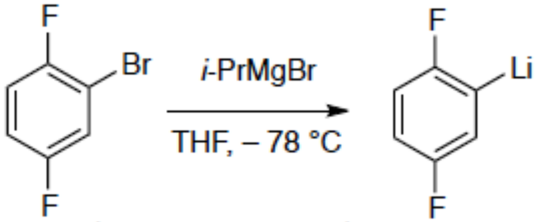
(here the same rules as for R-Li reagents apply: in general, alkyl-magnesium compounds are used to make aryl-magnesiums).



Aryl iodides are the best substrates, but electron poor aryl bromides can also be used.



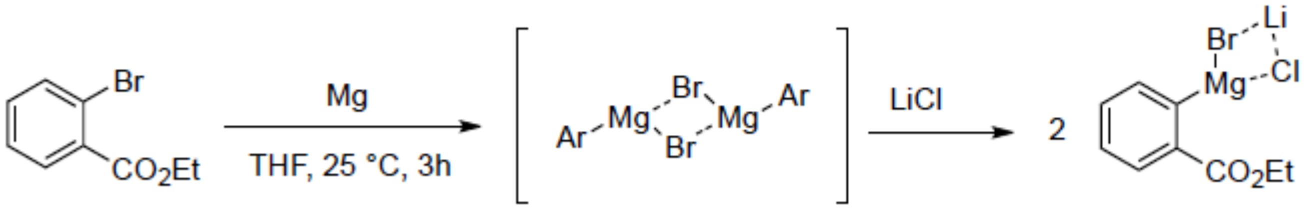
selective exchange of I vs Br



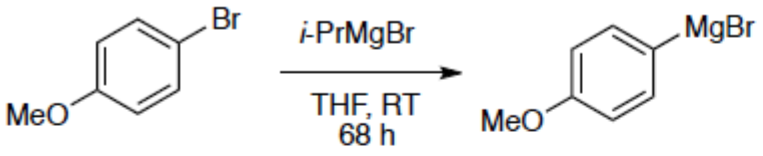
electron-poor Br exchange

A 1:1 combination of *i*-PrMgCl/LiCl is an extremely reactive combination that allows otherwise unreactive halides to be exchanged (the combination is called *TurboGrignard*TM). The LiCl is proposed to break up Grignard aggregates (salt clusters) leading to a more active reagent.

Magnesium clusters

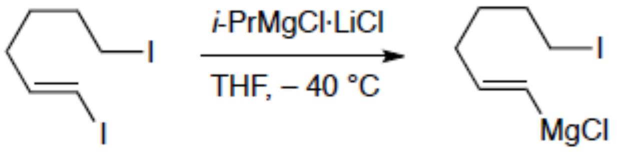


F. Piller, P. Appukkuttan, A. G, M. Helm, P. Knochel, Angew. Chem. 2008, 120, 6907–691



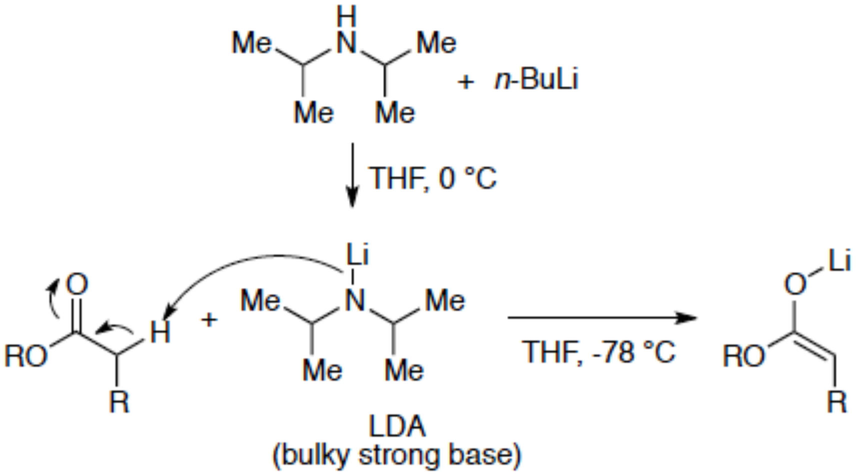
18% conversion

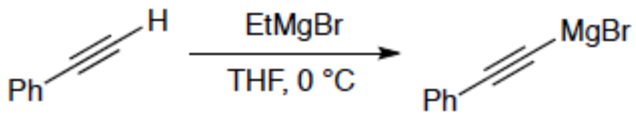
+ LiCl (1 equiv) 84% conversion



B) Some common reactions of R-Li and R-MgX are shown here as a review:
Keep in mind: Organometal compounds are always strong bases and strong C-nucleophiles.

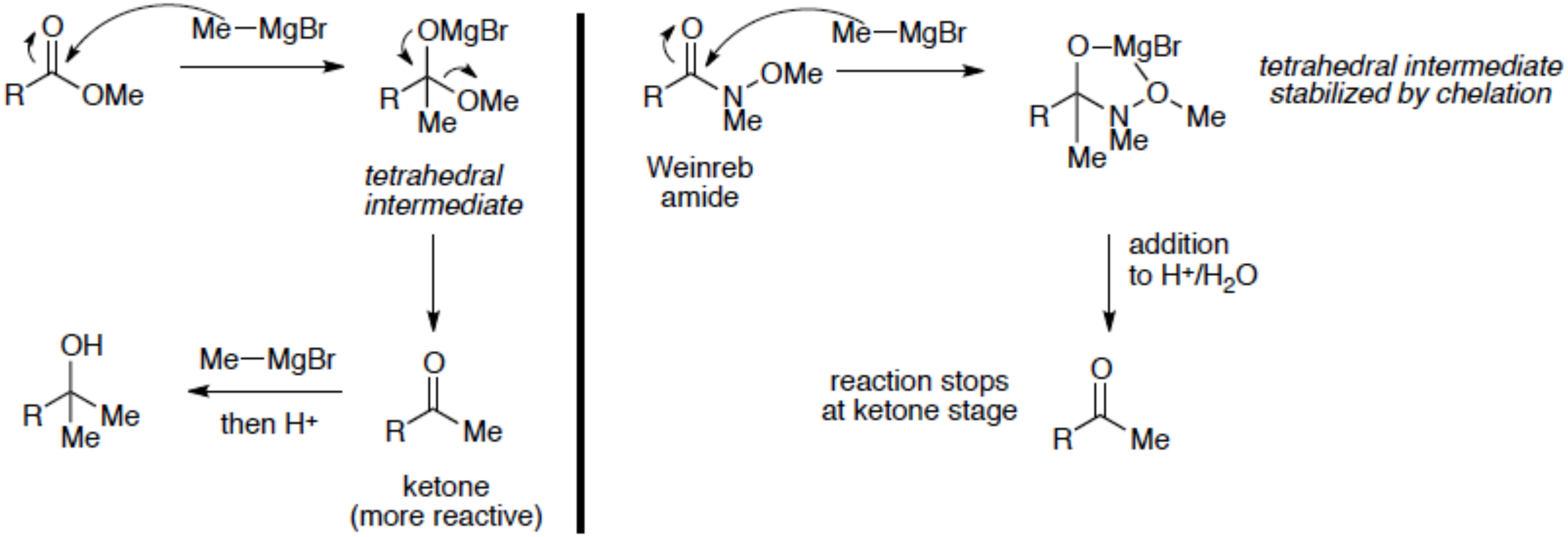
Use as base (especially for R-Li): Formation of alkyllithiums or Grignards is a good way of generating anions of groups with high pKa that cannot be deprotonated directly. Once the conjugate base of a very poor acid is formed, it can be used to remove protons from relatively stronger acids.



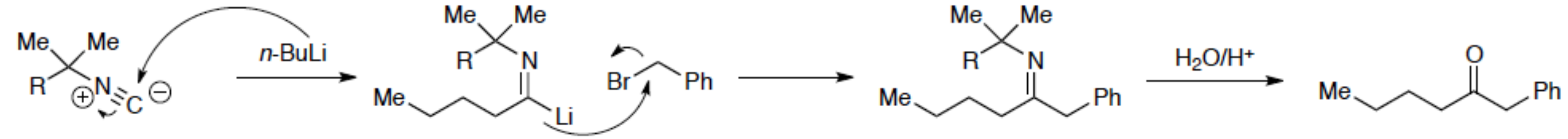


Use as nucleophiles: Grignards and organolithiums are particularly useful for additions to carbonyls and carboxylic acid derivatives (but they do not participate in simple SN2 reaction at alkyl halogen center).

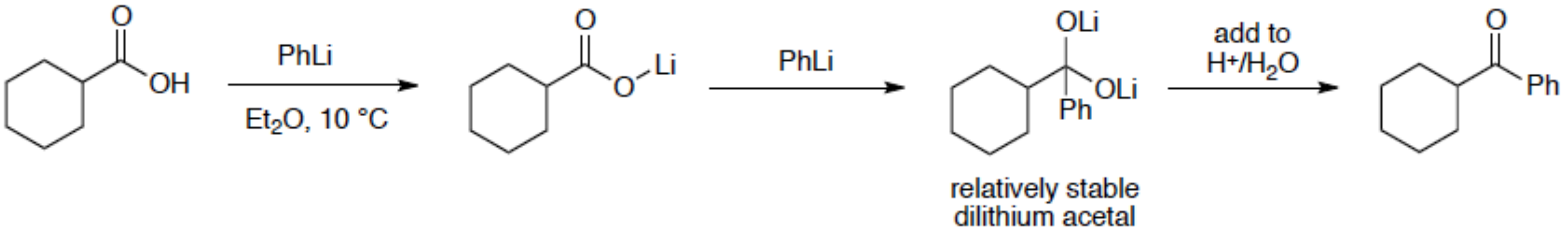
Double addition of Grignards to esters occurs because the ketone intermediate is more electrophilic than the ester starting material. Single addition can be realized using so-called Weinreb amides. Here, the tetrahedral intermediate is stabilized by chelation of O to Mg, and therefore the intermediate cannot collaps to the corresponding ketone until workup.



Alkyllithiums are extremely powerful nucleophiles, and can even add to the carbon atom of isonitriles, which already have a formal negative charge. This generates a new nucleophile that acts as the equivalent of an acyl anion (*umpolung*).



They can also add to anion lithium carboxylates – this gives a simple process for converting carboxylic acids into ketones. *Note: this reaction often forms a lot of tertiary alcohol by double addition- it is shown here as an example of the high reactivity of alkyllithiums and should not be considered a general way to prepare ketones*



Organocuprates

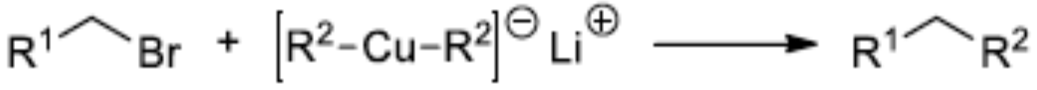
$$\mathrm{Cu^0} \longrightarrow \mathrm{Cu^+} + e^- \qquad \text{IE 745 kJ/mol}$$

With the electronegativity of copper being **1.90** (compared to 1.30 for magnesium), the metal-carbon bond has more covalent character than in the Grignard reagent, which makes organocuprates *softer nucleophiles*.
In contrast to organolithium and -magnesium compounds, organocuprates are not formed by direct metallation of halides, as the redox pair CuI/CuII gives rise to radical side reactions. Instead, organocuprates are generated by **transmetallation** from organolithium compounds.

Note: Transmetallation is the exchange of groups from one metal atom to another. This term will be used frequently in these notes, so keep it mind!

$$2\ \mathrm{R{-}Li} + \mathrm{Cu^{I}{-}X} \longrightarrow \underset{\text{Gilman cuprate}}{\left[\mathrm{R{-}Cu{-}R}\right]^{\ominus}\mathrm{Li}^{\oplus}} + \mathrm{LiX}$$

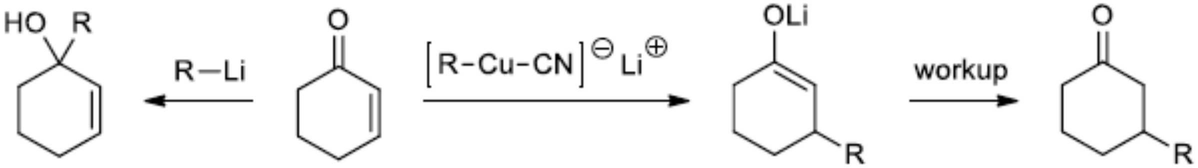
Gilman cuprates are employed for alkyl substitution reactions with alkyl halides. As only one of the two alkyl groups of the cuprate is transferred, only cheap and readily accessible moieties are used.



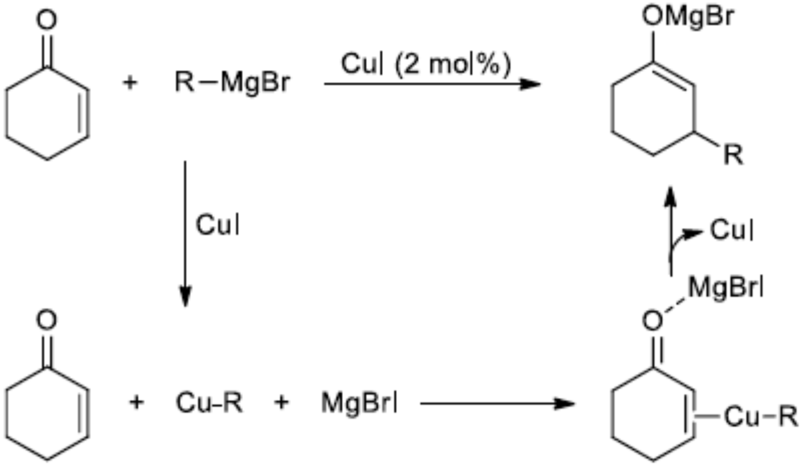
A good solution for using precious alkyl nucleophiles is to replace one of the groups on Cu with a so-called *dummy ligand* – this is a group that is bound tightly to copper and does not transfer easily compared to the second nucleophile. A commonly used dummy ligand is cyanide, because CuCN is a cheap source of Cu(I) and the sp-hybridized carbon atom is poorly nucleophilic.

$$\mathrm{R{-}Li} + \mathrm{Cu^{I}{-}CN} \longrightarrow \left[\mathrm{R{-}Cu{-}CN}\right]^{\ominus} \mathrm{Li}^{\oplus}$$

The more covalent Cu-C bond, combined with copper's lower oxophilicity and tendency to bind to alkenes makes organocuprates excellent nucleophiles for conjugate additions (additions to α,β-unsaturated carbonyls). In the case of α,β-unsaturated ketones, alkylithiums add to the *hard* carbonyl position (1,2- addition), while cuprates add to the *soft* conjugate position (1,4-addition).

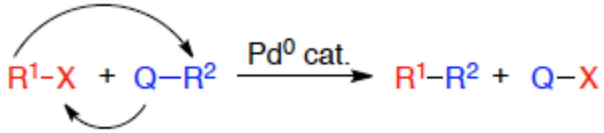


A very useful variation on this reactivity is to use catalytic amounts of copper salts in order to make a highly selective 1,4-addition. In this case the Grignard reagent first reacts with Cu(I) by **transmetallation**, and then the newly formed cuprate adds to the unsaturated carbonyl. Since Mg(II) is oxophilic, the new enolate intermediate will bind with Mg and return the original Cu(I) salt, that can react again with another equivalent of the Grignard reagent, forming a catalytic cycle.



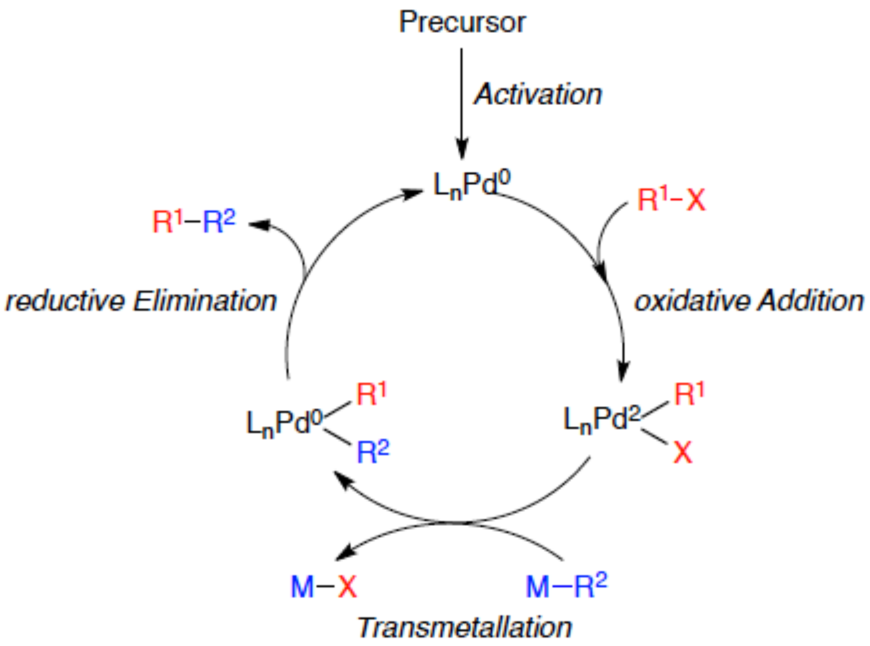
Cross Couplings

A cross coupling is a metal-catalyzed reaction where two different hydrocarbon fragments R1 and R2 are coupled. Mostly, Pd complexes are used as catalysts for cross-couplings.



General Mechanism and Elementary Steps

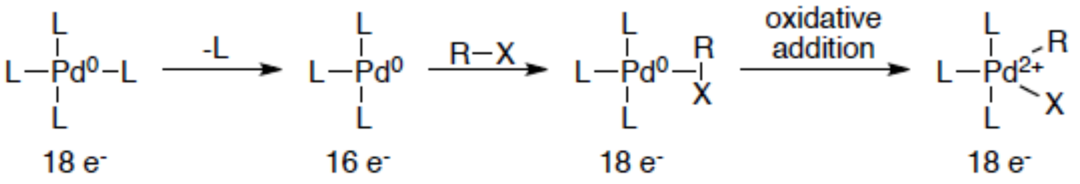
All transition metal catalyzed cross coupling reactions follow the same general mechanism:
A moiety R1-X adds to the activated transition metal complex and increases its oxidation state by 2 (***oxidative addition***). Subsequently, the organic part of an organo-metallic compound M-R2 is transferred to the catalyst (***transmetallation***). In the last step, the two coordinated organic moieties couple and dissociate from the catalyst. The catalyst is reduced in the process (***reductive elimination***)

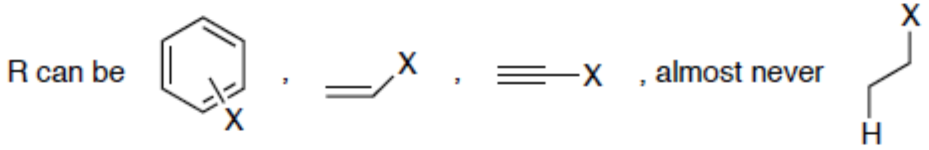


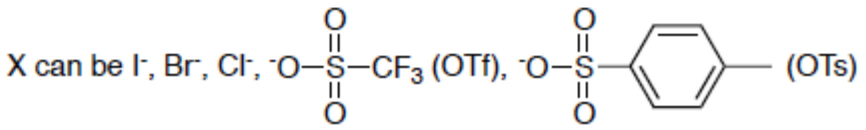
Oxidative Addition

Oxidative addition involves some preliminary steps depending on the number of ligands (solubilizing/stabilizing groups) are attached to the metal precursor. The important thing to keep in mind is that the transformation converts Pd(0) to Pd(II); this is essentially the same process happening when Mg(0) inserts into R-X to become Mg(II).

Like the formation of Grignard reagents, R-X for oxidative addition can be **I, Br, and Cl**; another common group is triflate (trifluoromethanesulphonate, **OTf**) because it can be formed directly from alcohols. The carbon atom is normally **sp2** (aryl or vinyl) or **sp** hybridized; sp3 carbons are more rare, for reasons we will see later.

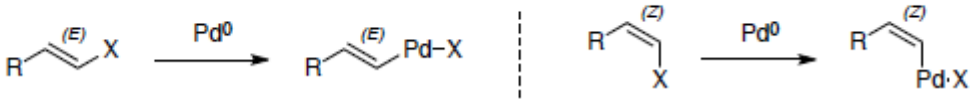






The rate of oxidative addition increases with decreasing C-X bond strength: I > Br ≈ OTf > Cl

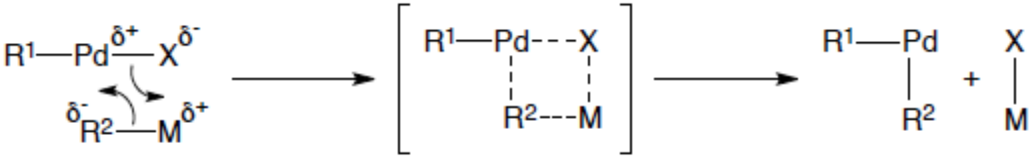
The oxidative addition is stereospecific, that means the olefin geometry of the starting material (here the vinyl-halogenide) determines the olefin geometry of the resulting vinyl-palladium complex.



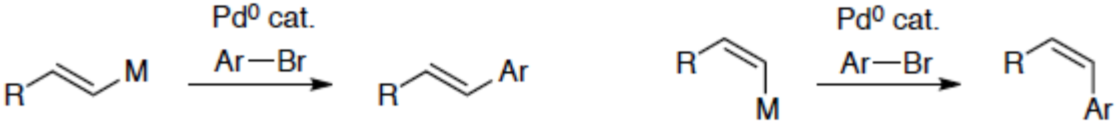
Transmetallation

The metal group used in cross-couplings can vary a lot, and seemingly every element in the periodic table has been attempted in cross-couplings. The important thing to keep in mind is that, with the exception of boron (which is not really a metal!), the steps involved in **transmetallation** are the *same for every metal*.

For Aryl-M, Vinyl-M and Alkynyl-M the transmetallation most likely proceeds via square-like σ-bond metathesis.

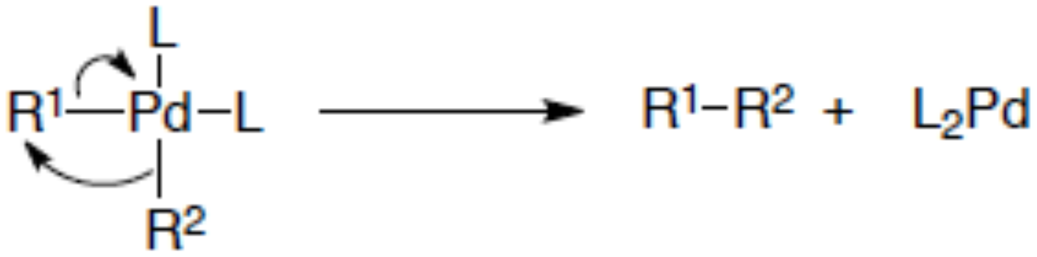


Since the group attached to the metal is transferred directly to palladium through the electrons of the C-M bond, the stereochemistry of the bond will be preserved. This means the reaction is *stereospecific*.



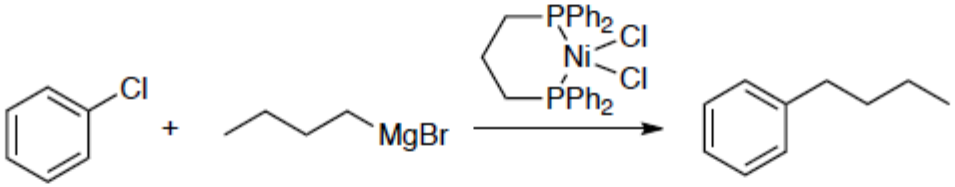
Reductive Elimination

The final step of the catalytic cycle, reductive elimination, is fast and irreversible (palladium will not insert into the C-C bond). This actual coupling step is stereospecific.

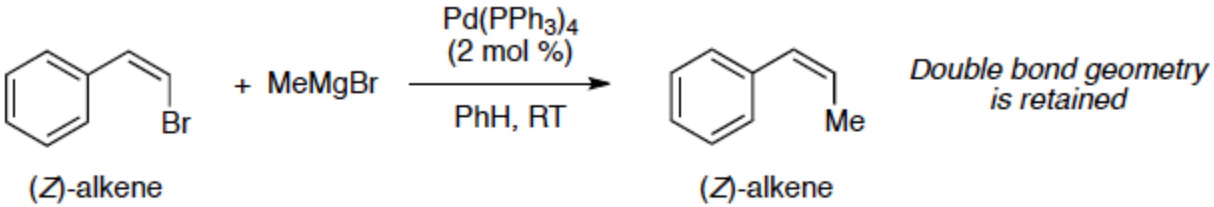


Kumada Coupling (RMgX)

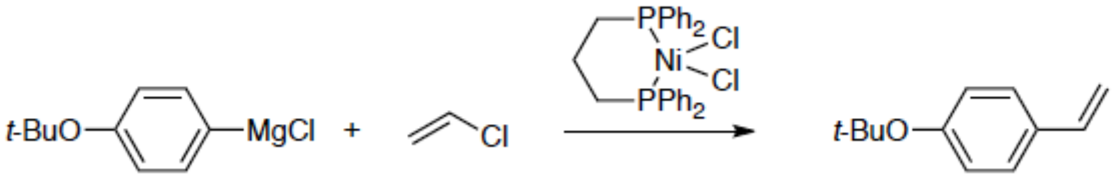
In 1972, Makoto Kumada reported the first transition metal-catalyzed cross coupling. Initially, he employed nickel complexes to couple aryl- or alkenyl halides with Grignard reagents. The mechanism of the reaction using nickel is the same as for palladium (insert Ni for Pd in the mechanism above – the oxidation states are the same as well).



Murahashi first described the palladium-catalyzed version (for historical reasons, the Pd-catalyzed variant is still referred to as the Kumada coupling).



A Kumada coupling is employed in the industrial synthesis of p-*tert*-butoxystyrene, a precursor for photoresist resins used in lithography:



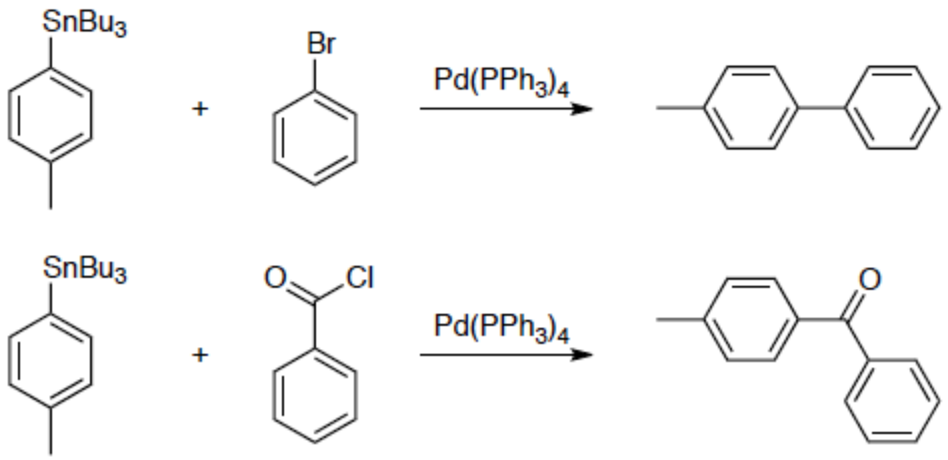
Banno *J. Organomet. Chem.*, **2002**, 653, 288

As Grignard reagents are also strong bases and react with a variety of functional groups, the scope of the Kumada coupling is limited to molecules void of these functionalities.

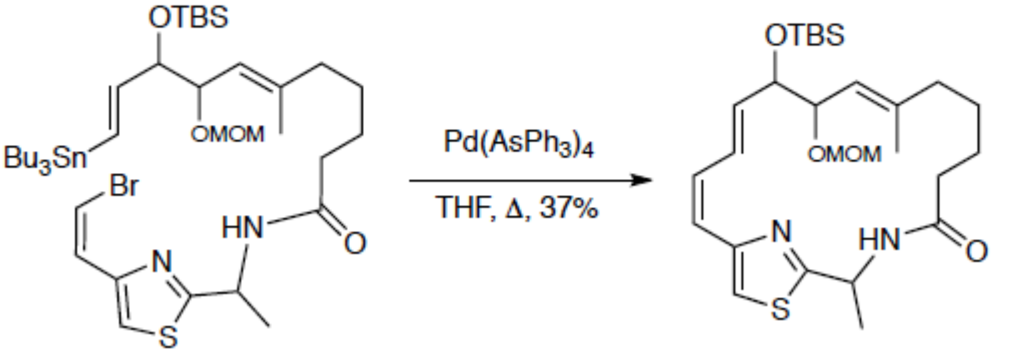
Stille Coupling ($RSnBu_3$)

The *Stille* cross coupling describes the palladium-catalyzed coupling of organostannanes (organo-tin compounds) with aryl-, alkenyl- and acyl-halides. Its mild reaction conditions, high functional group tolerance and the stability of organostannanes make it a useful reaction for the build-up of complex molecules. Of disadvantage are the toxicity of organo-tin compounds and the possible contamination of the product with Bu_3SnX.

The butyl ligands are “dummy ligands”; they do not take part in the reaction as they transmetallate very slowly.



A Stille coupling was employed in the macrocyclisation step in the synthesis of antitumor antibiotic leinamycin.

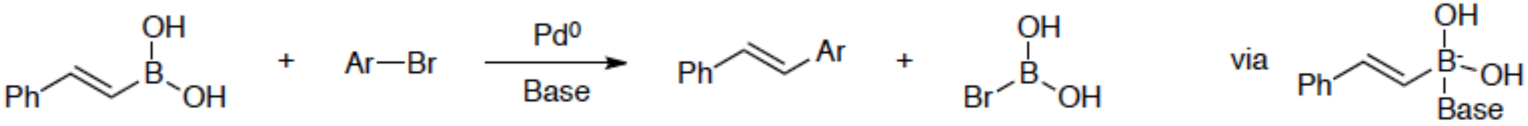


G. Pattenden *Synlett,* **1993**, 215

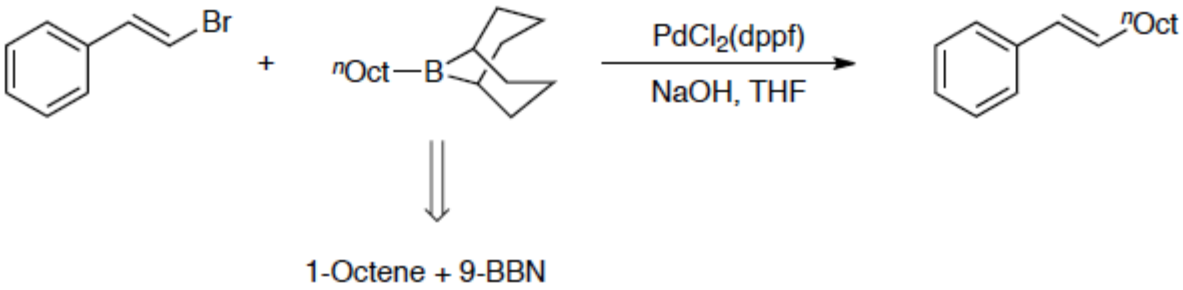
Suzuki Coupling (RBX_2)

The cross-coupling of organoboron compounds with halides, known as the *Suzuki* reaction, is probably the most used cross-coupling. Compared to the Stille coupling, the inorganic byproducts are more easily removed and much less toxic. This, combined with the good availability of boronic acids, makes the reaction suitable for industrial application.

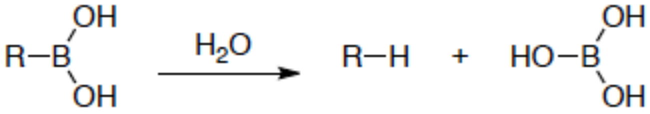
Because the C-B bond is not very polarized and boron is Lewis acidic, a nucleophilic base is added to the reaction in order to form a *boronate* (tetracoordinate boron species) that is the active species.



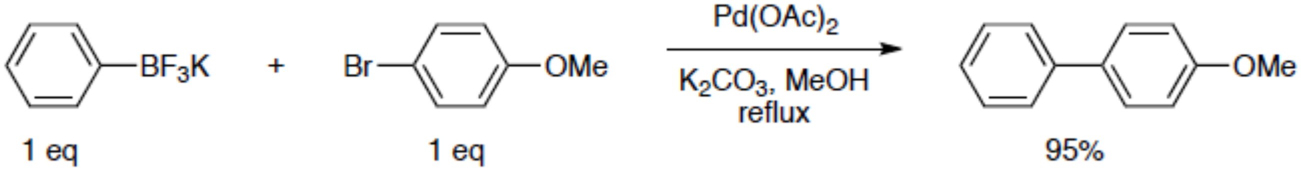
While the cross coupling of alkyl groups is generally limited due to unwanted β-hydride elimination, the Suzuki reaction can be performed with alkylboranes, which are easily obtained by hydroboration of the respective alkenes.



Drawbacks of the Suzuki reaction are the sometimes limited stability of the boronic acids to the reaction conditions, leading to proto-deboronation in aqueous solvents. This often which requires the boronic acid to be added in excess.



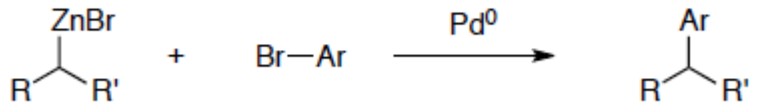
Those problems were recently overcome by the development of potassium alkyltrifluoroborates. These reagents are stable to air and humidity and can be employed in equimolar amounts.



Molander *JOC,* **2003**, 68, 4302

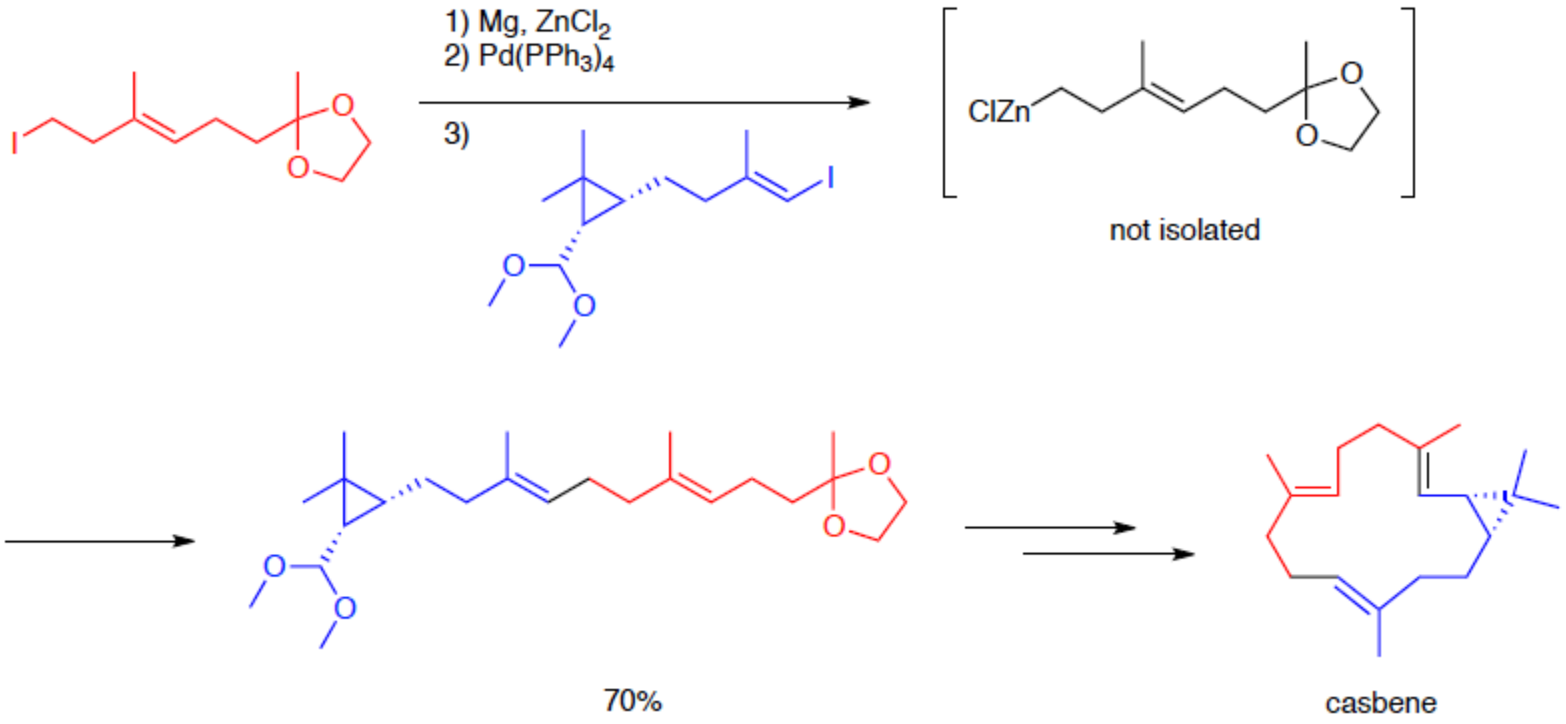
Negishi Coupling (RZnX)

To overcome the limitations set by the low functional group tolerance of the Kumada coupling, the cross coupling of organo-zinc compounds with halides was developed several years later and became known as the *Negishi* coupling.



The reactivity of organo-zinc compounds lies between that of Grignard reagents (harder, more reactive) and stannanes (softer, less reactive). Despite more and more organo-zinc compounds becoming commercially available, the scope of the Negishi coupling is still limited as in most cases the starting material has to be prepared by transmetallation of Grignard reagents or organo-lithium compounds.

The Negishi cross coupling was a central step in McMurry's convergent synthesis of the terpene casbene:

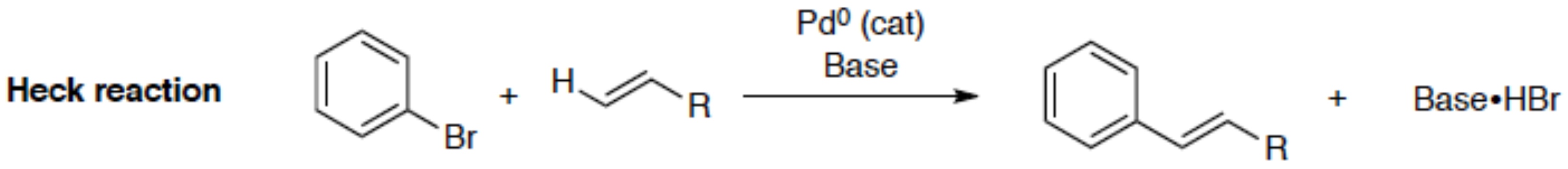


McMurry *JOC,* **1987**, 52, 4885

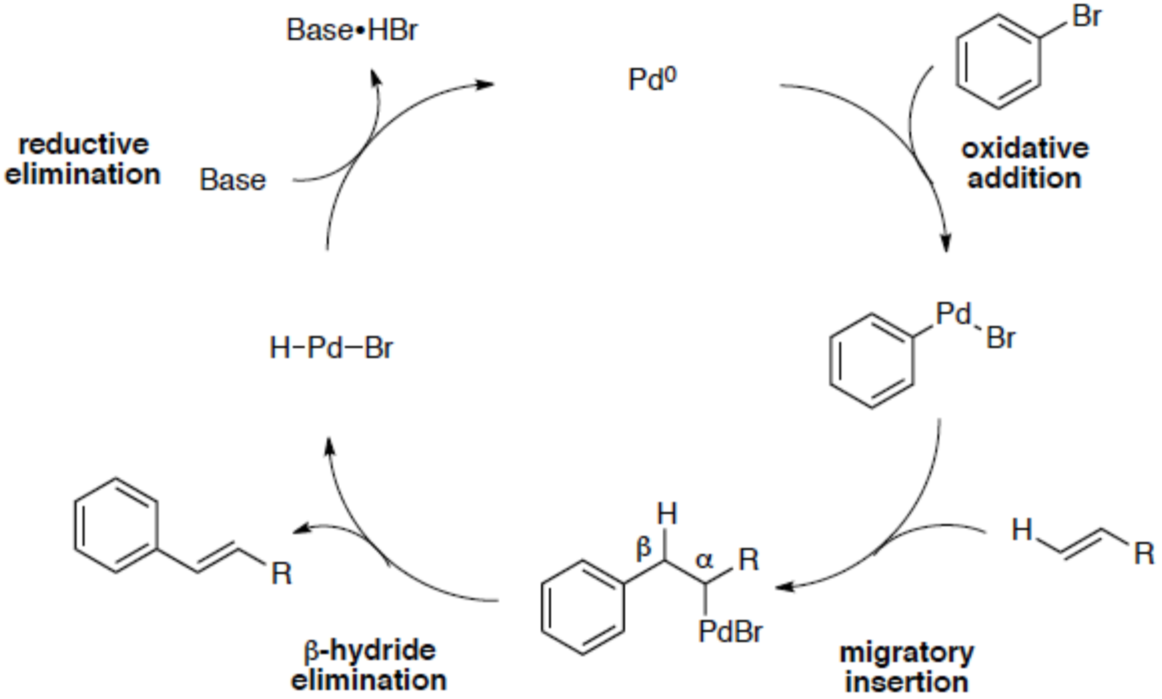
Heck Reaction

Reaction and Mechanism

The Heck reaction is the Pd-catalyzed reaction of an aryl or alkenyl halide (R-X) with an alkene that forms a new alkene product and eliminates HX. It is named after Richard Heck (Nobel Laureate 2010), who discovered it in the 1970’s while working at the Hercules company in Delaware USA



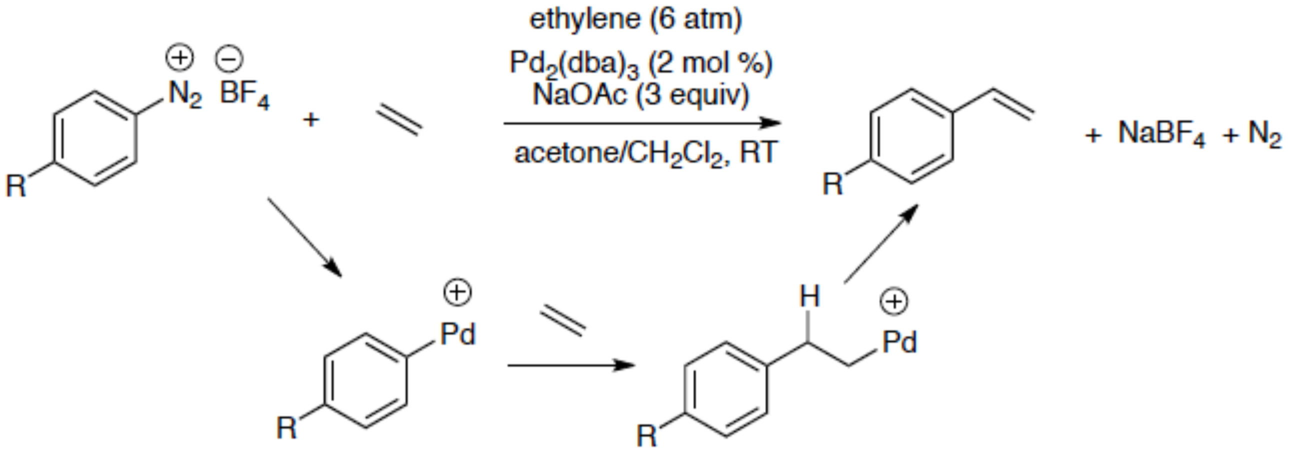
The mechanism of the Heck reaction is related to cross-coupling and has some familiar steps. It begins with a Pd(0) catalyst that undergoes **oxidative addition** with the R-X portion to give a Pd(II) intermediate. This reacts with the alkene by adding across the double bond (**migratory insertion**); this can also be called "carbopalladation" since a carbon and palladium atom are added to the alkene. At this point, a hydrogen atom at the β-position migrates to Pd – this is called **β-hydride elimination** and reforms the C=C bond and forms the Heck product and a Pd(II) hydride. The added base removes the hydrogen atom and facilitates **reductive elimination** to give the conjugate acid and regenerate Pd(0) to start the catalytic cycle over.



Oxidative addition

As for cross-couplings, the Heck reaction can be done with R-I, R-Br, R-Cl, and R-OTf. A useful variant is to use diazonium salts ([R-N2 +][BF4-]) that generate highly reactive cationic Pd(II) intermediates that can couple at mild conditions, such as the room temperature synthesis of styrenes using ethylene.

Other aspects of the oxidative addition step (i.e. stereospecificity, rates of addition etc) are identical.

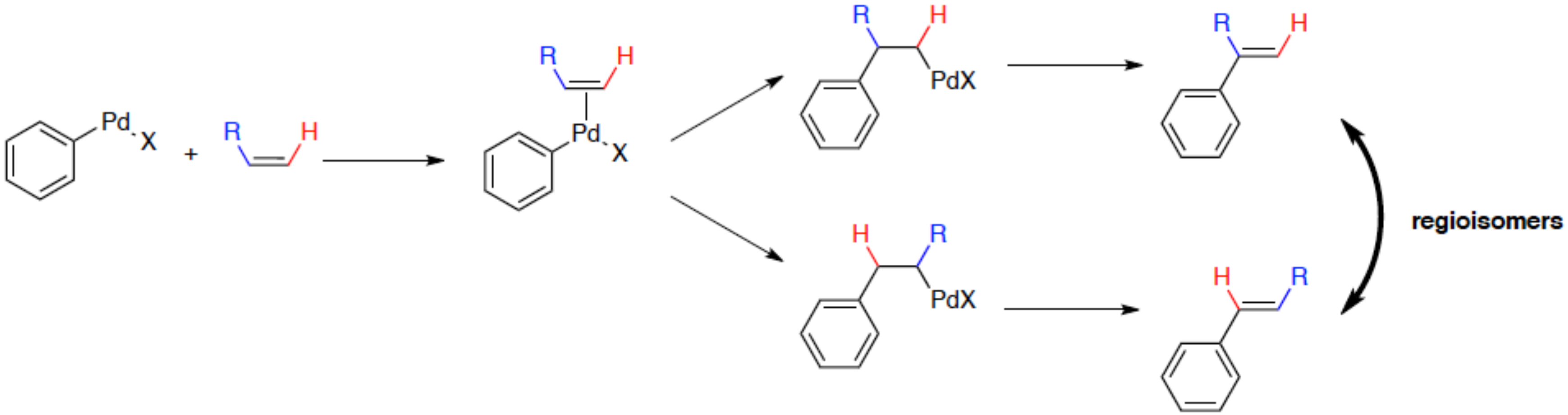


Migratory insertion

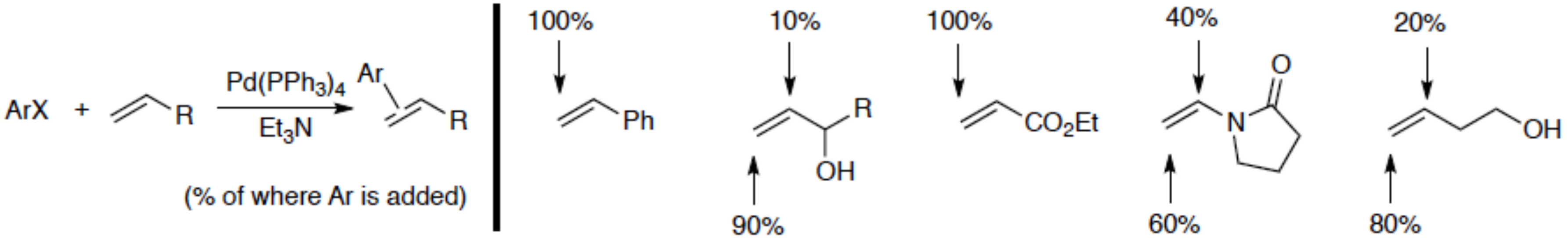
The mechanism presented above showed a relatively simplistic look at migratory insertion. In actuality, there is a step preceding oxidative addition and the insertion, which is coordination of the alkene to RPd(II)X; this is shown in the scheme below.

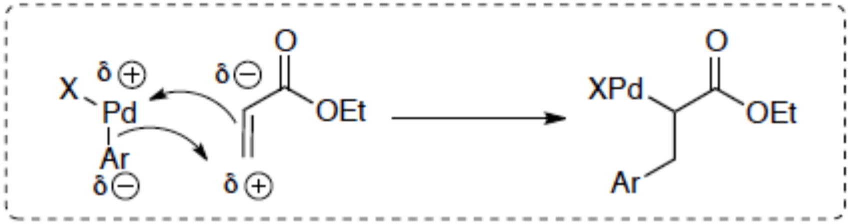
Two main considerations in the Heck reaction to keep in mind are the *regiochemistry* and *stereochemistry* of the insertion.

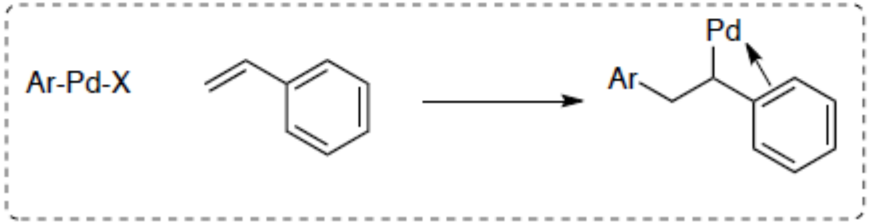
Regiochemistry: The insertion of RPdX into a terminal alkene can put either the carbon or the palladium on the more substituted position; after hydride elimination this will lead to different products – either a 1,1- disubstituted terminal alkene or a 1,2-disubstituted internal alkene.



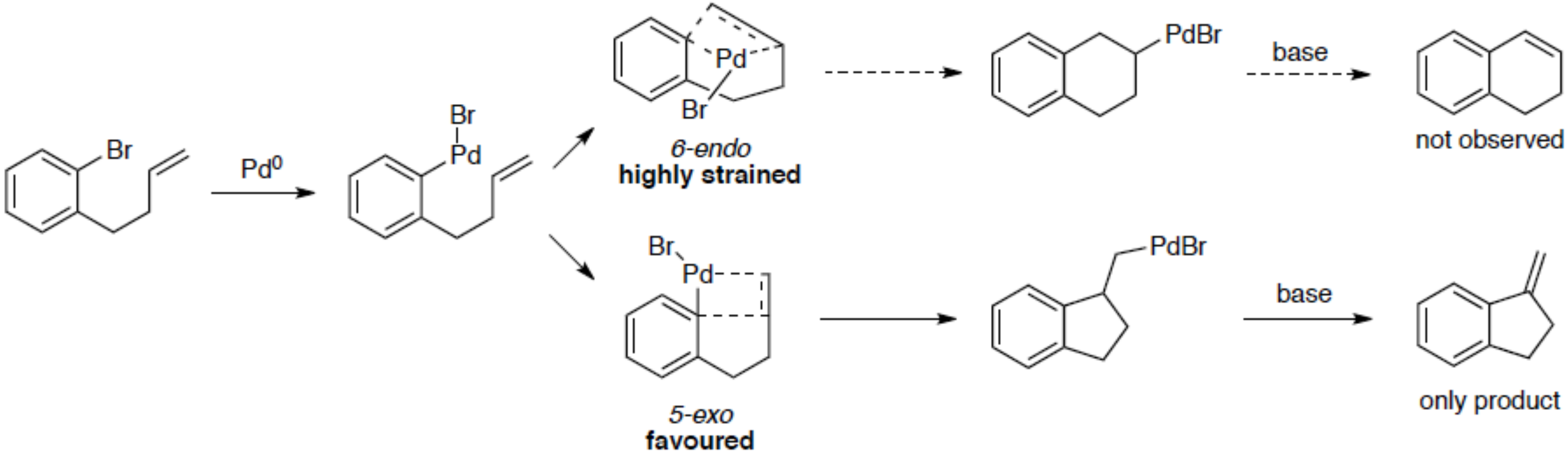
For insertion of neutral palladium species into terminal alkenes, consider steric and electronic properties of the alkene and R-Pd-X; in general the reaction proceeds to put the carbon group on the less sterically hindered (terminal) position. Electron-poor alkenes conjugate to carbonyl and styrenes are exceptional in that they give essentially 100% selectivity; other alkenes are not such good partners and give mixtures (*this is why alkene cross-coupling is so important- completely regioselective*). For unsatured alkenes, the selectivity can be explained by the alignment of the partial charges; for styrenes, coordination of Pd to the π- electrons stabilizes benzylic Pd species and puts the carbon on the opposite side.







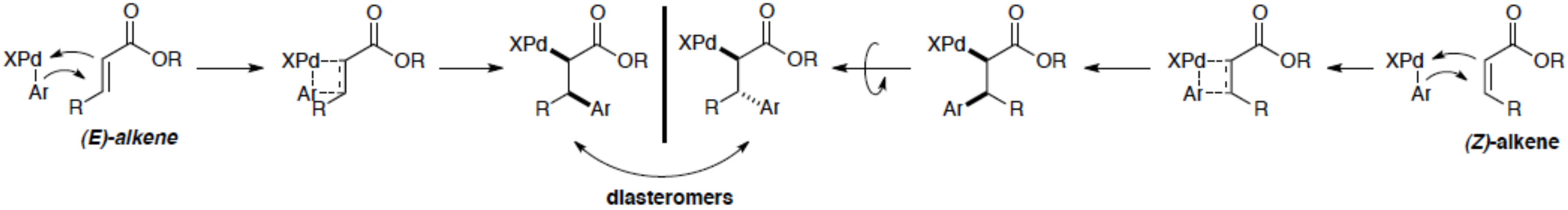
Since selectivity of unbiased alkenes is often poor, a useful alternative is the *intramolecular* Heck reaction, which is typically highly selective in the preparation of 5-7 membered rings. This is because the transitions states are bicyclic, so exo addition of the Pd across the double bond is preferred. The end result is that smaller rings are formed preferentially.



Stereochemistry: Migratory insertion is a four-centre, four-electron process that proceeds through a *concerted* pathway – in this way it is similar to reactions you know already such as *hydroboration* or *hydrogenation*. From that, it is clear that the addition must add to the same face of the alkene (*cis addition*).

This leads to migratory insertion being ***stereospecific*** -> opposite alkene isomers give diasteromeric carbopalladated products.

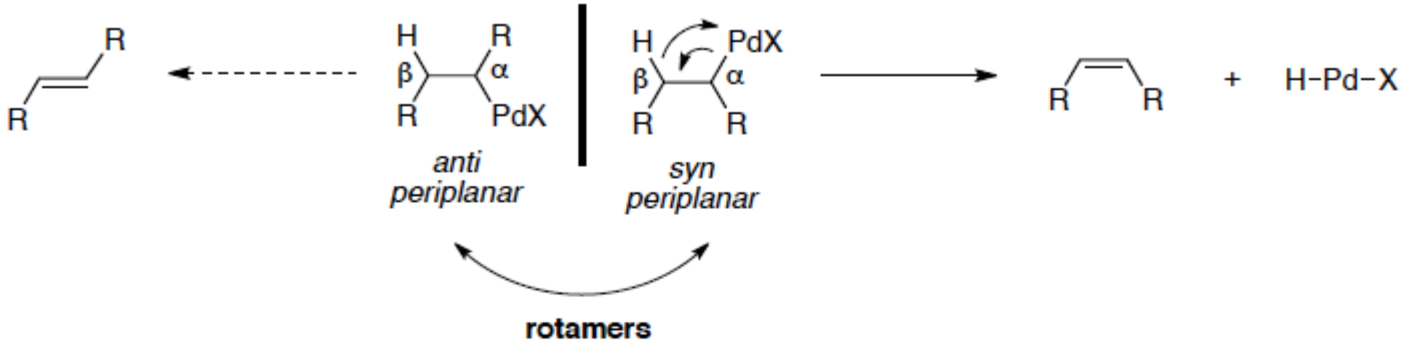
This is important because the next step, β-**hydride elimination**, is also stereospecific.



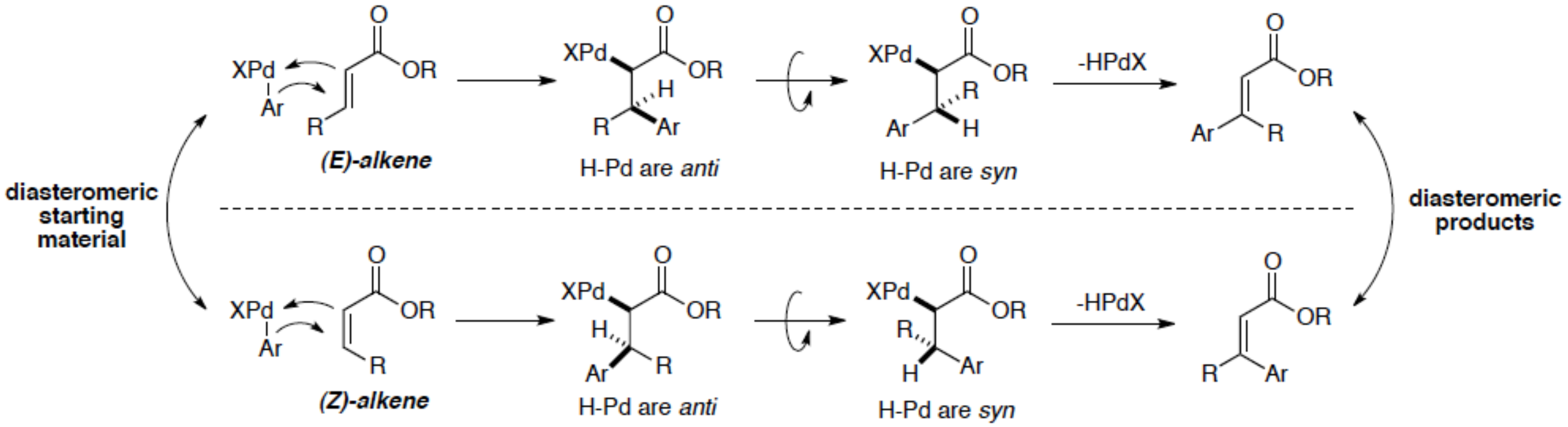
β-hydride elimination

Beta-hydride elimination is a reaction in which an alkyl group bonded to a metal atom is converted into the corresponding metal-bonded hydride and an alkene.
If Pd has a free coordination site, the β-hydride elimination of alkyl chains is thermodynamically and kinetically favored: alkyl-Metal bonds are weaker than metal-hydride bond and the process provide 2 electron to an empty d orbital of the metal.
As reverse reaction of 1,2 insertion this reaction happens through orbital overlap of the C-H bond with an empty cis d-orbital on the adjacent Pd. Therefore, unlike E2 elimination, the two groups must be *syn periplanar* to each other.

In a 2D fashion, this can be looked at this way:



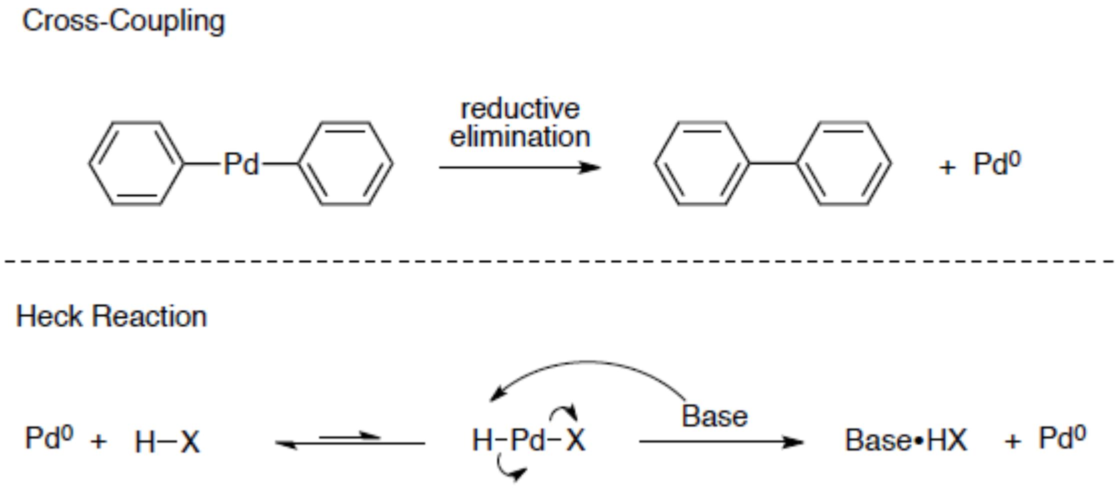
Looking again at the intermediate formed after migratory insertion in 3D, the reaction looks like this (Notice how the two alkene isomers result in different products):



Reductive Elimination

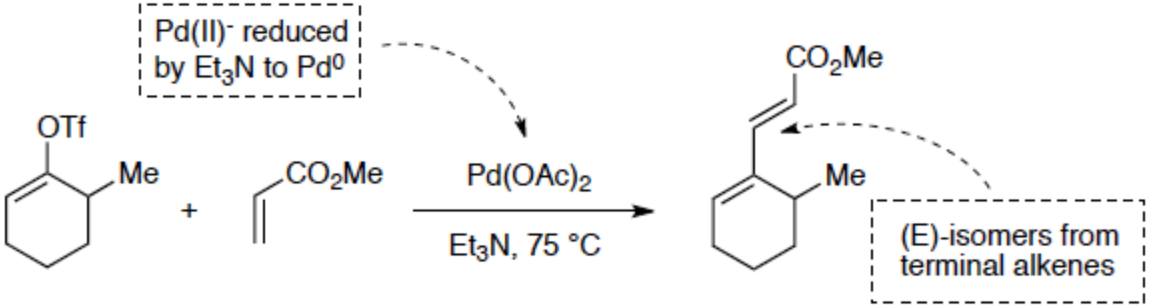
This is related to the same process in cross-coupling. The main difference is that in cross-coupling, the new C-C bond that is formed is inert to Pd(0) and is not capable of redoing oxidative addition -> irreversible step.

On the other hand, H-X can react with Pd(0) by oxidative addition, meaning that HPdX à H-X + Pd(0) is *reversible*. The base provides a thermodynamic sink for H-X that prevents the acid from tieing up the catalytic amount of Pd.



Examples of the Heck reaction in practice:

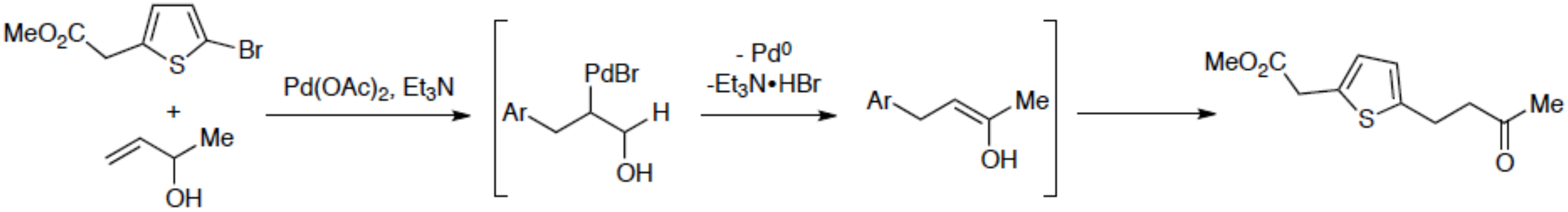
Reaction of vinyl triflates with acrylates:



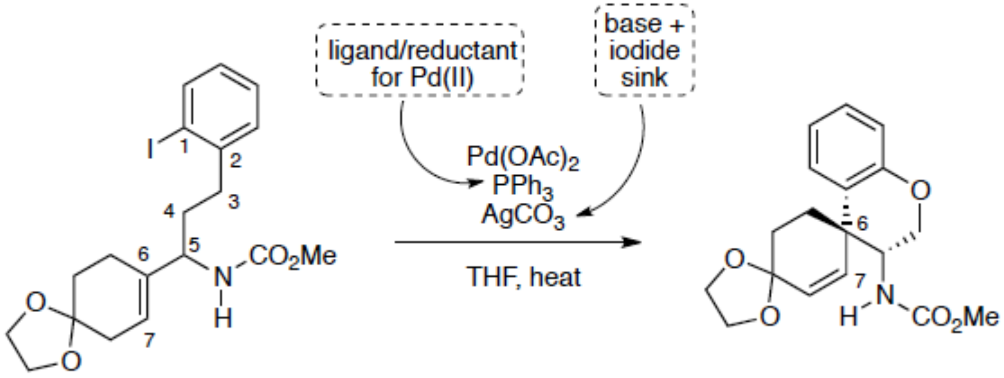
Pd(II)$^-$ reduced by Et_3N to Pd^0

(E)-isomers from terminal alkenes

Heck reaction of allylic alcohols can be used to prepare ketones; after hydride elimination, the resulting enol tautomerizes to the carbonyl



Intramolecular example: 6-membered ring forms preferentially over the possible 7-membered ring

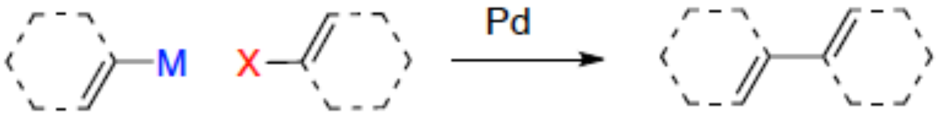


ligand/reductant for Pd(II)

base + iodide sink

C-M bond formation

Reagents containing C-M bonds are often used as one of the partners for different cross-coupling reactions.
In cases when they are not commercially available (complex or unstable molecules) they have to be synthesized.



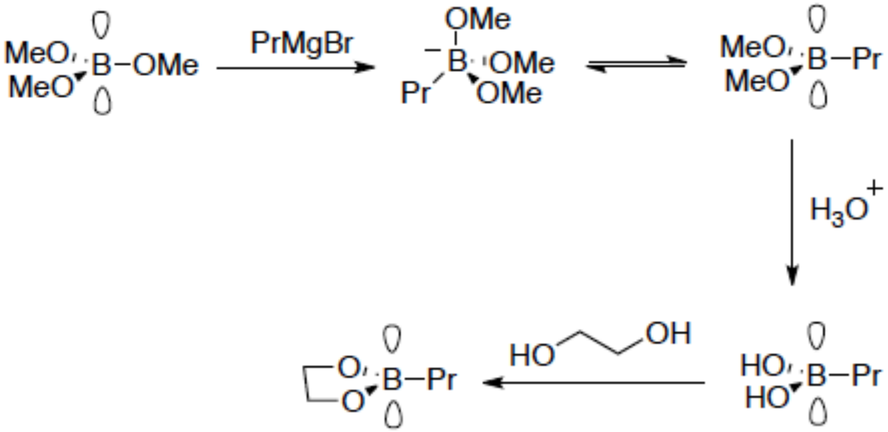
M = $-B(OH)_2$, $-B(OR)_2$, $-BR_2$, $-BF_3$ Suzuki-Miyaura
$-SnR_3$ Stille
$-SiR_3$ Hiyama

X = I; Br; Cl; OTf etc.

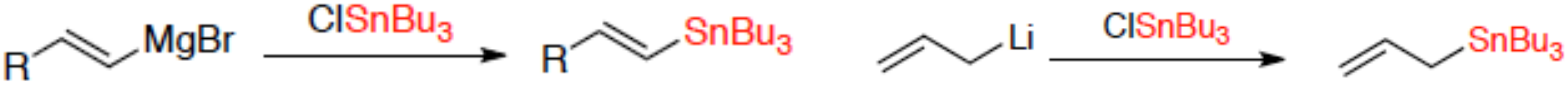
Trapping of organometallic nucleophiles

Synthesis of isolable boron and tin reagents.

Even if you are used to see metallic compounds as nucleophiles, M-X reagents can still act as electrophiles because they have a cleavable leaving group. Additions of strong carbon nucleophiles (RLi or RMgX) to M-X is a useful way of preparing new organometallics; the identity of X depends on the metal and the desired products.

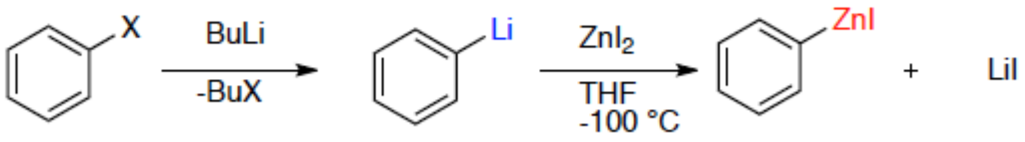


Note: organotin reagents are highly toxic and should be handled with caution.



Transmetallation

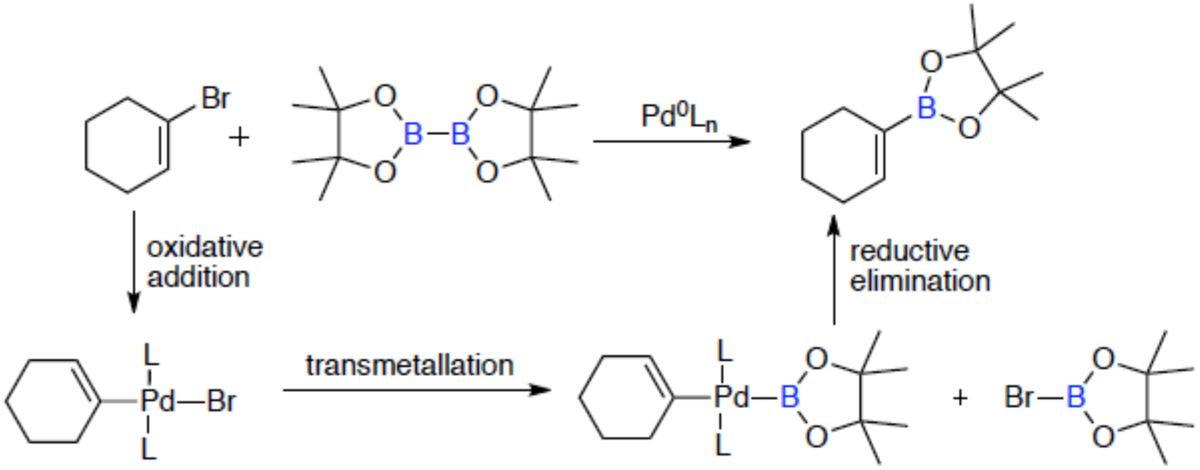
A lot of organometallic reagents are not isolated but are rather prepared in-situ by transmetallation from corresponding organolithium or organomagnesium compounds.



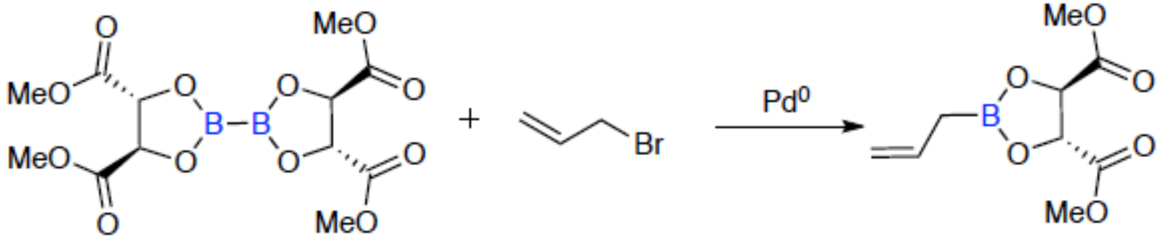
Organozinc reagents serve as coupling partners in Negishi cross-coupling.

Cross-coupling of M-M bonds

Miyaura arylborane synthesis (B-B cross-coupling)
This reaction is analogous to the Suzuki coupling, except that a nucleophile containing a B-B bond is used instead of one containing a C-B bond. The benefits of this method are that it is relatively mild and does not require formation of strongly nucleophilic carbanions.



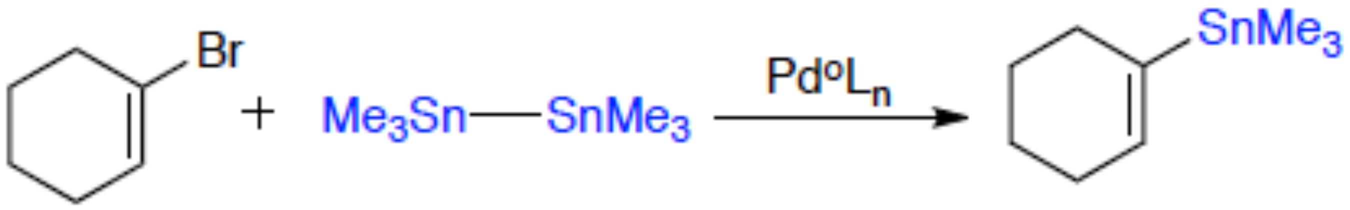
This method can be used to synthesize chiral allylboronic esters



Note: the chiral allylboronic esters are used in stoichiometric asymmetric allylation of carbonyls (-> OC III).

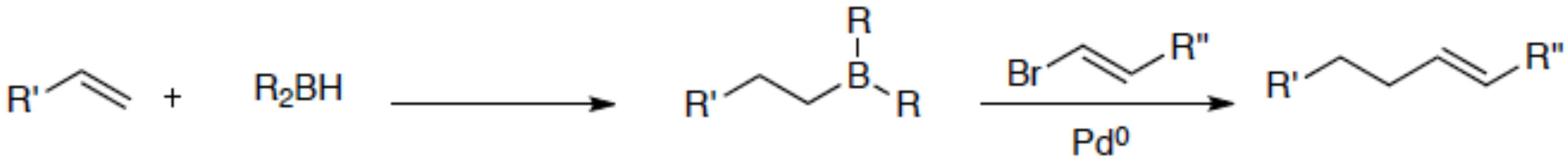
Stille cross-coupling

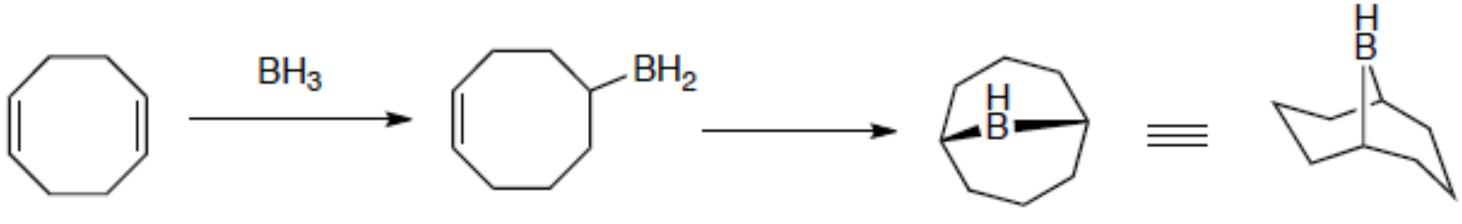
This is the tin analogue of the Miyaura cross-coupling, using a Sn-Sn reagent. Newly made organotin compounds can be used for Stille coupling.



Hydrometallation/Carbometallation

Preparation of alkyl or alkenyl metal species using a M-H type reagents.

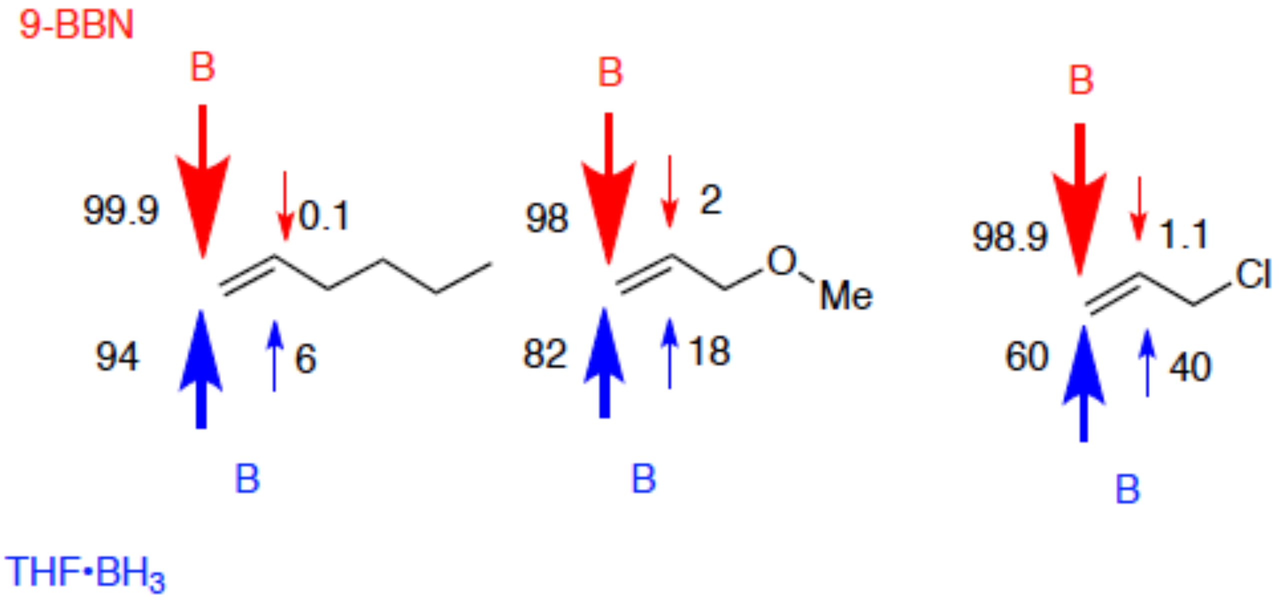




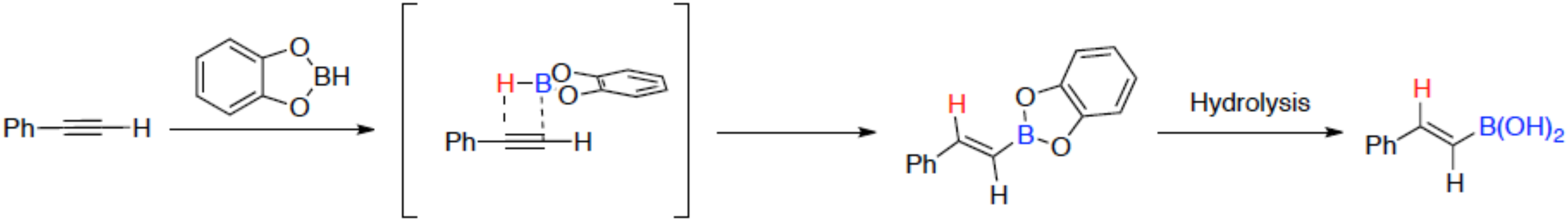
9-BBN

Reminder of hydroboration

Due to steric reasons 9-BBN is more selective than BH3.

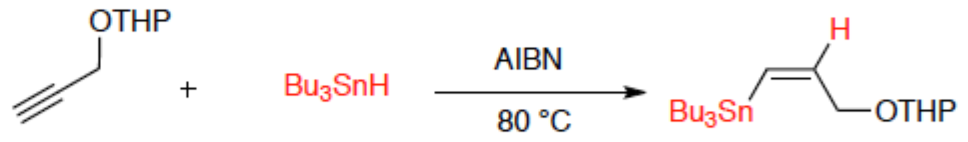


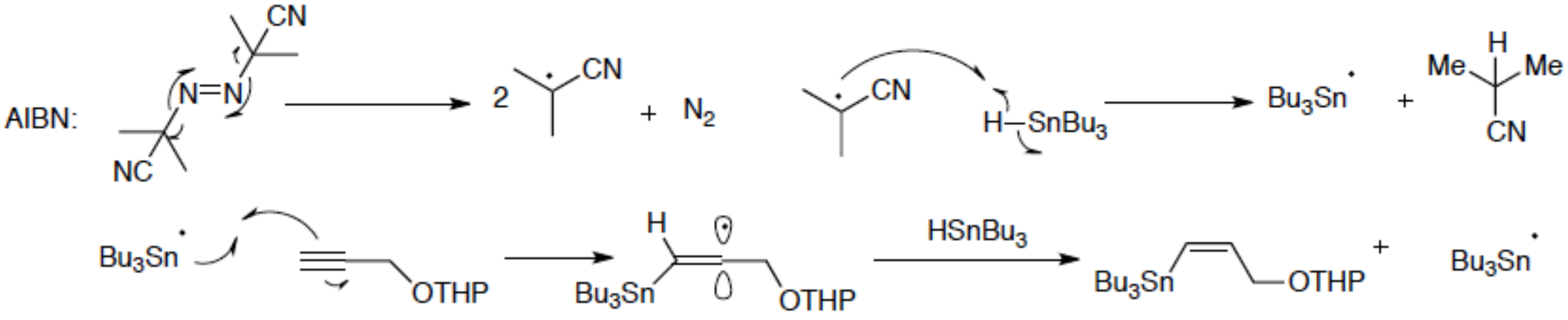
The uncatalyzed hydroboration of alkynes with catecholborane affords stereospecific and regioselective monohydroboration products. The reaction proceeds in a stereospecific *cis* manner with the boron being attached regioselectively at the less hindered carbon atom of the triple bond (E-alkene).



Hydrostannation

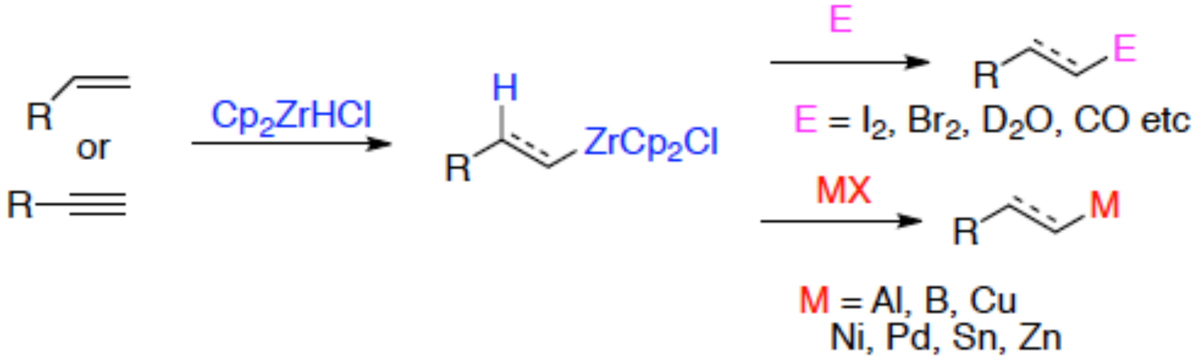
Reaction is initiated by AIBN and proceeds via a radical mechanism. Main regioisomer is formed when tin adds to the terminal carbon to generate a higher substituted radical intermediate. Z product is favored in most cases.

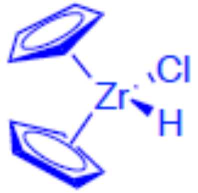




Hydrozirconation

Hydrozirconation is most commonly performed using stoichiometric amount of Schwartz reagent. The intermediate alkyl or alkenyl zirconium can be trapped with an electrophile or used for transmetallation to form new C-M bonds

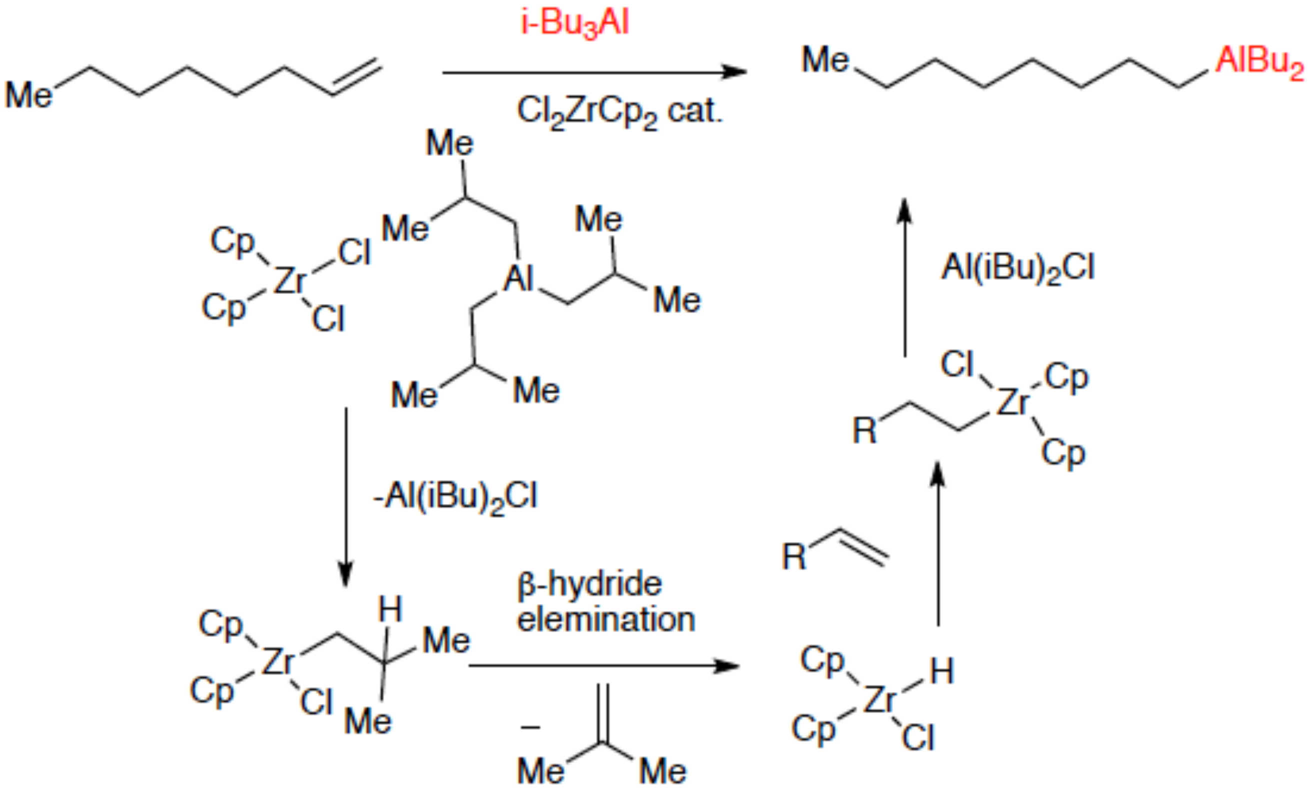




Schwartz reagent

Hydroalumination

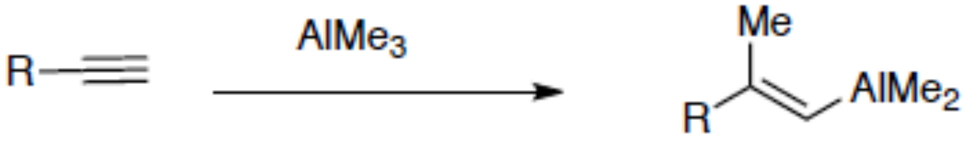
Alkenes can be treated directly with alkylaluminium species in the presence of Zr catalyst to form new C-Al bonds.

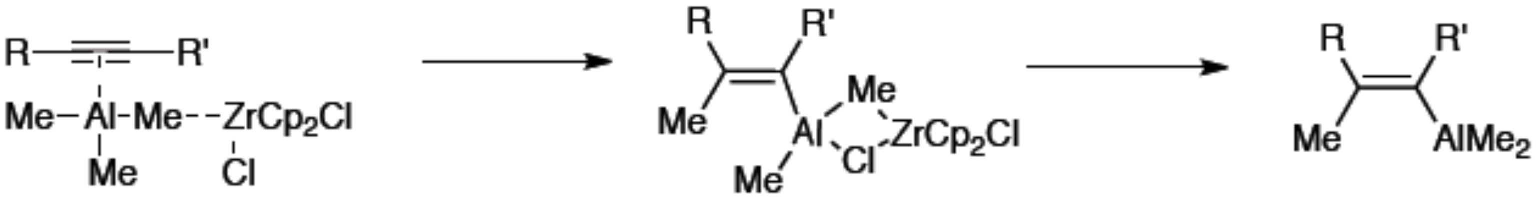


Methylalumination

Direct carboalumination of nonfunctionalized alkynes is possible but is slower and requires elevated temperatures compared to the catalyzed variant. For this reaction to proceed a Zr catalyst is needed.

Regioselectivity is substrate based, but syn addition product is observed.



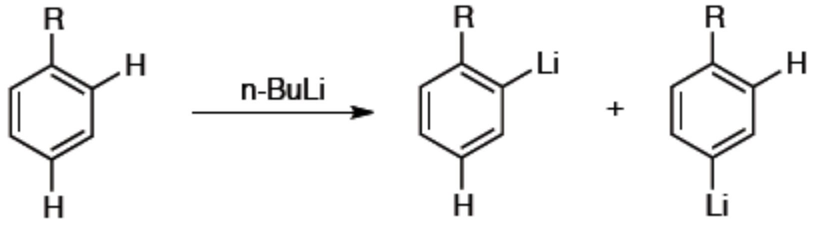


C-H Functionalization

C-H activation and functionalization is an interesting strategy: C-H-bonds are usually not recognized as functional groups but rather considered inert and unreactive. As will be shown, certain organometallic reagents are able to activate C-H bonds and subsequently allow the formation of new C-C or C-heteroatom bonds. There is also a strong interest in C-H functionalization from an economical perspective, as the most (cheap) raw materials for chemical synthesis originate from fossil sources and are therefore hydrocarbons.

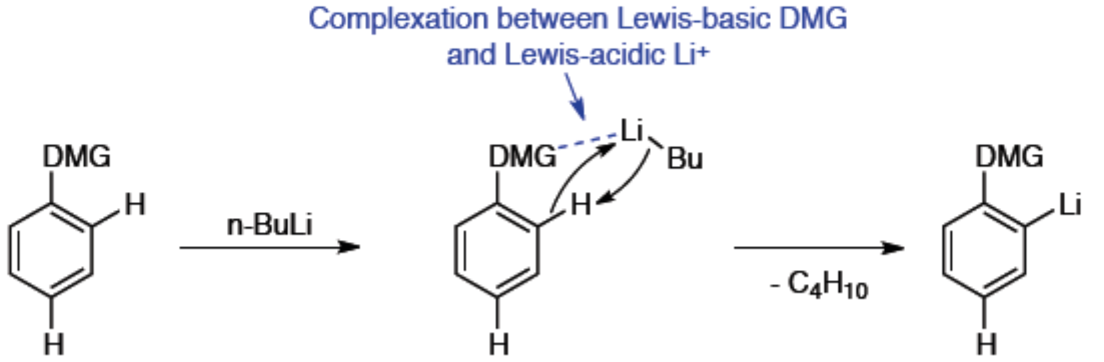
Directed ortho-lithiation

(Aromatic) C-H-bonds can be deprotonated with strong bases, for example *n*-BuLi:



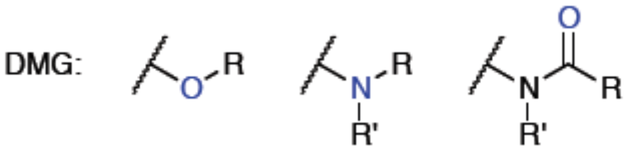
mixture of regioisomers

Usually, a mixture of regioisomers is obtained. This can be altered if the substrate contains a direct metallation group (DMG), or directing group:

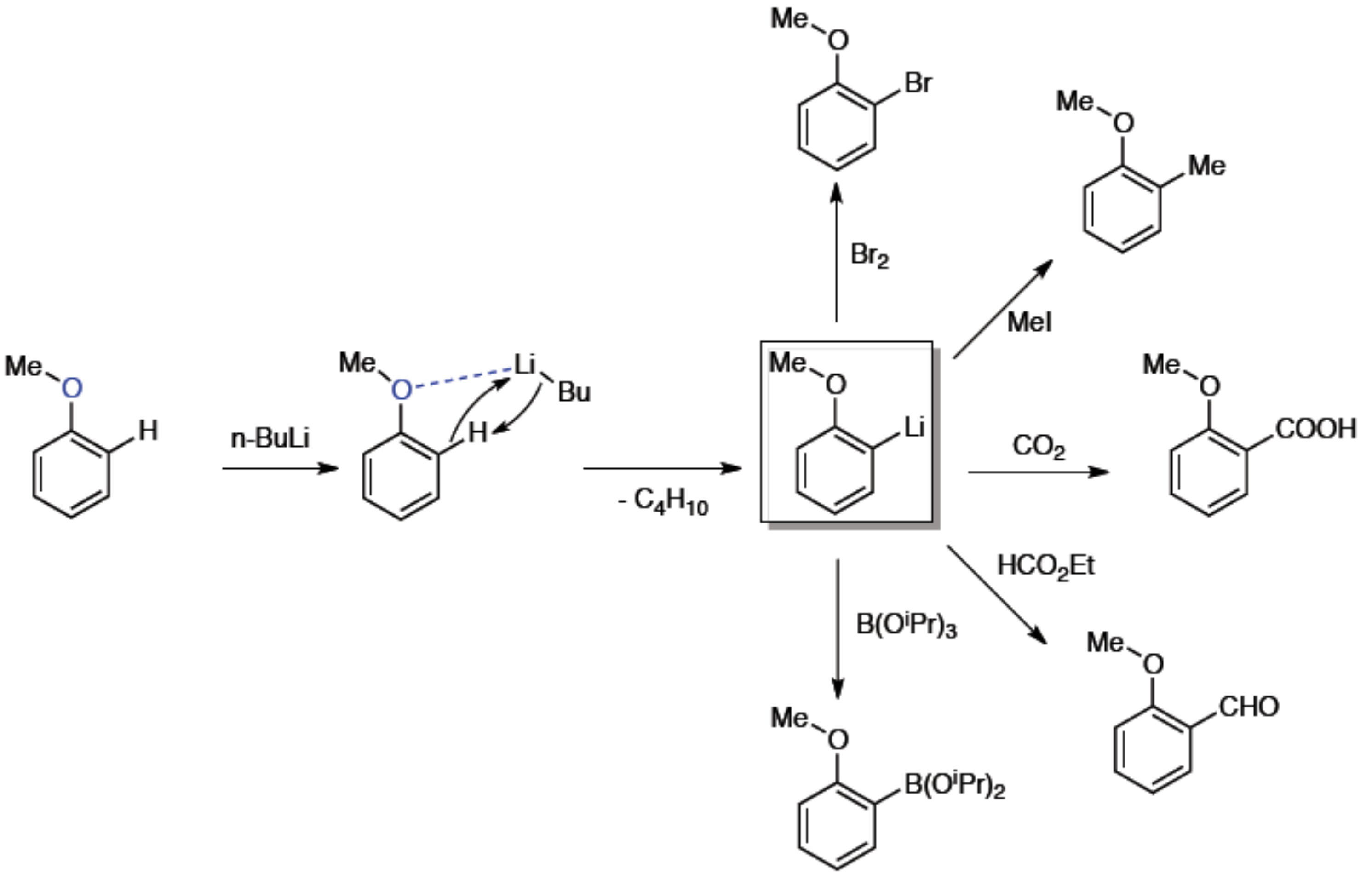


Ortho-selective Lithiation

Most commonly, the DMG are ethers, tertiary amines or tertiary amides (free alcohols or prim./sec. amines/amides would get deprotonated and coordinate its own Li+ instead of directing BuLi):



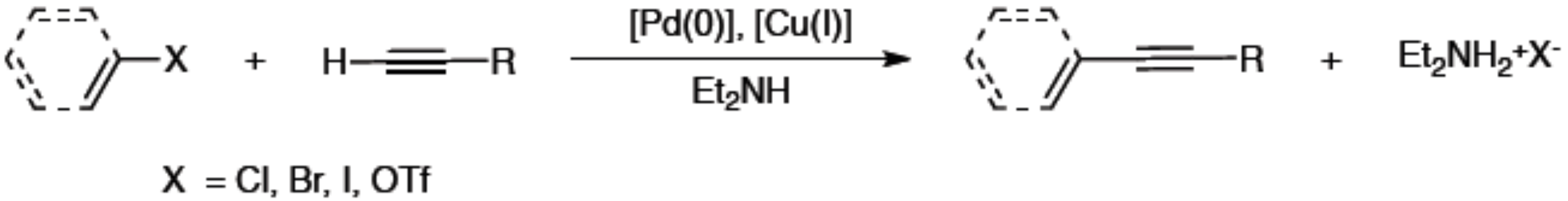
Example:



Me
O
H
n-BuLi
Me
O
Li
Bu
H
- C_4H_{10}
Me
O
Li
Br
Br_2
MeI
Me
CO$_2$
COOH
HCO$_2$Et
CHO
B(O^{i}Pr)$_3$
B(O^{i}Pr)$_2$

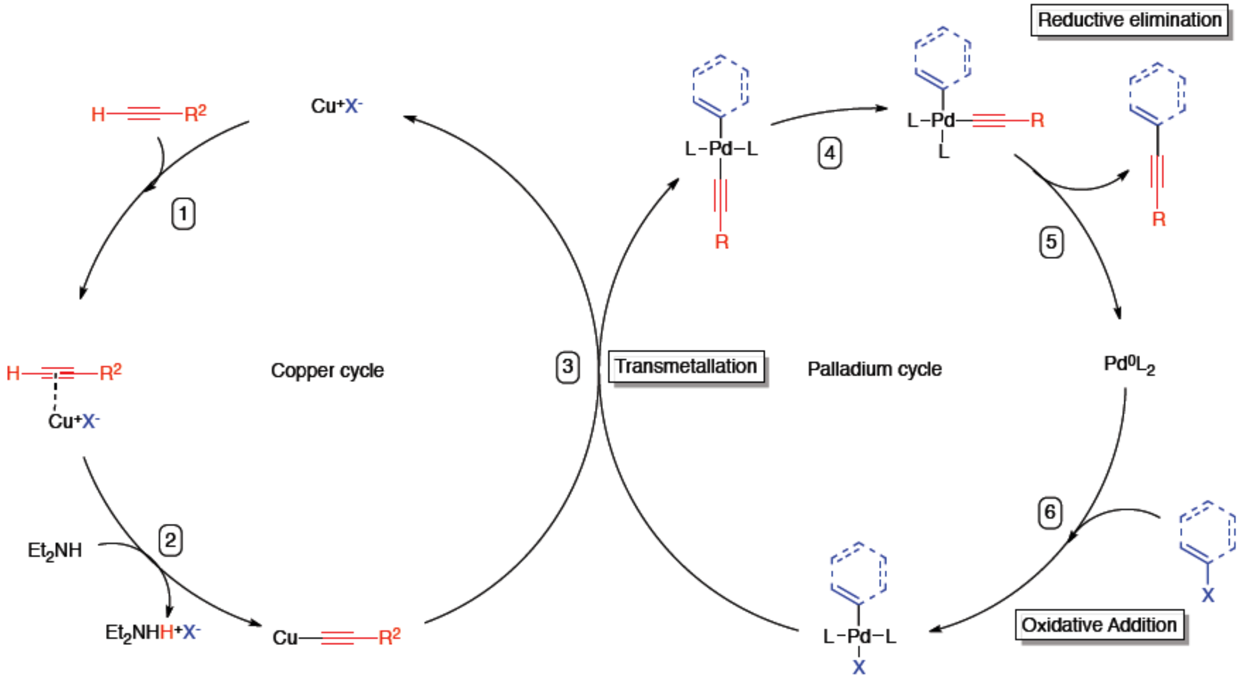
Sonogashira-Coupling

The coupling between aryl/vinyl halides/triflates and terminal alkynes is called Sonogashira coupling. It is related to the “normal” Pd-catalyzed cross-coupling reactions (e.g. the same elementary steps occur), but there are some important differences: Not only is a catalytic amount of Pd(0) required but also a Cu(I) salt.
Instead of a metal-vinyl or –aryl species (like an aryl boronic acid), a terminal alkyne is used. Finally a stoichiometric amount of base (usually an amine base like Et2NH) is crucial to deprotonate the activated alkyne (see catalytic cycle).



Catalytic cycles

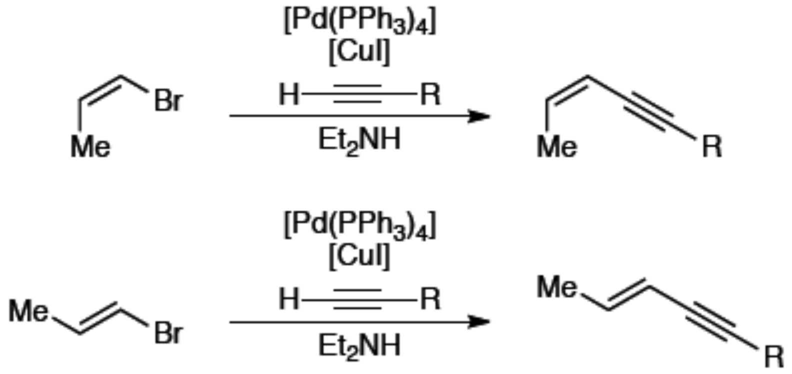
There are two catalytic cycles involved in this reaction:



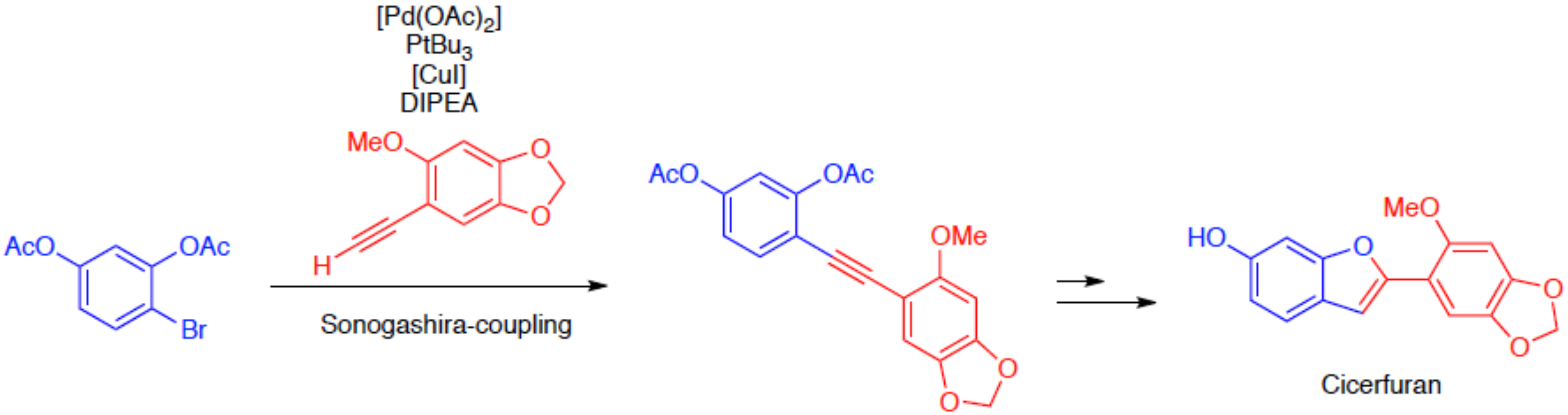
- Step 1: The copper(I) coordinates the terminal alkyne, rendering its proton more acidic.
- Step 2: The proton is removed by the base and a copper acetylide is formed.
- Step 3: **Transmetallation**: The acetylide is transferred onto palladium, forming a trans-alkynyl/vinyl- (aryl)-palladium(II) complex.
- Step 4: Isomerization to the corresponding cis-complex.
- Step 5: **Reductive elimination:** The cis-complex eliminates the product (en-yne or aryl-yne), forming a palladium(0) complex.
- Step 6: **Oxidative addition:** The palladium(0) complex inserts in the sp2-X bond in the step, completing the catalytic cycle.

Applications

The stereochemistry at the olefin is conserved:



The Sonogashira coupling is, due to its relatively mild conditions and chemoselectivity, widely employed in organic synthesis, for example in natural product synthesis:

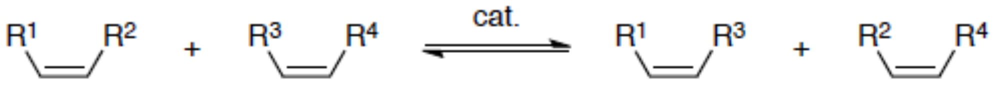


Tetrahedron, **2003**, 59, 7509-7513

Olefin metathesis

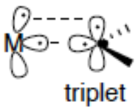
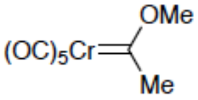
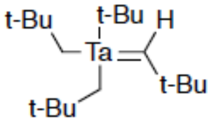
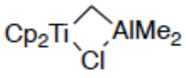
History of metathesis and *Fischer* Carbenes

The metathesis reaction describes the metal-catalyzed redistribution of carbon-carbon (multiple) bonds, most commonly olefinic C-C double bonds (Olefin metathesis). In the 1950s it was discovered that transition metals together with alkylating reagents or transition metals on solid support catalyze scrambling of carboncarbon double bonds:

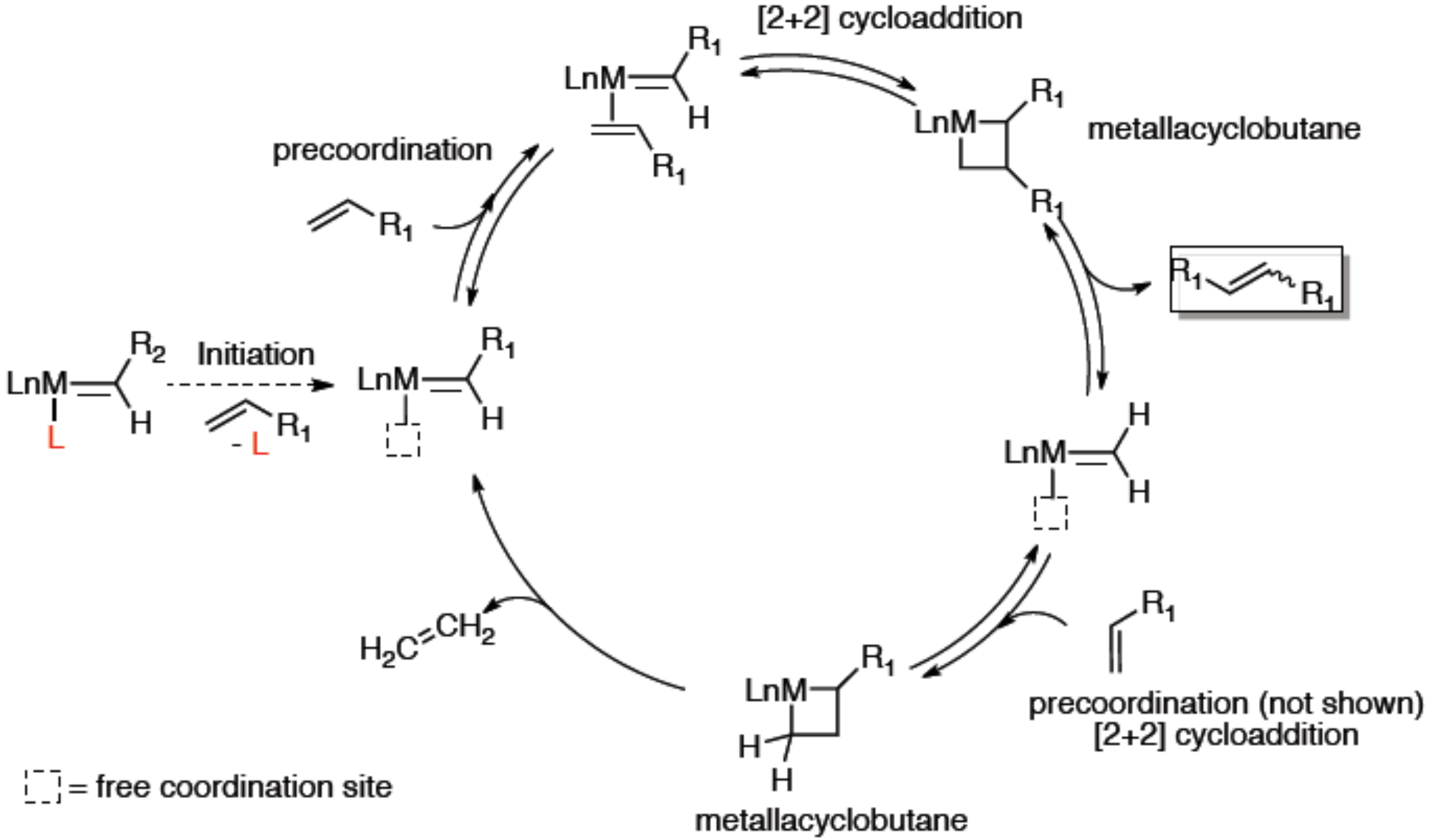


cat.: e.g. $WOCl_4/EtAlCl_2$; MoO_3/SiO_2

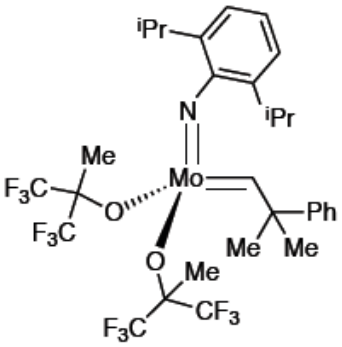
The employed catalysts are highly active and found important applications in large scale industrial processes (e.g. Shell Higher Olefin Process, SHOP), but have several drawbacks: Most importantly the catalysts are so highly reactive (Lewis acidity, oxophilicity) that they exhibited very low to no functional group tolerance which limits the application in organic synthesis. Also, the catalytic systems were often not well defined and only small amounts of the active catalytic species were formed during the reaction, which renders the whole process hard to control. Mechanistic insights were obtained through the work of *Chauvin* and *Hérisson* in 1971. In 1990, a breakthrough in terms of reactivity and chemoselectivity was reached by the application of molybdenum (*Schrock* 1990) and ruthenium (*Grubbs* 1994) carbenes as catalysts. Metal carbenes are historically divided into two categories, the *Fischer* carbenes and the *Schrock* carbenes. A short and simplified overview:

Fischer carbenes	**Schrock carbenes**
Low oxidation state metals	High oxidation states
Middle and late transition metals (e.g. Fe, Mo, Cr)	Early transition metals (Ti, Ta)
π–electron acceptor metal ligands (e.g. CO)	π–donor metal ligands (e.g. alkyl)
π–donor substituents on methylene group (e.g. OR,NHR)	Hydrogen and alkyl substituents on methylene group
Carbene carbon reacts as electrophile	Carbene carbon reacts nucelophilic
Binding situation: 	Binding situation: 
Example: 	Example:  Tebbe reagent

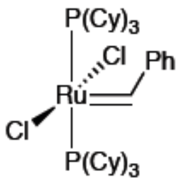
Catalytic cycle



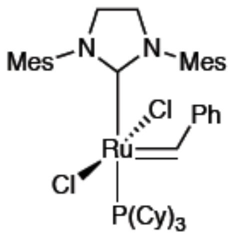
Common catalysts



Schrock-Catalyst



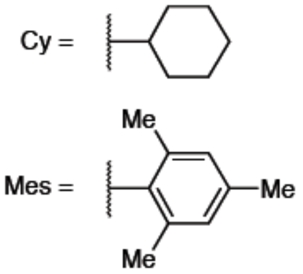
First generation Grubbs

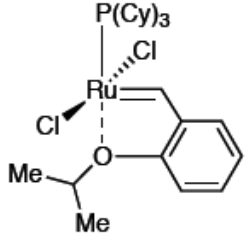


Second generation Grubbs

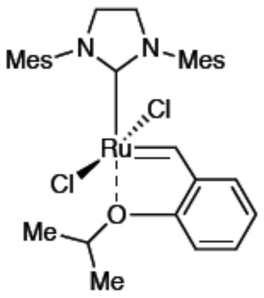
high reactive but air and water sensitive
lower functional group tolerance

air and water stable
high functional group tolerance





First generation Hoveyda-Grubbs

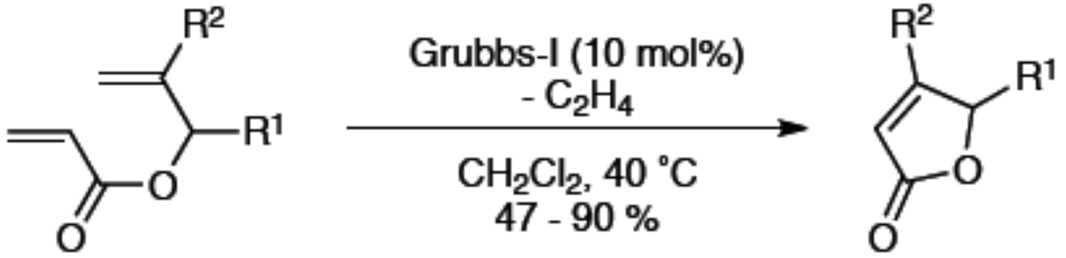


Second generation Hoveyda-Grubbs

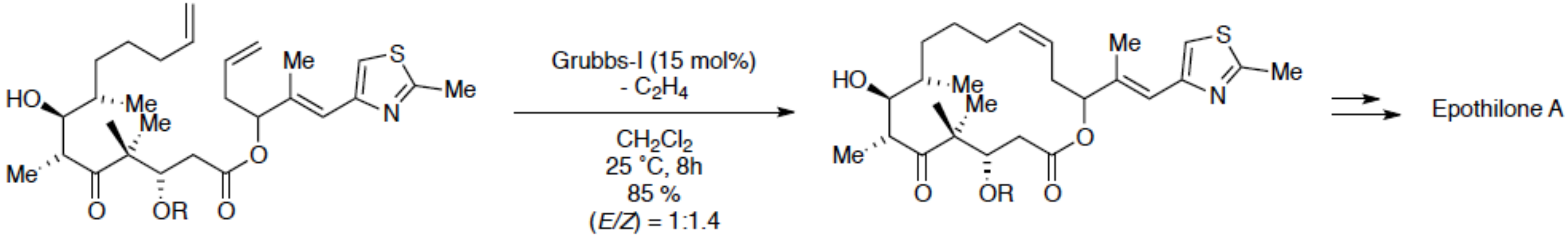
The Mo-containing *Schrock*-catalyst displays very high reactivity but does not tolerate oxygen-containing functional groups like carboxylic acids, alcohols or aldehydes. Also it is very air and moisture sensitive and has to be handled in a glove box. The ruthenium based *Grubbs* catalysts are less active compared to the *Schrock* catalyst but they tolerate alcohols, amides, aldehydes and carboxylic acids and the catalysts are air and water stable; there are even variants in which the metathesis reaction is run in aqueous solvent systems. The second generation of the catalyst is generally slightly more reactive due to the trans effect of the NHC ligand: the ruthenium-phosphorous bond is weakened and facilitates the necessary ligand dissociation. The mayor advantage of the *Hoveyda-Grubbs* catalysts is a higher stability of the catalyst that allows higher reaction temperatures.

Ring-closing metathesis (RCM)

One of the most important applications of metathesis in organic synthesis is to form cycles (5 members to "large"). The thermodynamic driving force is usually the release of ethylene. The (*E/Z*)-selectivity depends on both the catalyst and the substrate and is not easy to predict. Up to eight-membered rings, (*Z*)-isomers are usually obtained.



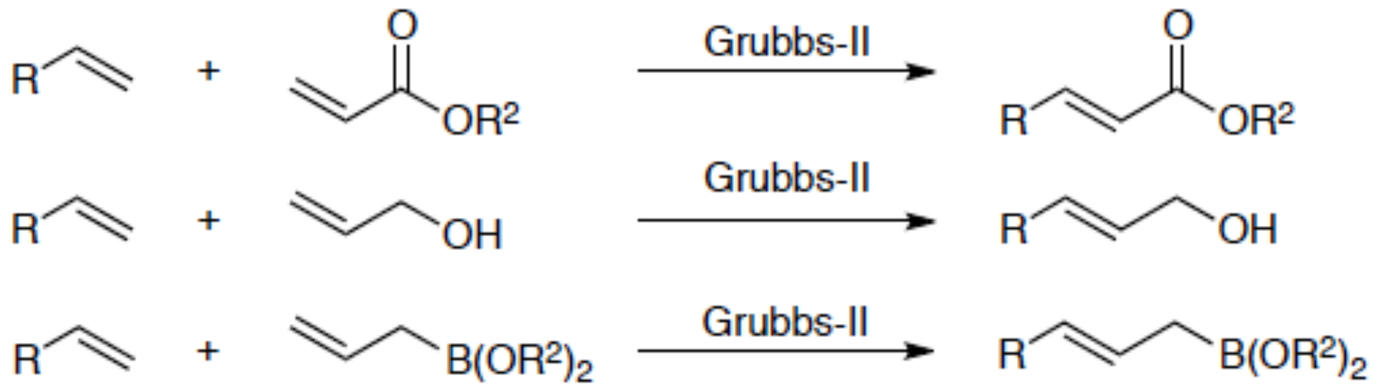
An example of RCM employed to form the 16-membered ring structure in the synthesis of Epothilone A, a natural product.



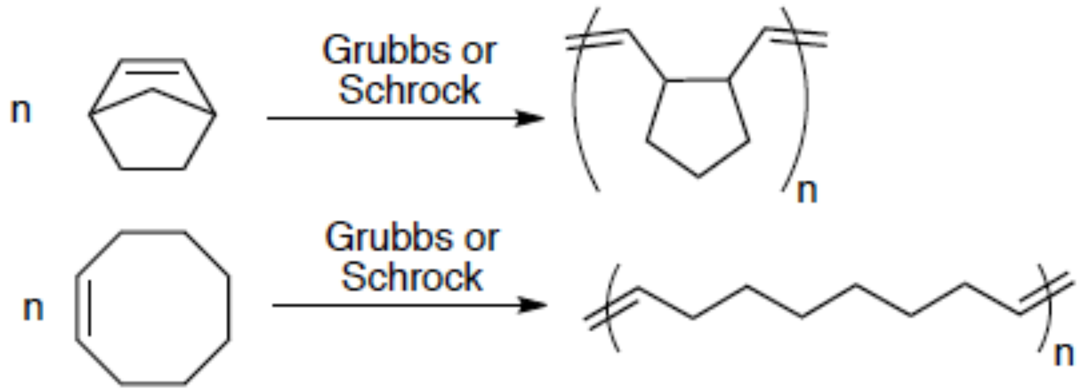
ACIE, **1997**, 36, 166-168

Cross Metathesis (CM)

The intermolecular metathesis between two different olefins is called cross metathesis. Challenges are to avoid homodimerization and (*E/Z*)-selectivity, which can be achieved in many cases by choosing the right reagents and catalysts.



Ring opening metathesis polymerization (ROMP)



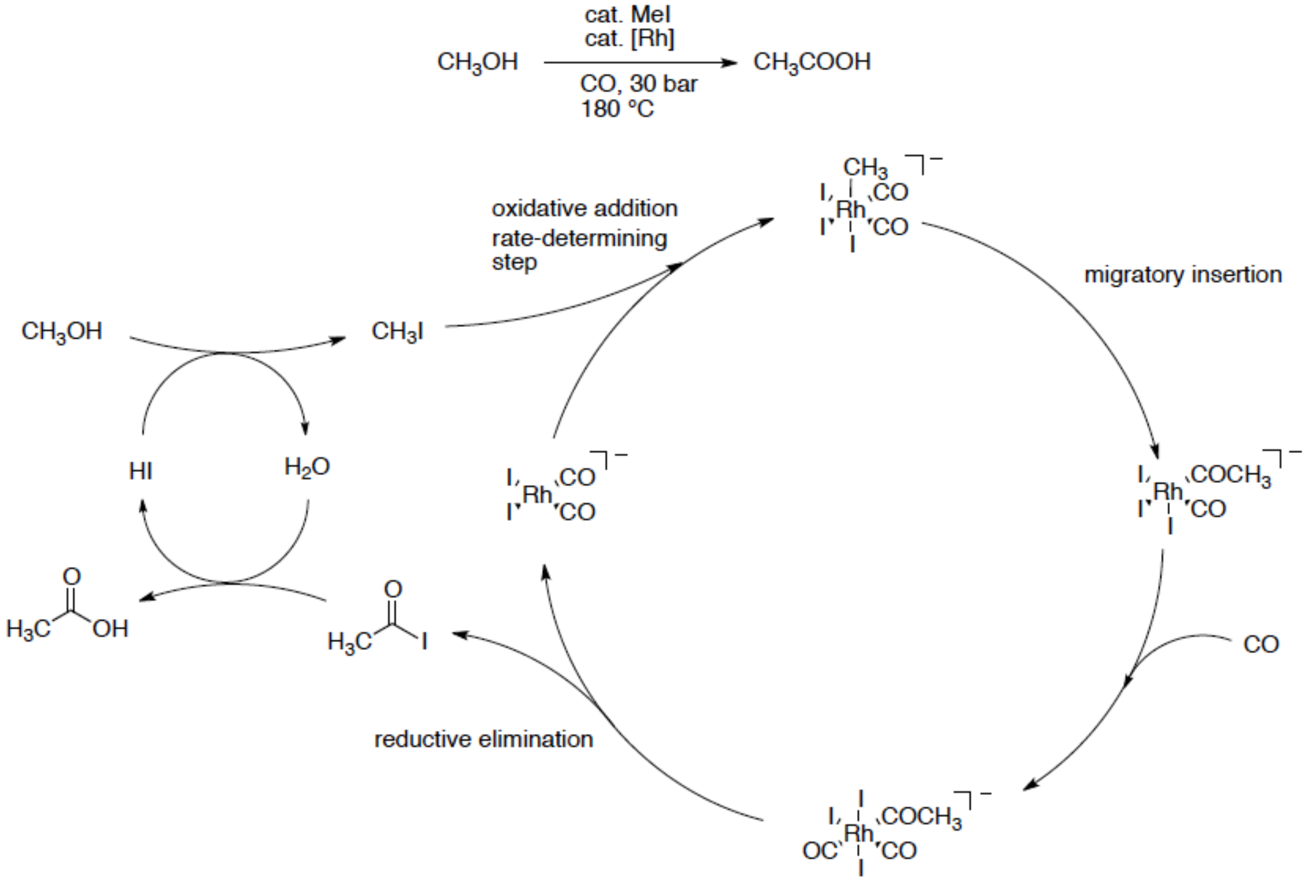
ROMP is very important in polymer chemistry. With more elaborate catalysts, properties like tacticity can be controlled.

Industrially important reactions

Monsanto acetic acid process

Scale – over 8 million tons a year of acetic acid derivatives are produced by carbonylation of methanol. The process is 100% atom economic.

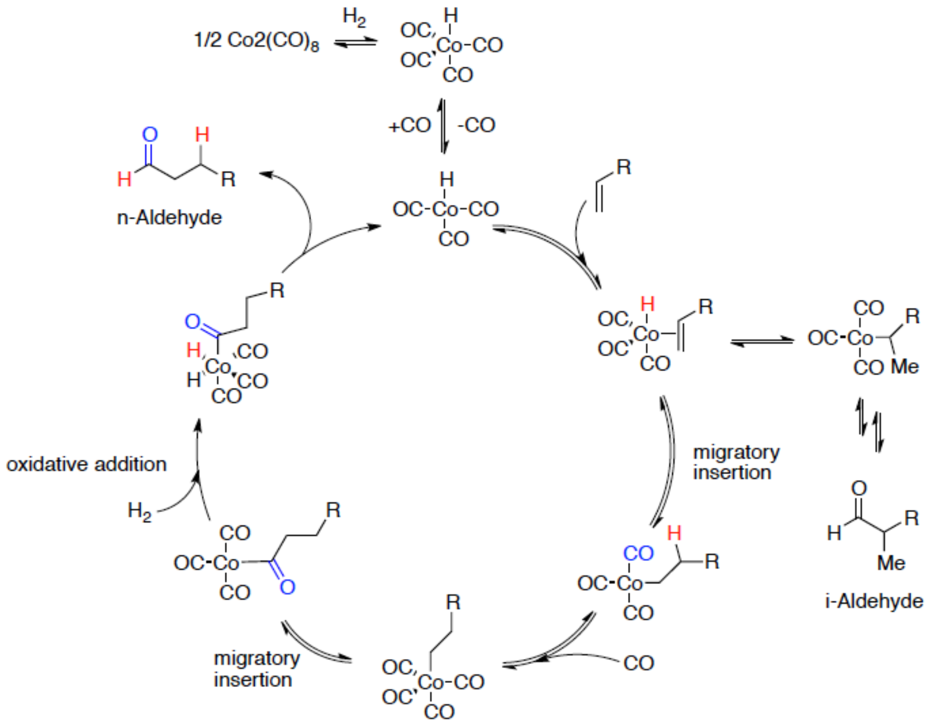
MeI is used in catalytic amount as an initiator of the reaction.



$$CH_3OH \xrightarrow[\text{CO, 30 bar, 180 °C}]{\text{cat. MeI, cat. [Rh]}} CH_3COOH$$

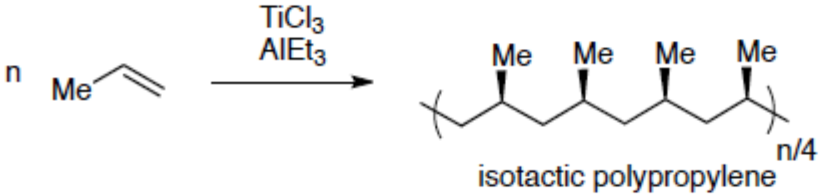
Hydroformylation

Hydroformylation is the conversion of an olefin to an aldehyde by addition of an extra carbon atom. It is the most industrially important reaction for preparation of aldehydes. The hydroformylation is the most important application of homogenous catalysis on industrial scale with worldwide production capacities of about 6 million ton per year (2002).
Product distribution can be controlled with catalyst. Typical catalysts HCo(CO)4, HRh(CO)2(PR3)2 and others.



Ziegler-Natta polymerization

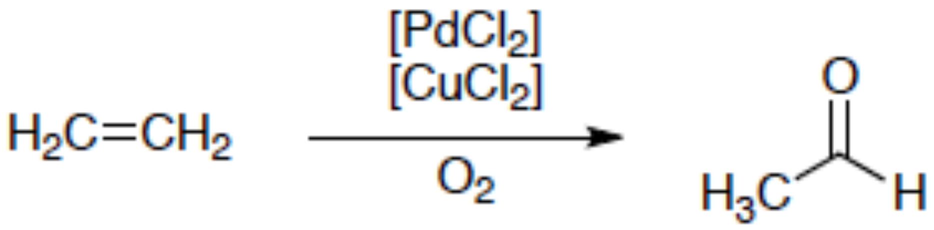
The Ziegler-Natta polymerization is a very important process in polymeric chemistry to polymerize alkenes, for example propene. It is based on various organometallic catalysts that were first developed by K. Ziegler and G. Natta in the 1950s. The first catalytic system was a mixture of TiCl3 and AlEt3, which gave interestingly only isotactic polymers:



Modern catalytic systems, including for example metallocenes, are very efficient catalysts, the loading can go down to 1 g Ti per 150’000 kg polymer. The worldwide production of polypropylene with the Ziegler-Nattaprocess was 45 billion tons in 2007 (ca. 80 billion CHF).

Wacker oxidation

The Wacker oxidation# (or Wacker process) is used to synthesize aldehydes and ketones from the corresponding alkenes. The reaction is catalytic in palladium(II) and copper(II) and requires a stoichiometric oxidant, most commonly oxygen gas or simply air. The most important application is the synthesis of acetaldehyde, which is done on a billion ton scale per year:



Unlike the hydroformylation process, there is no chain extension and no need for (more) expensive rhodium catalysts.

Named after the german chemical company Wacker, not after a chemist.

Catalytic cycle