Organometallic Chemistry and Homogeneous Catalysis

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Methanol carbonylation (Monsanto Process)

Carbonylation reactions

Carbonylation of alcohols:

$$CH_3OH + CO \longrightarrow CH_3COOH$$

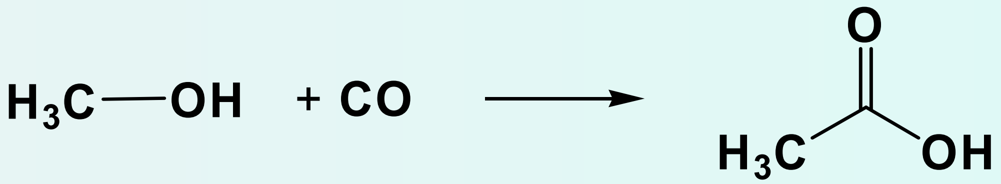
Carbonylation of alkenes and alkynes:

$$R\text{-}CH{=}CH_2 + CO + H_2O \longrightarrow R\text{-}CH_2\text{-}CH_2\text{-}COOH$$

$$R\text{-}CH{=}CH_2 + CO + H_2 \longrightarrow R\text{-}CH_2\text{-}CH_2\text{-}CHO$$

Prior to 1970, acetic acid was made using cobalt catalysts (BASF process)

In 1970 Monsanto commercialized a rhodium carbonyl iodide catalyst that is commonly called the Monsanto Acetic Acid Process



Precatalyst: $[Rh(CO)_2I_2]_-AsPh_{4+}$

Other possible precatalysts: $RhCl_3{*}3H_2O$, Rh_2O_3

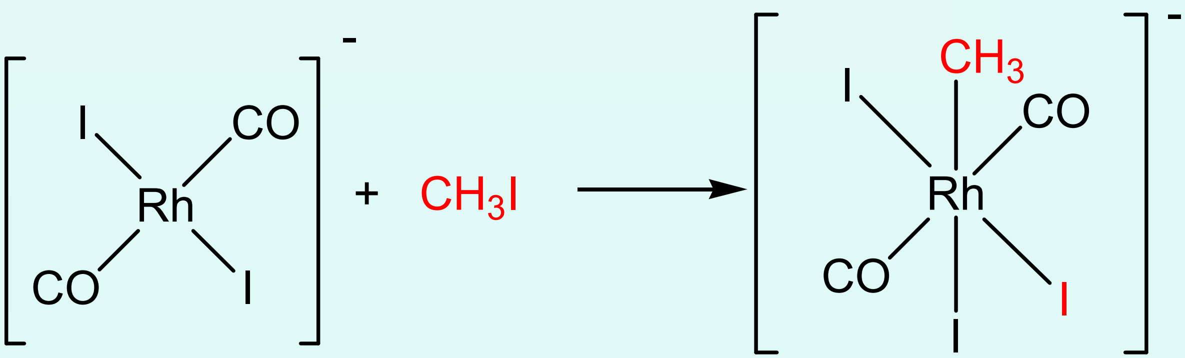
For the reaction to be possible the source of I_- should exist (usually HI)

Mechanism of “Monsanto” carbonylation:

1. CH_3I generation:

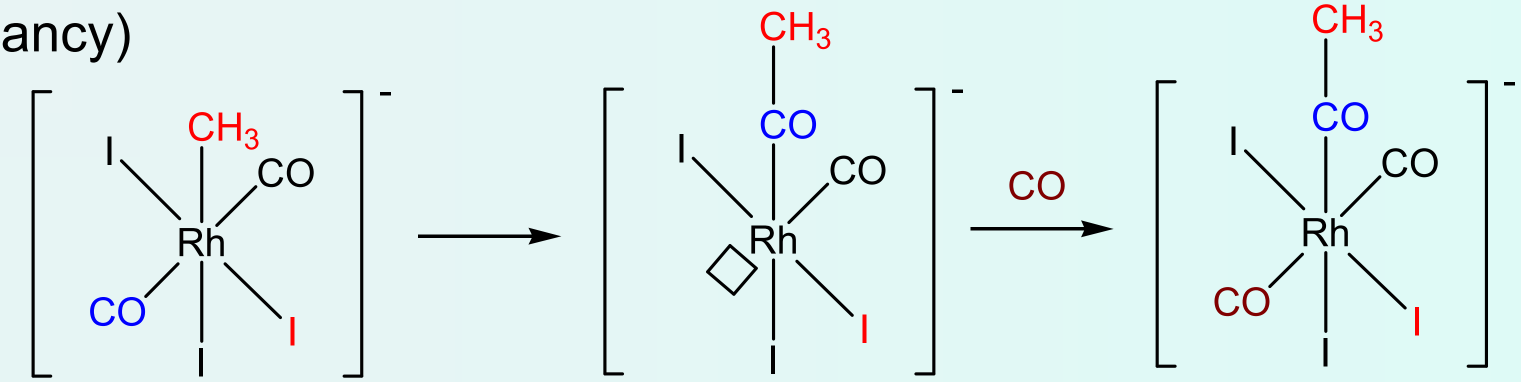
$$CH_3OH + HI \rightleftarrows CH_3I + H_2O$$

2. Oxidative addition of CH_3I to the Rh^I-complex

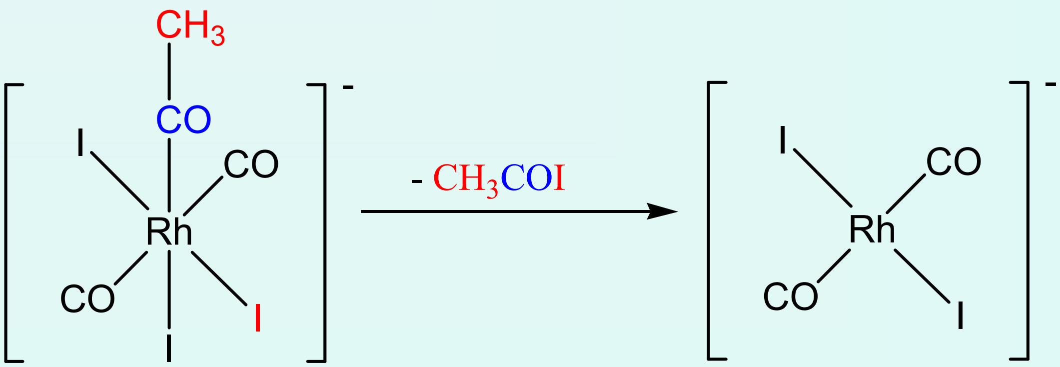


This is the slowest stage of the process

3. Migration insertion of CO (plus new CO addition to the coordination vacancy)



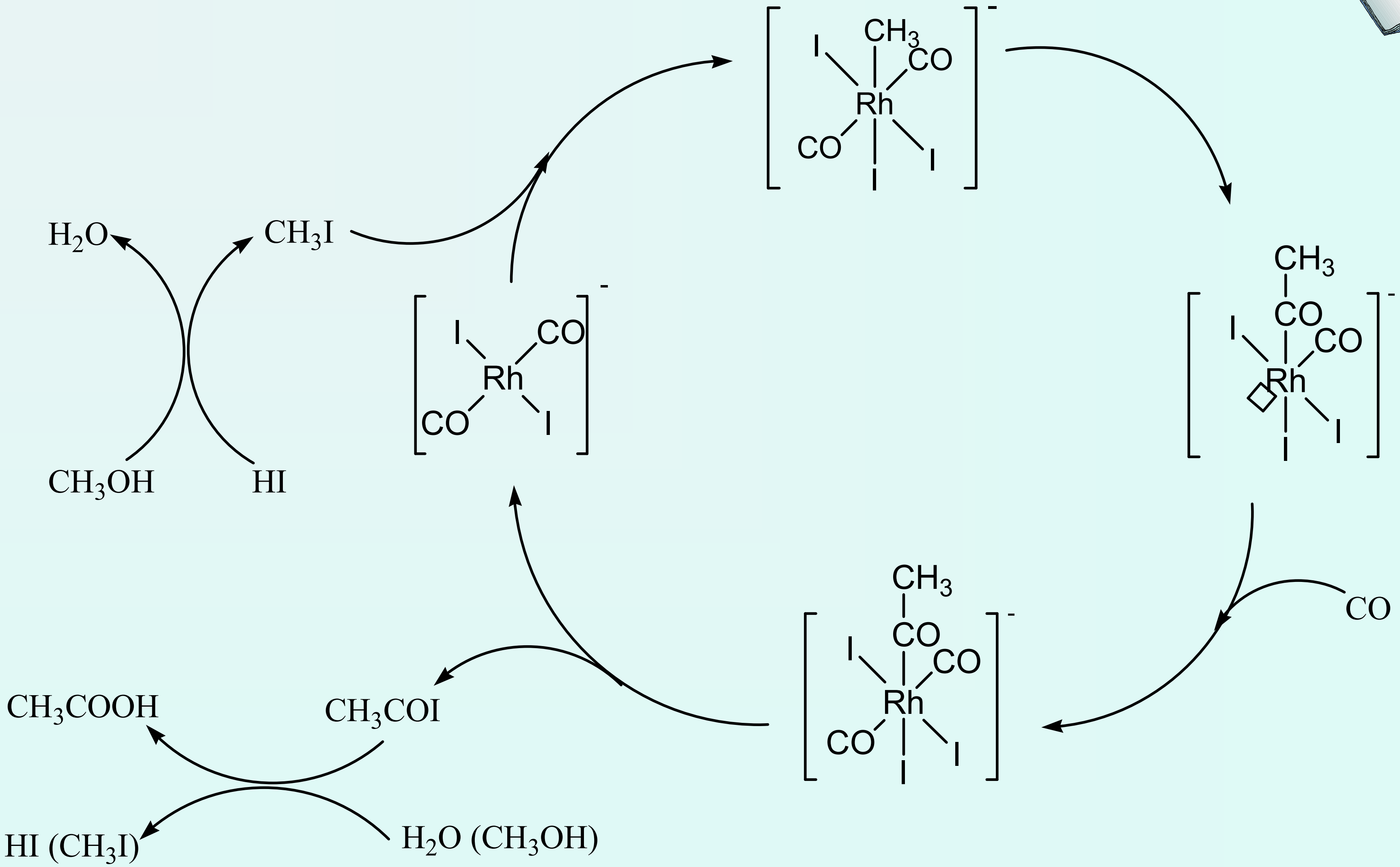
4. Reductive elimination of CH_3COI



5. Formation of acetic acid through the following processes:

$$CH_3COI + H_2O \longrightarrow CH_3COOH + HI$$

$$CH_3COI + CH_3OH \longrightarrow CH_3COOH + CH_3I$$


H2O
CH3I
CH3OH
HI
[Rh(CO)2I2]-
[CH3Rh(CO)2I3]-
[CH3CORh(CO)I3]-
CO
[CH3CORh(CO)2I3]-
CH3COI
CH3COOH
HI (CH3I)
H2O (CH3OH)

Other catalysts in the alcohols carbonylation

Cobalt is less effective catalyst in this reaction:

	Cobalt	**Rhodium**
Concentration	~ 10^{-1} M	~ 10^{-3} M
Temperature	~ 230° C	~180° C
Pressure	500-700 atm	30-40 atm
Selectivity	90%	> 99%

The main reason is that CH_3I oxidative addition to Co takes place much slower than to Rh

Iridium-based catalyst system was announced in 1999 by Cativa

The rate determining step for Ir is the migratory insertion of the Ir-CH_3 and Ir-CO ligands. The MeI oxidative addition step is faster for Ir due to its lower electronegativity

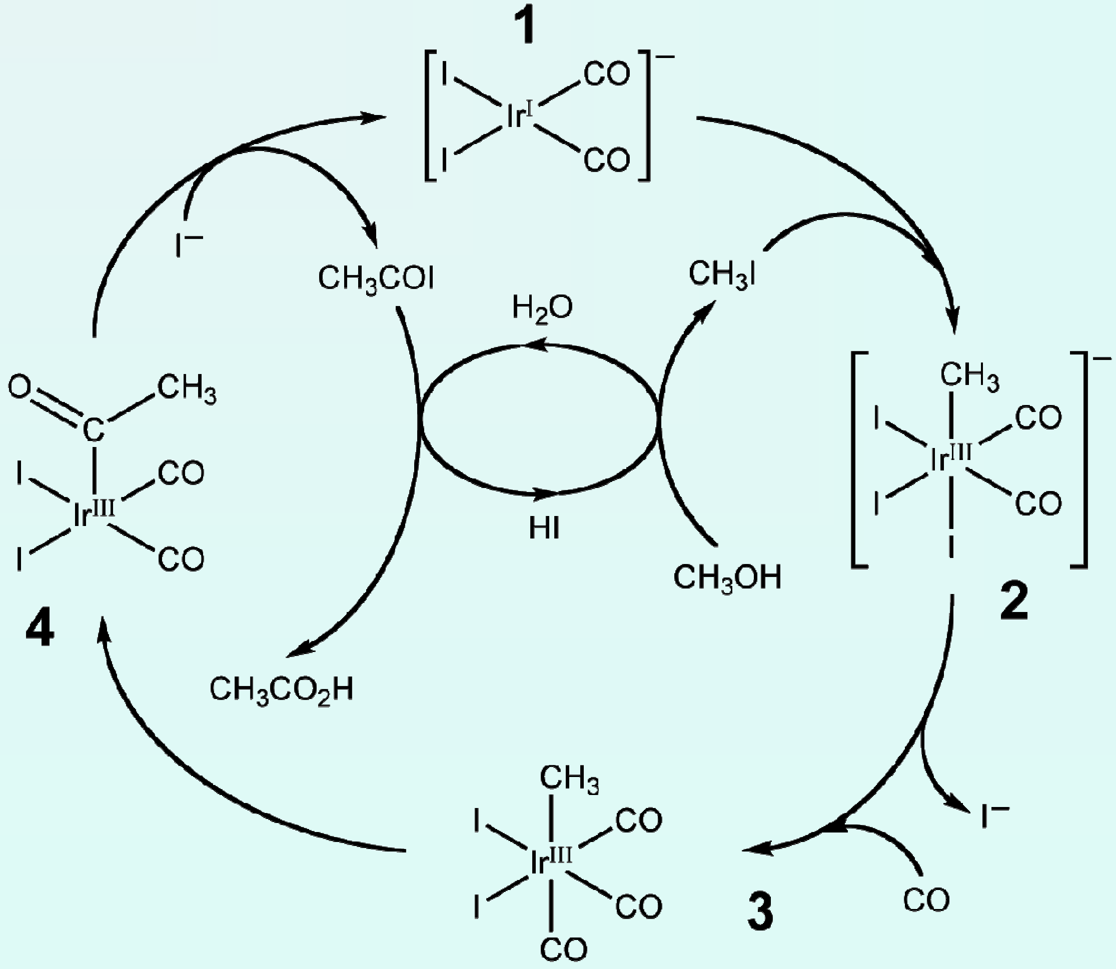
The switch from rhodium to iridium:

1) allows the use of less water in the reaction mixture

- reduces the number of drying columns necessary

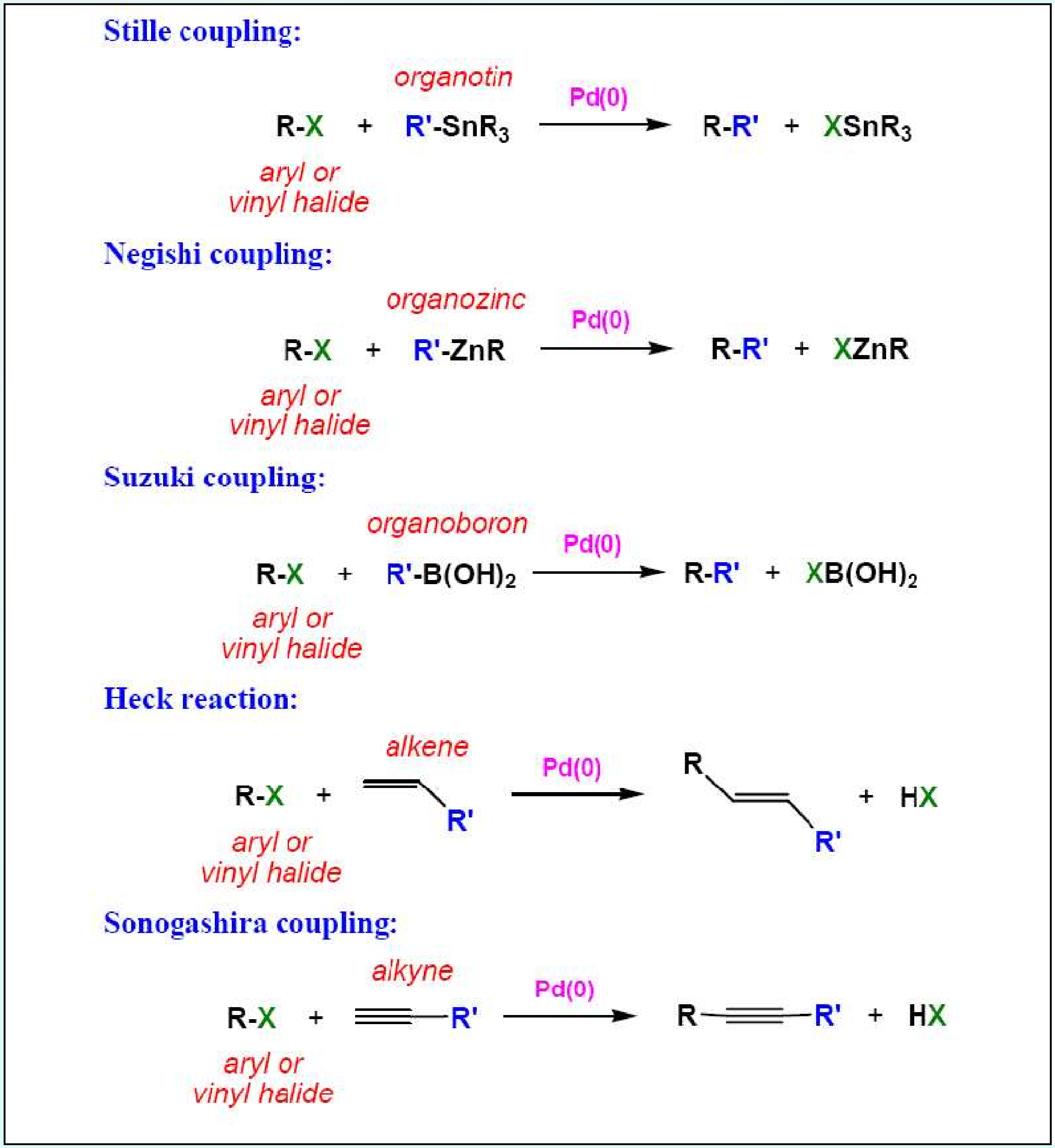
- suppresses the water-gas shift reaction

2) allows to generate less propionic acid as a by-product



C-C Coupling reactions

Reaction	year	Reactant A		Reactant B		homo/ cross	catalyst	remark
Wurtz reaction	1855			R-X	sp^3	homo	Na	
Glaser coupling	1869			R-X	sp	homo	Cu	
Ullmann reaction	1901			R-X	sp^2	homo	Cu	
Gomberg-Bachmann reaction	1924			R-N_2X	sp^2	homo		requires base
Cadiot-Chodkiewicz coupling	1957	alkyne	sp	R-X	sp	cross	Cu	requires base
Castro-Stephens coupling	1963	R-Cu	sp	R-X	sp^2	cross		
Kumada coupling	1972	R-MgBr	sp^2, sp^3	R-X	sp^2	cross	Pd or Ni	
Heck reaction	1972	alkene	sp^2	R-X	sp^2	cross	Pd	requires base
Sonogashira coupling	1973	alkyne	sp	R-X	sp^3 sp^2	cross	Pd and Cu	requires base
Negishi coupling	1977	R-Zn-X	sp^3, sp^2, sp	R-X	sp^3 sp^2	cross	Pd or Ni	
Stille cross coupling	1977	R-SnR_3	sp^3, sp^2, sp	R-X	sp^3 sp^2	cross	Pd	
Suzuki reaction	1979	R-$B(OR)_2$	sp^2	R-X	sp^3 sp^2	cross	Pd	requires base
Hiyama coupling	1988	R-SiR_3	sp^2	R-X	sp^3 sp^2	cross	Pd	requires base
Buchwald-Hartwig reaction	1994	R_2N-R SnR_3	sp	R-X	sp^2	cross	Pd	N-C coupling, second generation free amine
Fukuyama coupling	1998	RCO(SEt)	sp^2	R-Zn-I	sp^3	cross	Pd	



Stille coupling:

$$R\text{-}X + R'\text{-}SnR_3 \xrightarrow{Pd(0)} R\text{-}R' + XSnR_3$$

Negishi coupling:

$$R\text{-}X + R'\text{-}ZnR \xrightarrow{Pd(0)} R\text{-}R' + XZnR$$

Suzuki coupling:

$$R\text{-}X + R'\text{-}B(OH)_2 \xrightarrow{Pd(0)} R\text{-}R' + XB(OH)_2$$

Heck reaction:

Sonogashira coupling:

$$R\text{-}X + {\equiv}\!\!-R' \xrightarrow{Pd(0)} R-{\equiv}-R' + HX$$

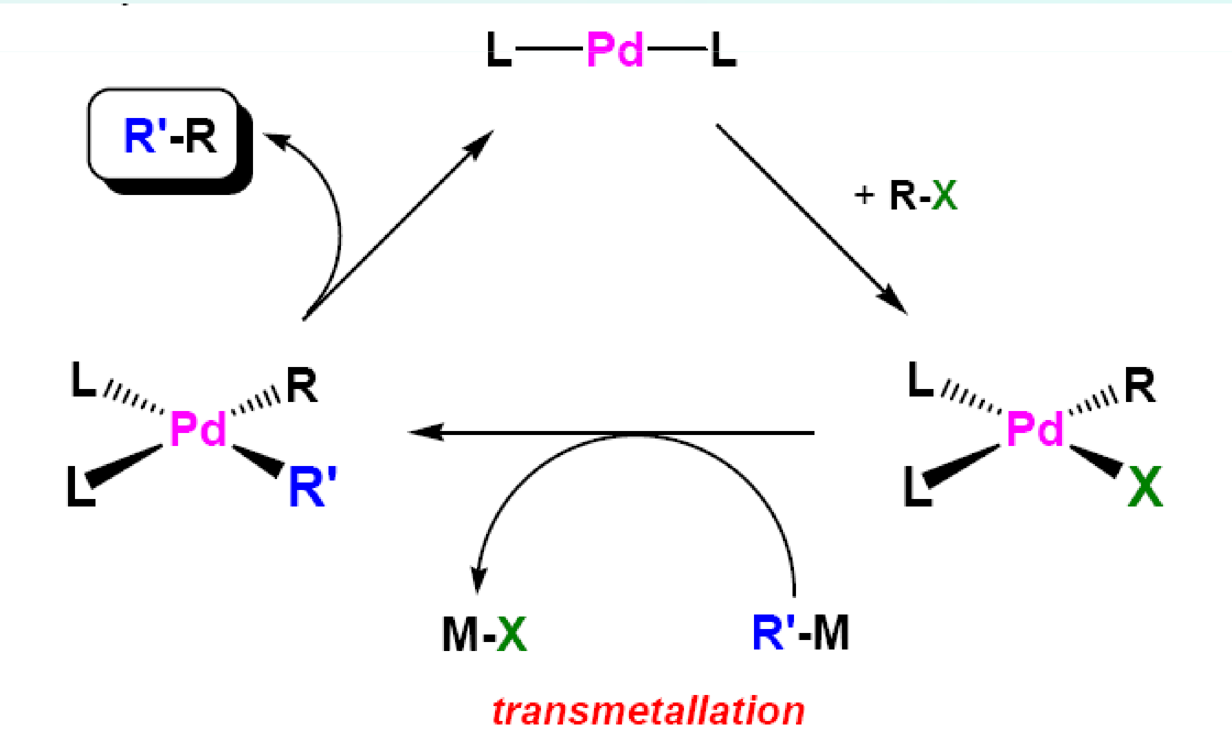
Coupling reactions often bear the name of their discoverer

Common mechanism of Pd-catalyzed C-C coupling

$$R\text{-}X \quad + \quad R'\text{-}M \xrightarrow{Pd(0)} R\text{-}R' \quad + \quad MX$$

$M = MgX, ZrCp_2Cl, ZnX, SnR_3, B(OR)_2, AlMe_2, SiR_3, Cu, \ldots$

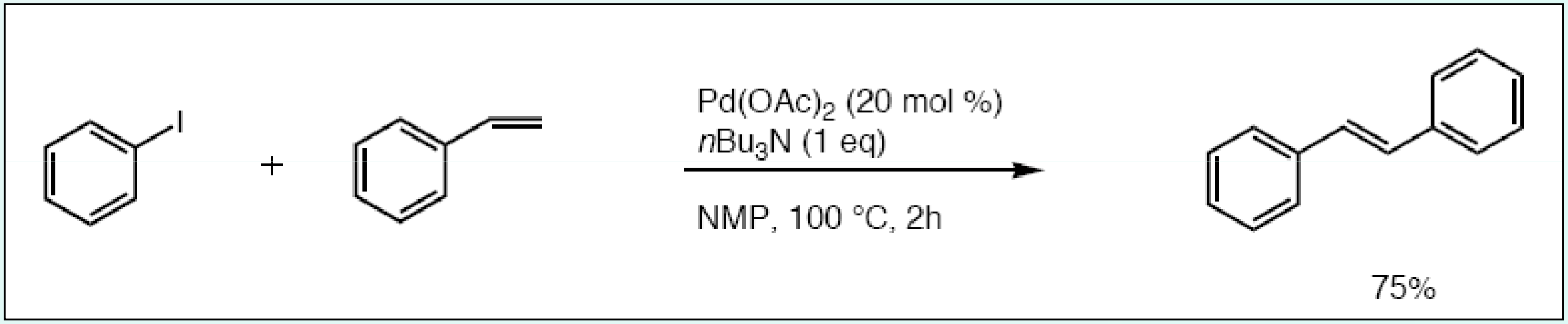
The mechanism involves oxidative addition of the halide or triflate to the initial Pd(0) phosphine complex to form a Pd(II) species. The key slow step is a transmetallation



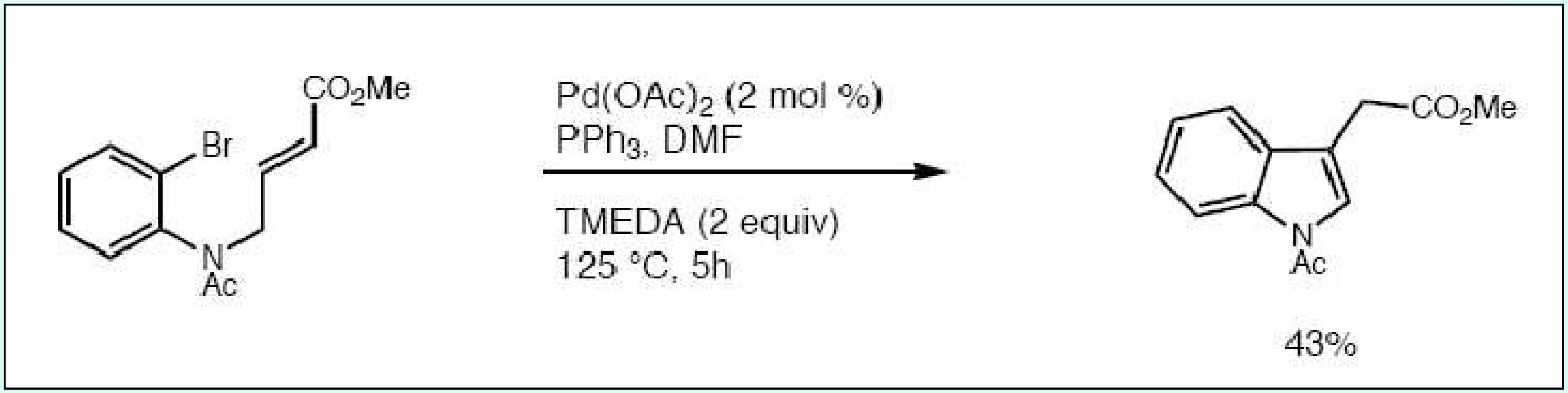
Heck reaction (historical perspective):

In the late 1960s, palladium(0)-mediated arylation and alkenylation of alkenes were independently discovered by Japanese (Moritani-Fujiwara) and American (Heck) groups. The stoichiometric version of the reaction was further refined into a catalytic system, mainly by Richard Heck and his group

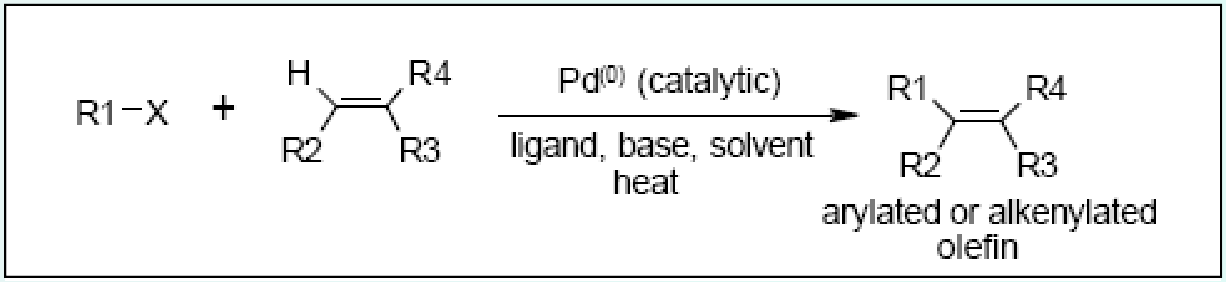
The first intermolecular Heck reaction (catalytic) was reported by Heck in 1972



The first intramolecular Heck reaction was reported by Mori and Ban in 1977



The Heck reaction is a palladium-catalyzed cross-coupling reaction of organyl halides to alkenes



The substituents can be electron-donating or electron-withdrawing, but the electron poor olefins generally give higher yields

The degree of substitution of the olefin plays an important role in the rate of the reaction. Generally, the more substituted olefins undergo a slower Heck reaction

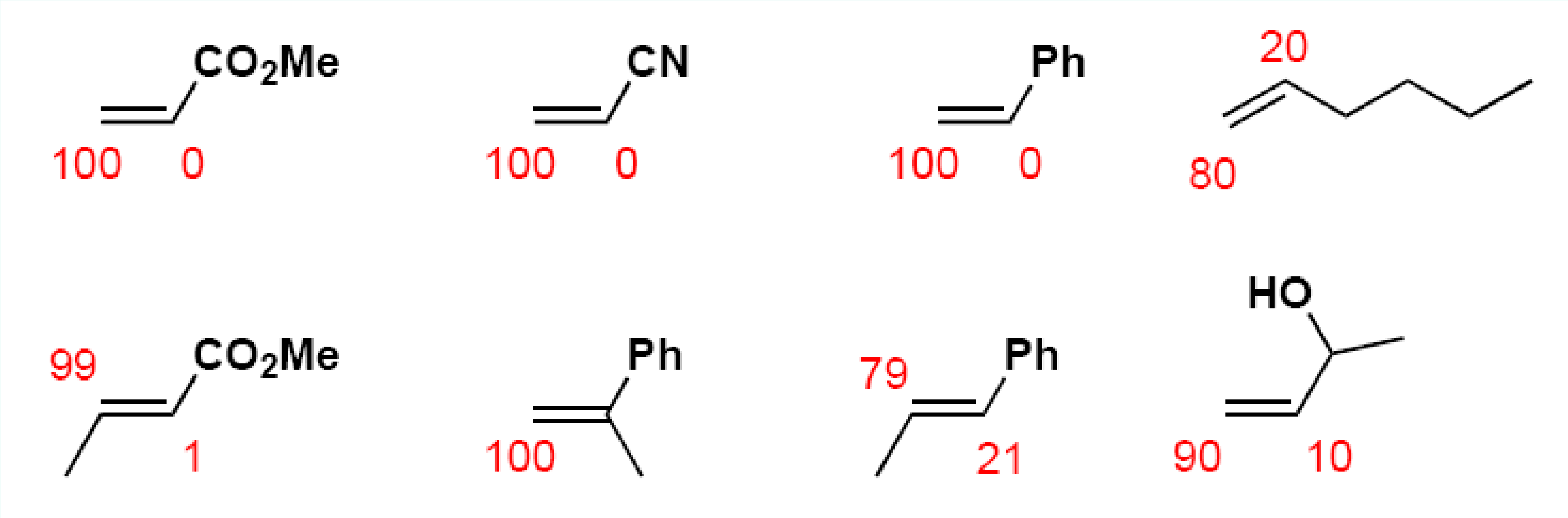
The X group on the aryl or vinyl substituent also plays an important role in the reaction rate: X= I > Br ~ OTf >> Cl

The R1 group usually is aryl, heteroaryl, alkenyl, and benzyl. Alkyl groups are rarely found at position R_1

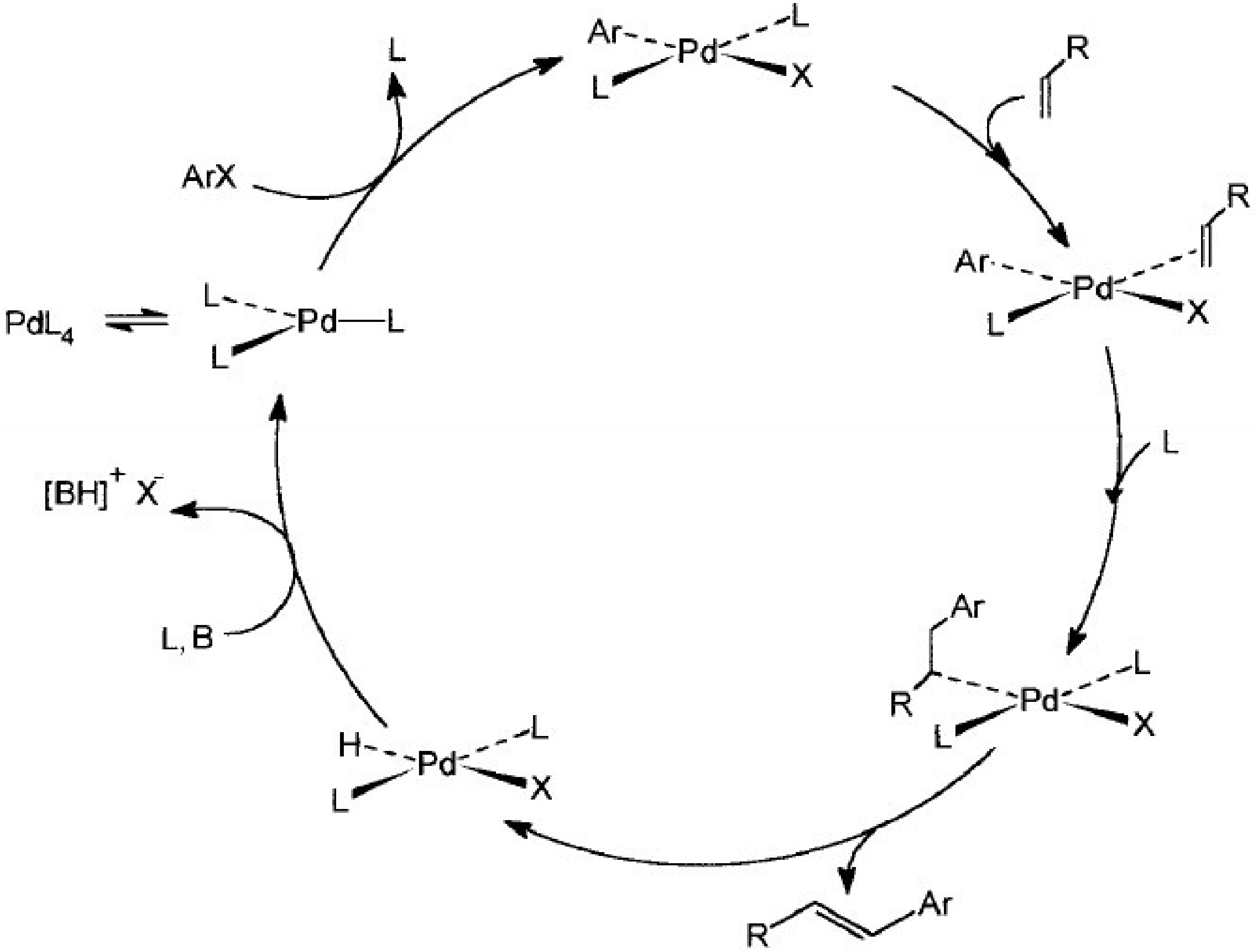
For simple aryl halides reacting with alkenes, the rate of reaction as a function of alkene substitution varies according to the following sequence:

	$CH_2{=}CH_2$	>	$CH_2{=}CH\text{-}OAc$	>	$CH_2{=}CH\text{-}Me$	>	$CH_2{=}CH\text{-}Ph$	>	$CH_2{=}C(Me)Ph$
k_{rel}:	14,000		970		220		42		1

The regioselectivity of addition: although electronic effects may play a small role in directing attack by the metal in the insertion step, steric effects seem to be the dominant factor by far



Heck reaction catalytic cycle:



The Heck reaction differs from the earlier Pd(0)-catalyzed cross-coupling reactions because:

1) it involves an insertion after the oxidative addition step

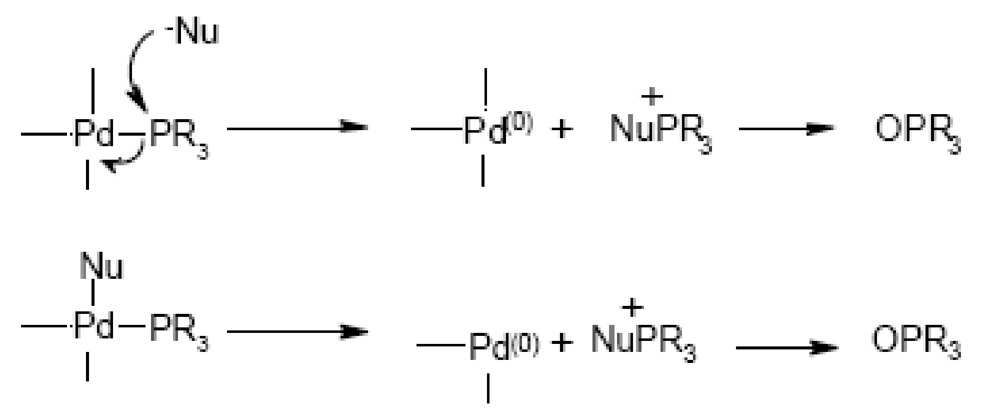
2) the catalytic cycle is closed with a β-hydride elimination, whereas the other couplings end with a reductive elimination

Pre-catalysts and true catalyst formation

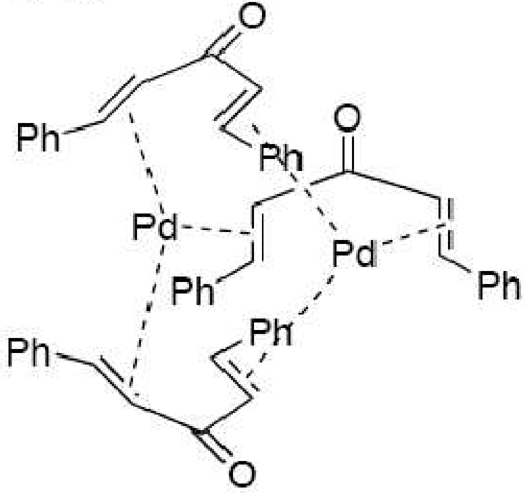
1) Pd(0) complexes, which form the true catalysts through the ligand dissociation

$$Pd(PPh_3)_4 \rightleftharpoons Pd(PPh_3)_3 + PPh_3$$

2) Pd(II) complexes, which form true catalysts through the reduction reaction:



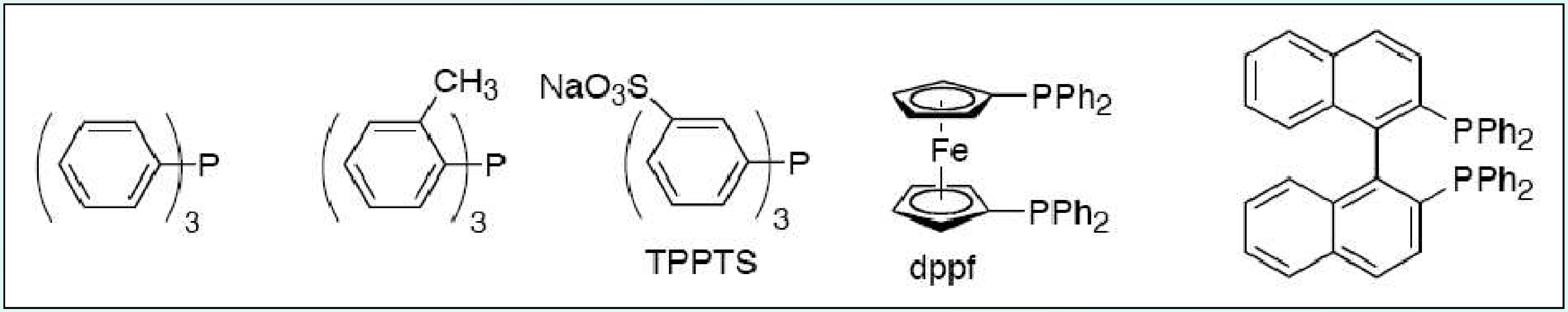
Metal Sources: Both Pd(0) and Pd(II) sources can be used, although the active species is Pd(0) in all cases.

Pd^0	Pd^{II}
$(Ph_3P)_4Pd$	$(Ph_3P)_2PdCl_2$
$Pd_2(dba)_3$ $Pd(dba)_2$  	$Pd(OAc)_2$
Pd/C	$PdCl_2$
	$(CH_3CN)_2PdCl_2$

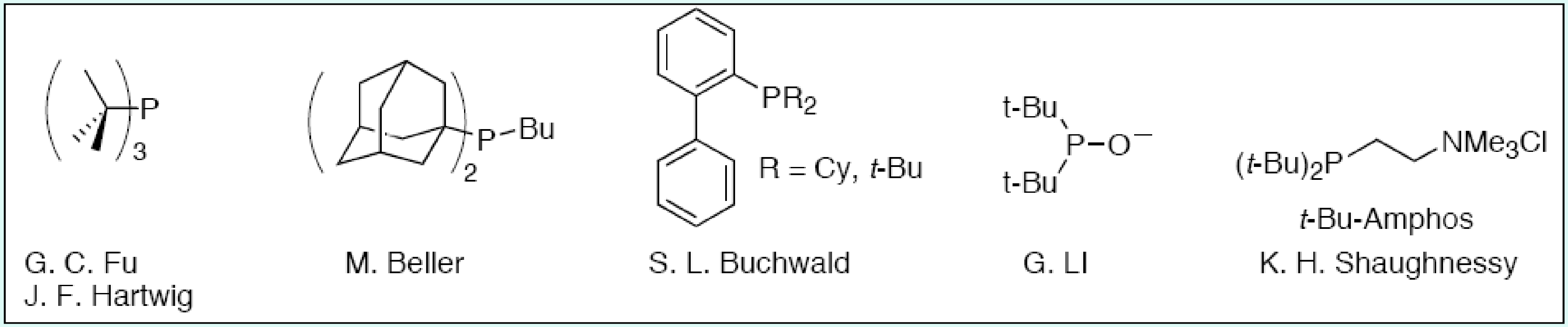
Nickel can catalyze many of the same reactions as palladium. Nickel is attractive because it is much less expensive than palladium. Nickel-based catalysts tend to be less active and general, however. Nickel is better at activating aryl chlorides than palladium in some cases, however. Platinum has shown no activity in cross-coupling chemistry.

Ligands: Palladium alone can catalyze cross-coupling reactions, but usually only with reactive substrates and/or high temperatures. Ligands are usually necessary to give more active catalyst systems. The ligand serves to stabilize the Pd0 intermediate, solubilize thecatalyst, and increase the rate of oxidative addition.

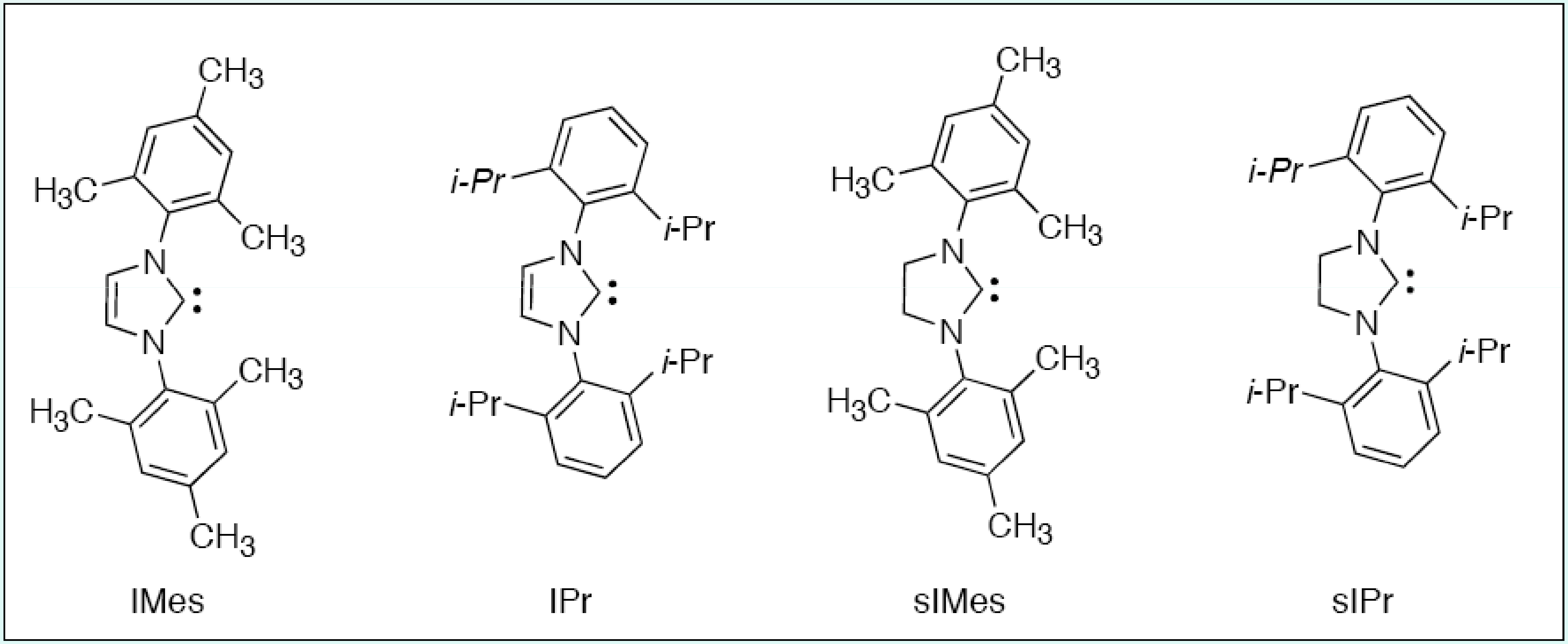
<u>Phosphines:</u> Phosphines remain the most widely used ligands:



Sterically demanding, electron rich phosphines have received increasing attention as they provide more effective catalysts for less reactive substrates, such as aryl chlorides:

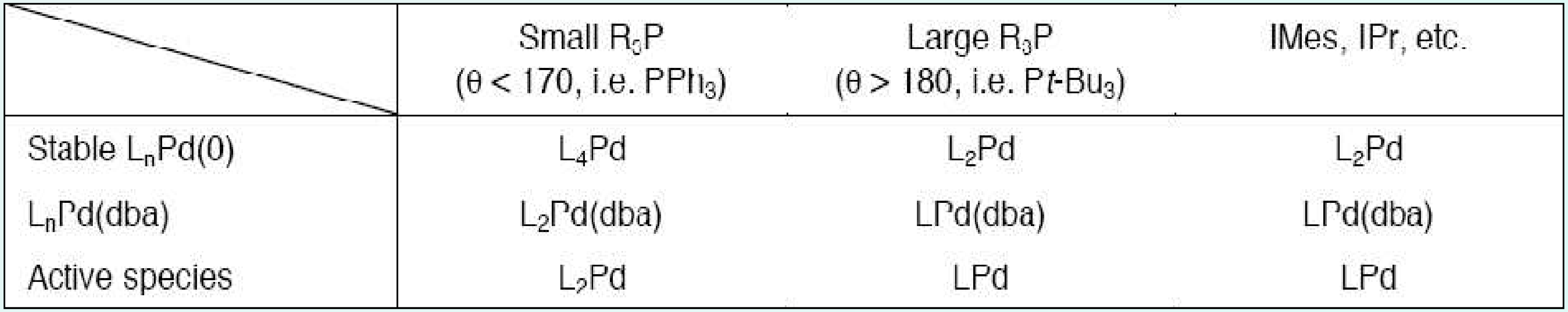


N-Heterocyclic Carbenes: Recently, *N*-heterocyclic carbenes have attracted increasing attention as ligands for cross-coupling reactions. NHCs are stronger electron donors than phosphines and they tend to have stronger M-L bonds, thus they may give more stable catalysts.



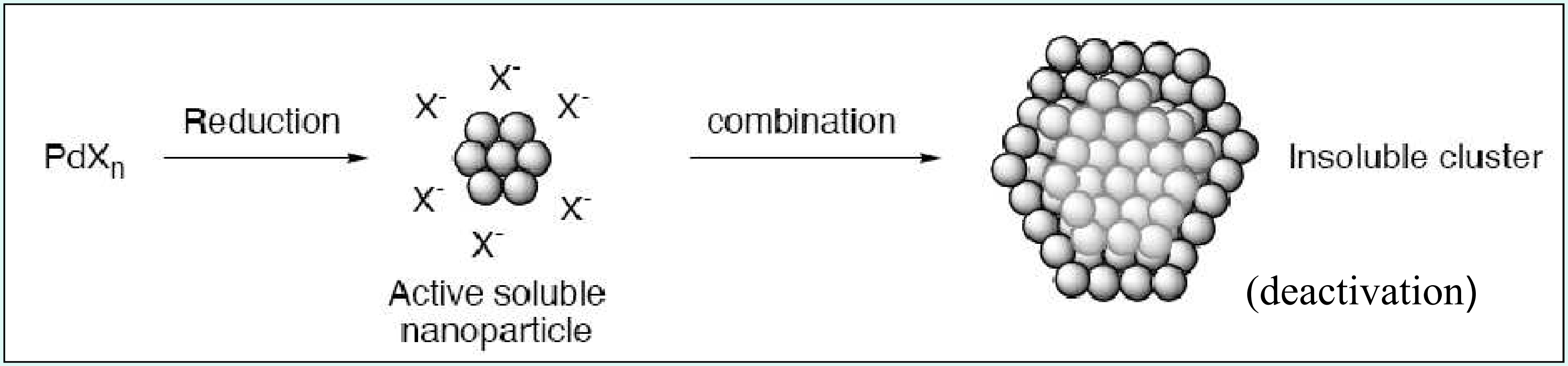
Major players in the application of carbene ligands to cross-coupling are Wolfgang Herrmann, Steve Nolan, and John Hartwig

<u>Preferred Ligand:Pd ratios</u>*:* Depending on the size of the ligand, there will be a preferred ligand to Pd ratio for the stable complex. The true active species will have a lower coordination number due to the need for an open site for oxidative addition to occur.



	Small R_3P ($\theta < 170$, i.e. PPh_3)	Large R_3P ($\theta > 180$, i.e. $Pt\text{-}Bu_3$)	IMes, IPr, etc.
Stable $L_nPd(0)$	L_4Pd	L_2Pd	L_2Pd
$L_nPd(dba)$	$L_2Pd(dba)$	$LPd(dba)$	$LPd(dba)$
Active species	L_2Pd	LPd	LPd

<u>"Ligand free"</u> catalyst systems are believed to be catalyzed by soluble Pd(0) clusters. These clusters can be highly active, but tend to grow until they precipitate as unreactive Pd metal precipitate (Pd black). Halide salts, surfactants, polymers, and other weakly coordinating ligands have been shown to stabilize these nanoparticles:



(deactivation)

Application of the Heck reaction

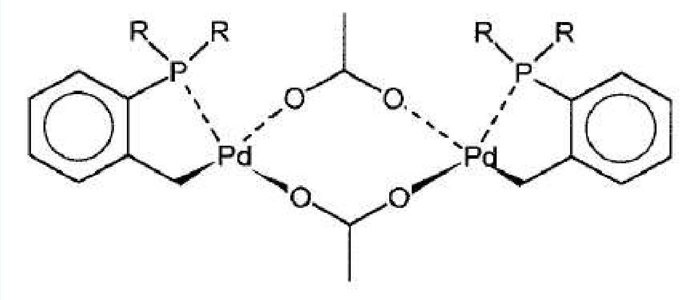
Although these reactions are highly versatile, so far they have not found significant industrial applications. The main reasons for this are relatively low thermal stabilities and turnover numbers of the catalytic systems, and the salt waste problem

The Heck reaction is applied industrially in the production of naproxen:

Reaction conditions:

$T = 130^0C$, $P = 20$ atm

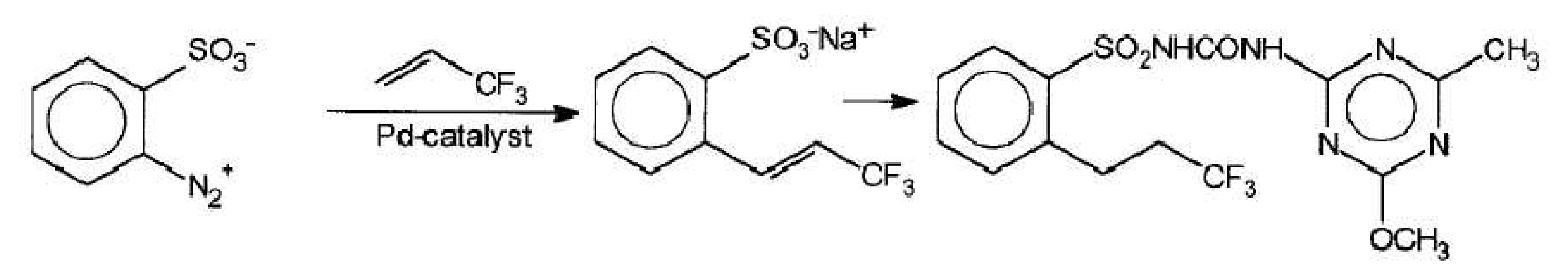
Catalyst:



(R = o-tolyl)

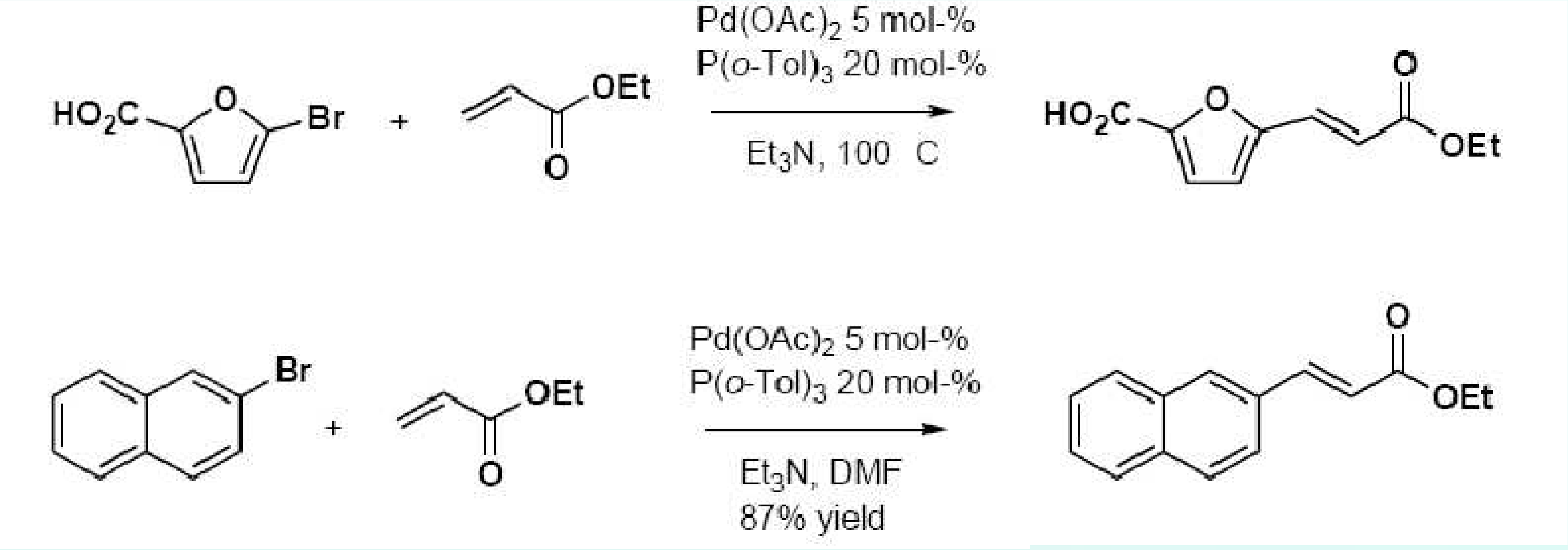
Other application is the synthesis of pesticide prosulfuron

The first reported example of industrial use of the Heck reaction was for the production of Prosulfuron™, a new and highly active herbicide, by Ciba–Geigy (now Novartis). The Heck reaction was performed at 15°C in HOAc using $Pd_2(dba)_3$ (0.5–1 mol%) as catalyst:

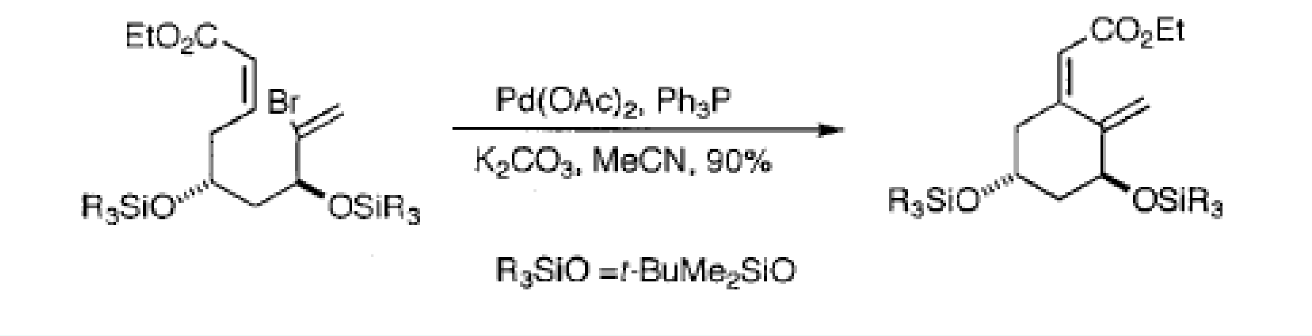


It was not necessary to isolate the Heck product. After addition of some active carbon to deposit the palladium on, the double bond was hydrogenated. Not only was the catalyst used in two consecutive steps, this method also allowed the catalyst to be reclaimed by filtration in 95% yield. The reaction is performed in a single reactor without isolation of the intermediates. The average yield per step is in excess of 90%.

Application of the Heck reaction in organic synthesis:

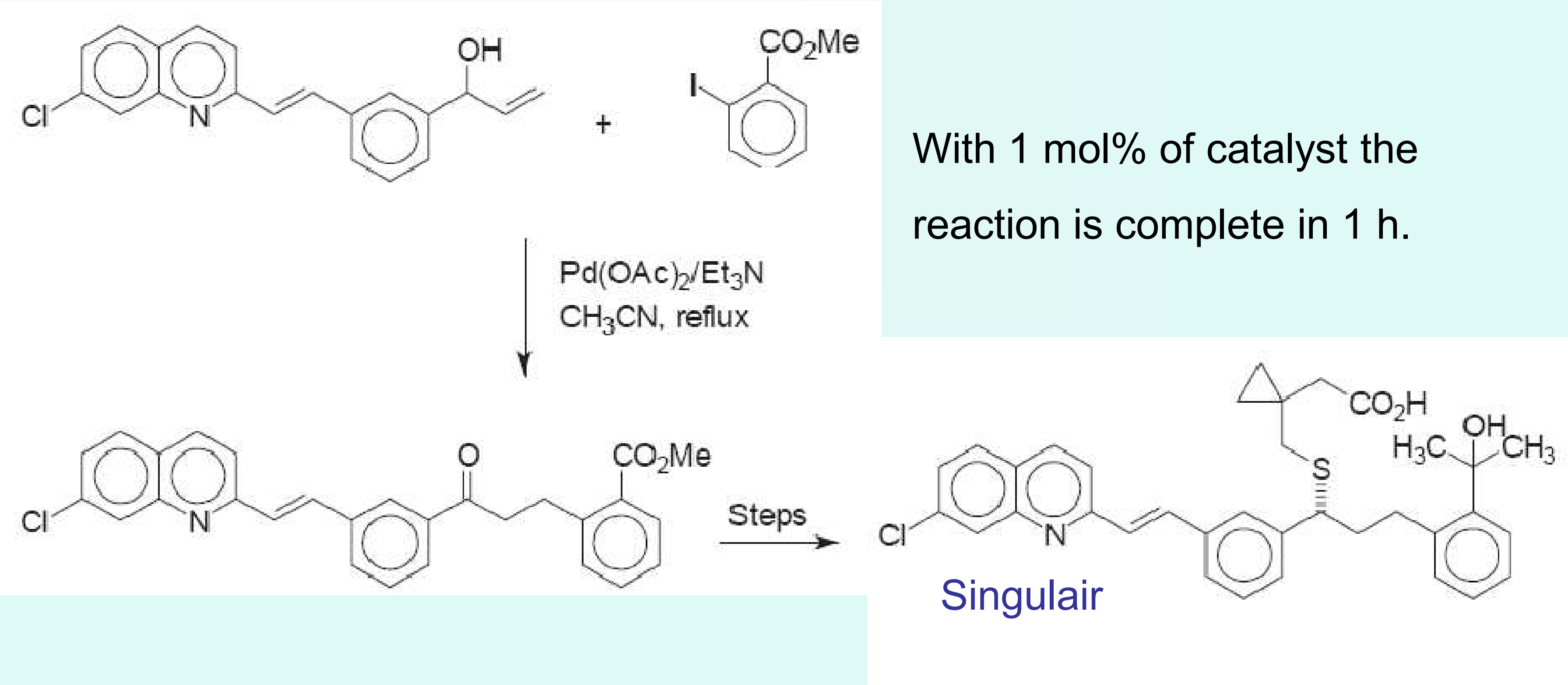


An example of intramolecular Heck reaction:



The Heck reaction as the key step in the production of an antiasthma agent:

An important aspect of the attractiveness of the Heck reaction is the ability to form carbon—carbon bonds without the use of strongly basic reagents such as Grignards and lithiated carbon nucleophiles. Hence, the functional group tolerance of the Heck reaction is very wide allowing its use in the latter stages of a total synthesis. This aspect is very important in the production of Merck’s antiasthma agent Singulair



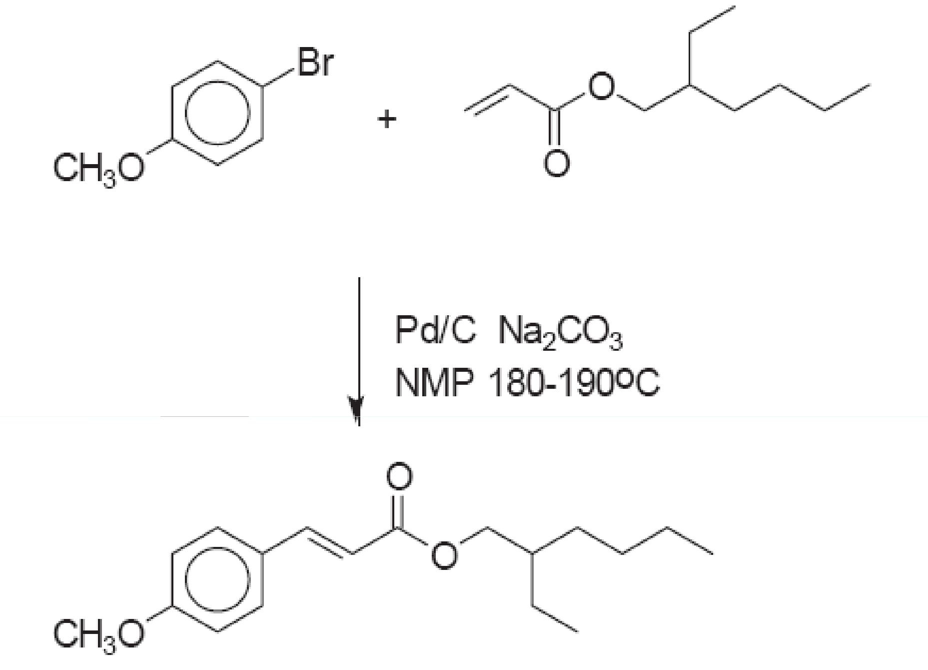
Singulair

With 1 mol% of catalyst the reaction is complete in 1 h.

The Heck reaction in the UV-B sunscreen production:

This has been pioneered by IMI/Bromine Co Ltd for the industrial production of the UV-B sunscreen 2-ethylhexyl-*p*-methoxy-cinnamate.

At high temperatures *p*-bromoanisole is treated with 2-ethylhexylacrylate to yield the desired product and some side products – most likely due to the 180–190°C reaction temperature (the yield is 75–92%):

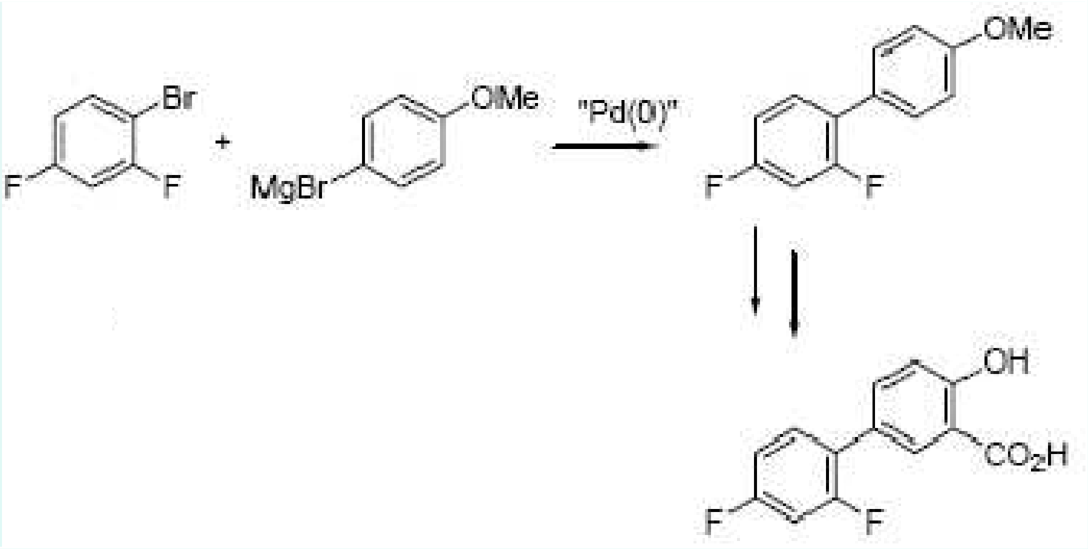


Companies producing bromine and aromatic bromides are in an excellent position to apply the Heck reaction (not limited to the raw material position). Also it involves the ability to recycle the bromide salts that are formed as waste. Because of the presence of large deposits of bromide, Israel has a flourishing organobromide industry (IMI/Bromine Co Ltd).

Other important industrial applications of the cross-coupling:

Synthesis of Diflunisal, a non-steroidal antiinflammatory drug.

One problem occurs with aspirin and other antiinflammatory drugs is that it has a destructive effect on the blood vessel walls and inhibit the synthesis of prostacyclin. Diflunisal is without such a shortcomings.



Sales price is around € 300 / kg and a hundred tons are made worldwide per annum.

A very pure product is required. The palladium content may not exceed 10 ppm and the impurities should be below 0.1 %. Classical syntheses cannot be applied because they give a lot of by-products.

Main disadvantages of the Heck reaction (and ways of solving):

1) One of the major disadvantages is that the palladium catalyst is usually lost at the end of the reaction. Thus, a process for recycling the catalyst system is of great importance.

The employment of ionic liquids could solve the problem. Ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmin][PF_6]) areinsoluble in water and alkanes, but readily dissolve many transition metal catalysts.
By providing a medium that dissolves the palladium catalyst, the products and by-products can be easily separated and the catalyst can be recycled

2) Another disadvantage of the Heck reaction is the employment of phosphine ligands because they are expensive, toxic, and unrecoverable. Thus, it is important that research is conducted on phosphine-free ligands in order to improve the overall catalytic efficiency and economical feasibility of the Heck catalytic process.

Some important steps of the coupling reactions:

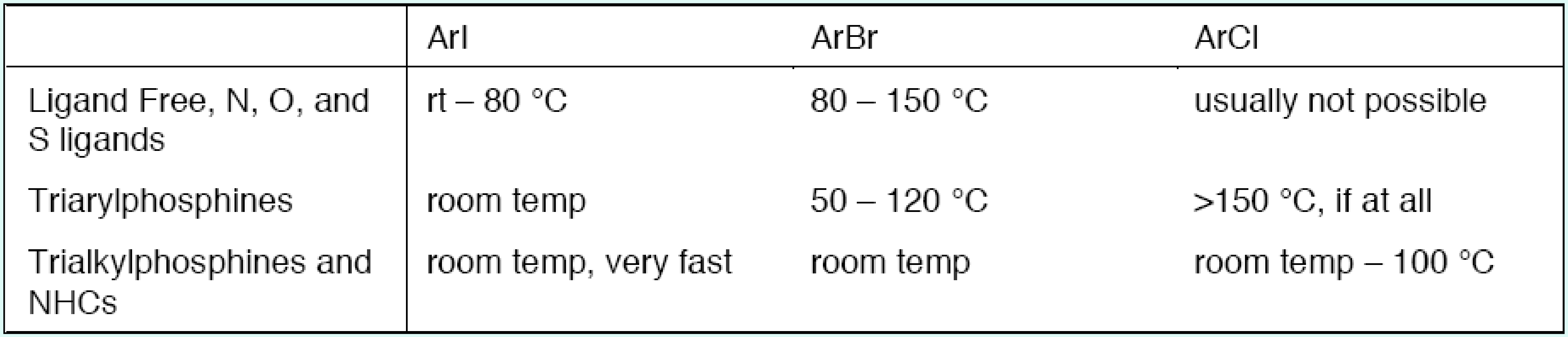
1. Oxidative addition:

Oxidative addition is the rate limiting step in many cross-coupling reactions, particularly with less reactive *bromide* and *chloride* substrates. All classes of organic halides have been successfully used in cross-coupling reactions, although sp^2-organohalides are the most commonly used substrates. In addition, a variety of other leaving groups, such as triflates, tosylates, diazonium ions, phenyl iodonium ions, etc. have been explored. Halides remain the most common class of substrate.

Aryl Halides: the rate of oxidative addition is:

ArI > ArBr >> ArCl.

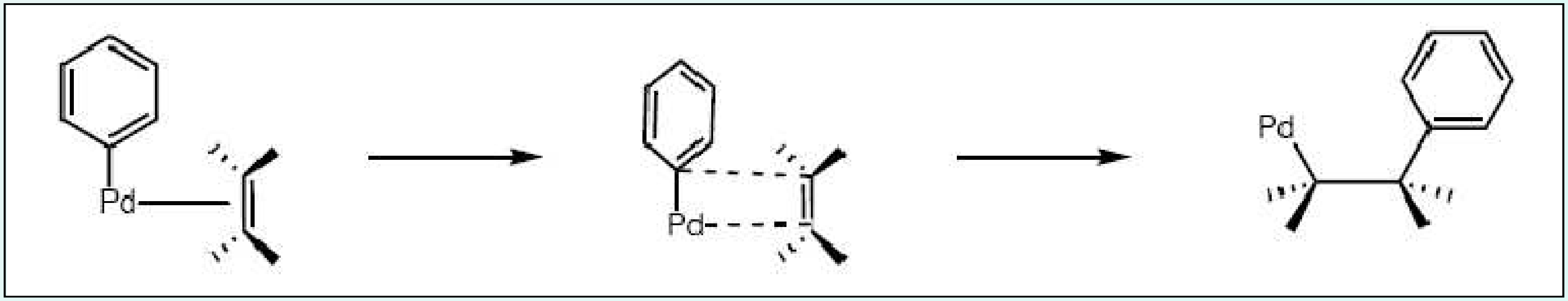
Aryl triflates generally fall between iodides and bromides. Electron-withdrawing groups make the aryl halide more reactive, while electron-donating groups deactivate the aryl halide.



	ArI	ArBr	ArCl
Ligand Free, N, O, and S ligands	rt – 80 °C	80 – 150 °C	usually not possible
Triarylphosphines	room temp	50 – 120 °C	>150 °C, if at all
Trialkylphosphines and NHCs	room temp, very fast	room temp	room temp – 100 °C

2. Migratory insertion

Migratorty insertion is a basic organometallic transformation and is the carbon-carbon bond forming step in the Heck reaction



Main features:

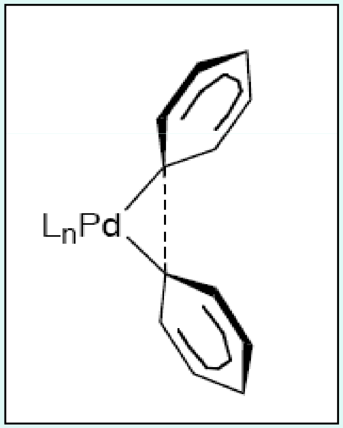
- The reaction is considered to be a concerted process
- The regiochemistry of the intermolecular Heck insertion step is highly sensitive to the electronics of the substrate, the reaction manifold, and steric congestion. As a result regioselectivity can be poor for certain classes of substrates
- The elimination of entropic factors in the intramolecular Heck allows insertion into trisubstituted and tetrasubstituted olefins, which is not possible in the bimolecular process

3. Reductive Elimination:

Reductive elimination is usually a fast step in the catalytic cycle, so there is less focus on designing ligands to promote it. Reductive elimination is favored by electron deficient ligands (opposite of oxidative addition) and sterically demanding ligands (same as oxidative addition).

Main features of Reductive elimination:

- Occurs only from *cis*-L_nPdRR'
- aryl-aryl ≈ vinyl-vinyl/aryl > alkyl-aryl/vinyl > alkyl-alkyl > Me-Me
- For $(Ph_3P)_2PdMe_2$, rate of R.E. is $\propto$ to $1/[PPh_3]$
- For $(Ph_3P)_2PdPh_2$, R.E. occurs directly from the 4-coordinate species:



- Electron-withdrawing and sterically demanding ligands facilitates the reductive elimination.
-For bulky ligands, the steric properties dominate over the electronic properties.

Conclusions & limitations

The Heck reaction is an incredibly powerful method for the construction of acyclic and polycyclic structures and quarternary carbon stereocenters

The incredible functional group tolerance of palladium make Heck reactions possible on even the most sensitive of substrates

For the Heck reaction extensive optimization studies are often required to develop optimal conditions for every new substrate

Reactions are easily poisoned by molecular oxygen

Future Directions

Introduction of new recoverable ligands that will broaden substrate scope amenable to asymmetric catalysis

Further investigation of tandem reactions involving the Heck and application in complex molecule synthesis

Finding milder reaction conditions that also allow for lower catalyst loadings