TM organometallics with σ M-C bonds

First compound of this kind discovered and characterized in 1909 (Me_3PtI, Pope and Peachey), then no further compound for more than half a century…unstable compounds?

The energy of the M-C **σ** bond in TM is appreciable (120-350 kJ/mol) and comparable to that of analogous compounds of main group metals.

<u>Consequently, the problem is kinetic, not thermodynamic</u>! Availability of several decomposition pathways with low activation energy:

- **β-elimination**;

–α-elimination (also γ, δ…):

- reductive elimination;
- insertion…

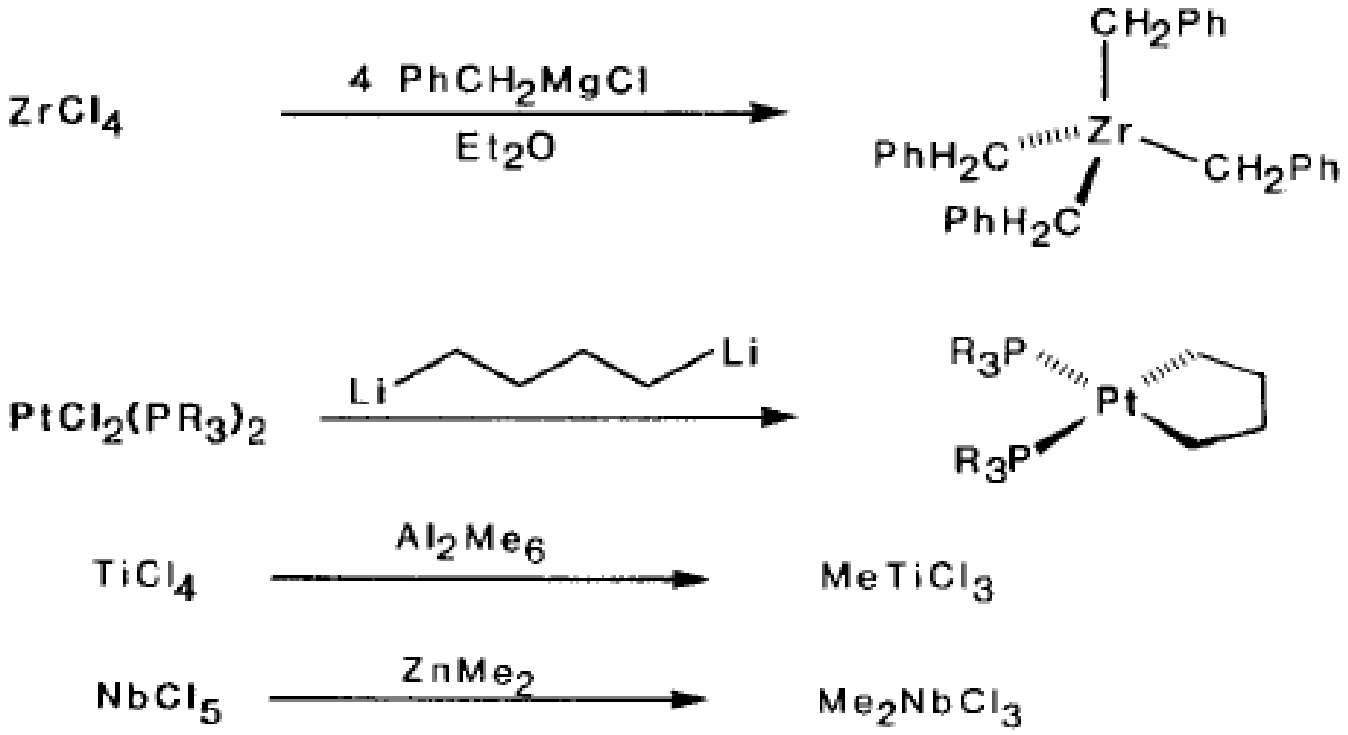
TM organometallics with σ M-C bonds

M-C σ bonds in TM are essentially covalent and polarization is limited. Consequently, care should be taken in deriving conclusions on the chemical behaviour of these compounds from simple metal oxidation state considerations!

Example: in both $W(CH_3)_6$ and WCl_6 the metal is in the formal oxidation state +6. However, the electron density on the metal in the former compound (which can be determined e.g. by XPS) is more coherent with an oxidation state zero!.

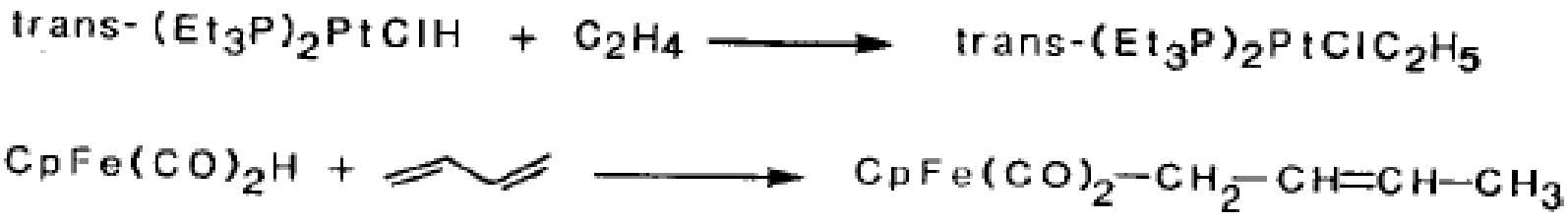
Synthetic methods

1) Metathesis: main group organometallics can be employed (Li, Mg, Zn, Hg, B, Al, Tl, Si, Sn, Pb, Bi…) and also some TM organometallics (Zr). More reactive compounds are employed for complete substitution reactions, less reactive ones for partial substitutions.



Synthetic methods

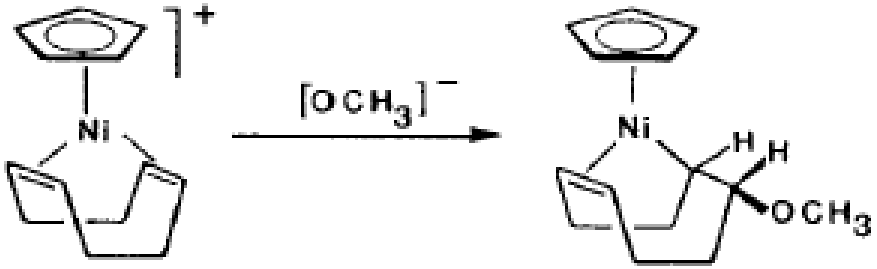
2) Insertion (hydrometallation): Problems deriving from the fact that this reaction is an equilibrium, often shifted to the left (see below). Control of regio- and stereoselectivity is also an issue.



1,4 addition, cis and trans

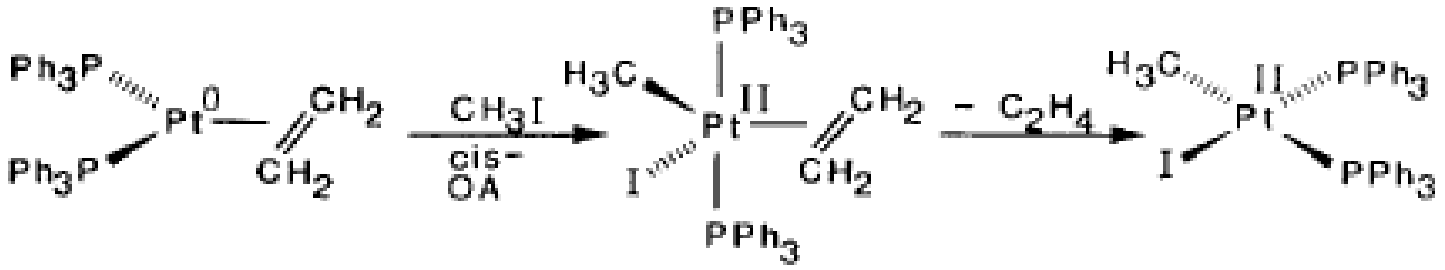
Synthetic methods

3) External nucleophilic attack on coordinated alkenes, alkynes, polyenes… dual possible mechanistic pathway: true external nucleophilic attack or insertion after precoordination of the nucleophile to the metal centre. Different stereochemical consequences!



Synthetic methods

4) <u>Oxidative addition (concerted, S_N2, radicalic)</u>;



$$Mn_2(CO)_{10} \xrightarrow{Na/Hg} Na[Mn(CO)_5] \xrightarrow{CH_3I} CH_3Mn(CO)_5 + NaI$$

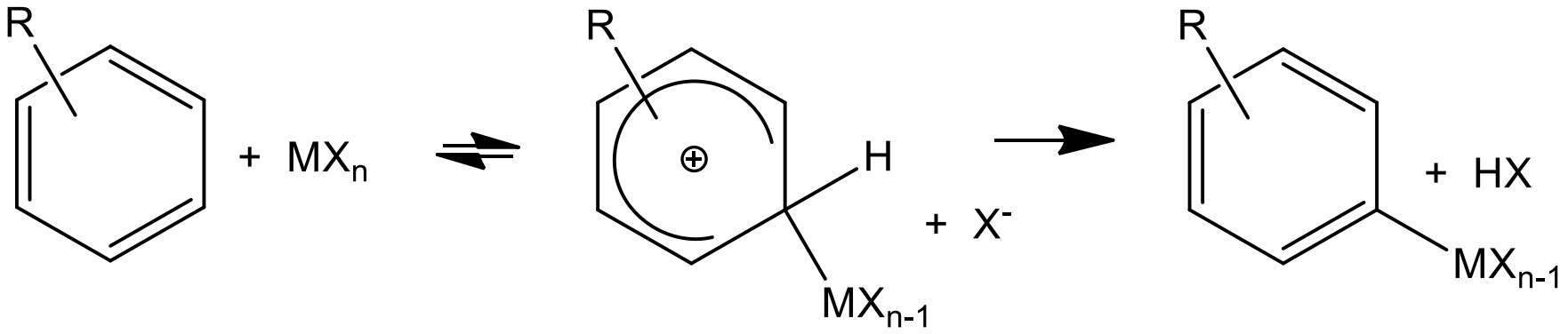
$$W(CO)_6 \xrightarrow[-3CO]{NaCp} Na[CpW(CO)_3] \xrightarrow{C_2H_5I} CpW(CO)_3C_2H_5$$

Under suitable conditions, it is possible to oxidatively add R-H bonds (C-H activation), instead of R-X bonds…

Synthetic methods

5) <u>Electrophilic metallation</u>:

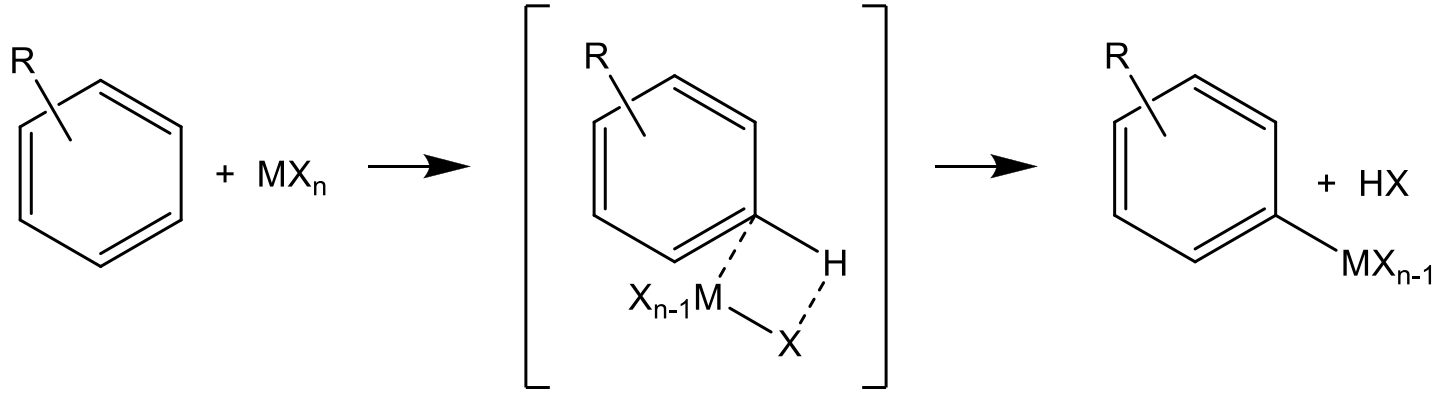
$CH_4 + PtClS_2^+ \rightarrow PtCH_3ClS_2 + H^+$ S= solvent



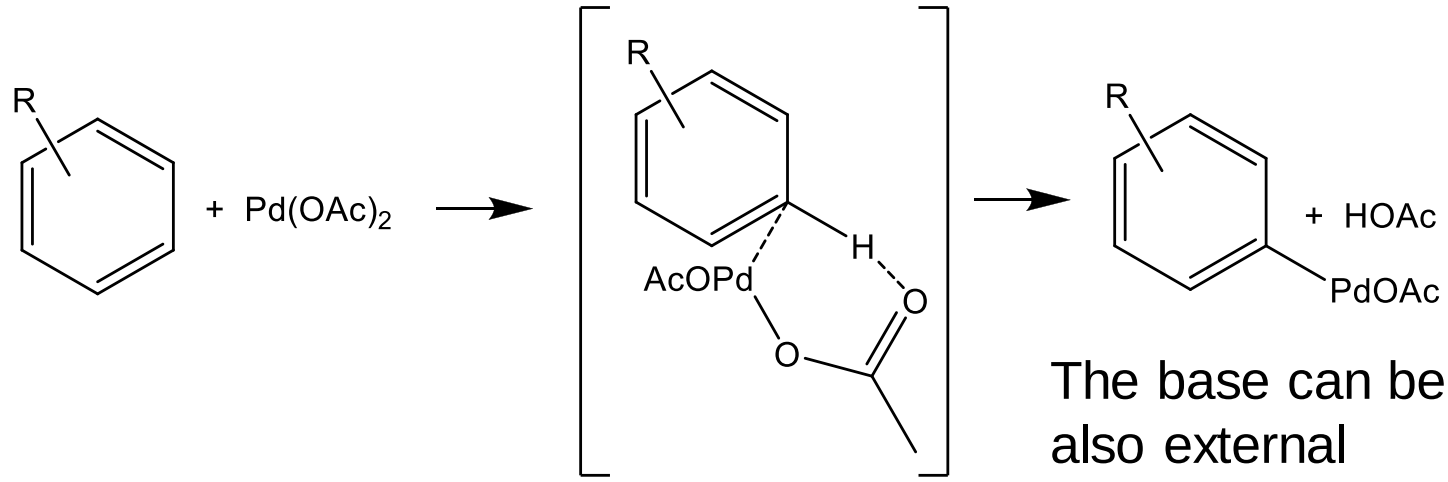
<u>Electrophilic metal centres are needed</u> (electronegative metals in medium-high oxidation state, no electron-donating supporting ligands, cationic complexes…). Often simple salts of late transition metals are employed ($Pd(OAc)_2$, $AuCl_3$, $PtCl_2$, $PtCl_4$, $RhCl_3$…). Alternatively, electronegative, carbophilic, heavy non-transition metal salts (HgX_2, TlX_3) can be employed as well…

Synthetic methods

5b) <u>Sigma-bond metathesis</u>; C-H and M-X bond are broken simultaneously, H migrates on X



5c) <u>Concerted metallation-deprotonation</u> (CMD):



The base can be bound to M or also external

C-H metallation mechanisms

- Electrophilic metallation involves a Wheland-type intermediate, which impacts on the arene π system, as in a classic electrophilic aromatic substitution reactions;

-Sigma bond metathesis (and also CMD) impacts on the σ electron density of the C-H bond, as in an acid-base reaction (heterolytic C-H scission);

Consequently, the substituents effect, the optimal reaction conditions etc. will be very different in the two cases!

The main problem in these reaction is the selectivity. Directing groups can be employed to functionalize one peculiar C-H bond (the group precoordinates the metal and directs the attack generally *ortho* to it), and/or steric and electronic effects of the substituents.

Stabilization of TM compounds with σ M-C bonds

The stabilization of these compounds is extremely important, particularly in view of their application as reaction intermediates in e.g. polymerizations, C-C coupling reactions etc.

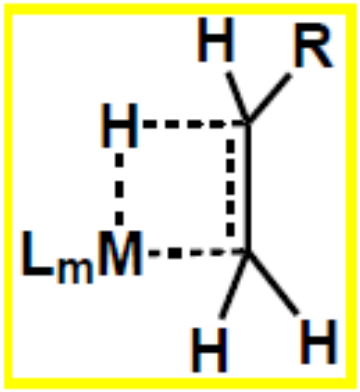
Heteroleptic organometallics of this kind (containing also other kinds of ligands beside organic groups) are usually more stable than homoleptic compounds.

The stability towards air and moisture generally increases along the period (the polarization of the M-C bond decreases) and along the group (the strength of the M-C bond increases)

In order to stabilize these compounds, it is necessary to inhibit the various possible decomposition mechanisms, particularly the most efficient ones (β-elimination).

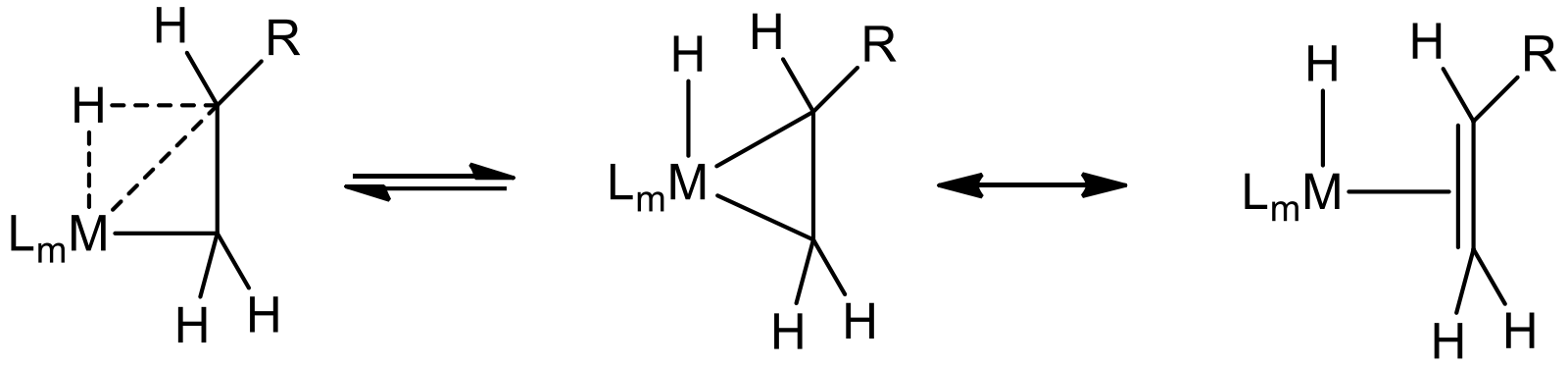
Inhibition of β-elimination

In order to inhibit β-elimination, it is first of all necessary to become aware of the intimate mechanism of the reaction:



1) The β-C-H bond assumes with the M-C bond a *syn*-coplanar conformation;
2) The σ orbital of the β-C-H bond interacts with an empty orbital with suitable simmetry and energy on M;
3) Backbonding from a full metal orbital with suitable simmetry towards the σ* antibonding orbital of the C-H bond takes place;

Inhibition of β-elimination



4) The combined action of donation/retrodonation produces C-H bond breaking (“formal” oxidative adition of C-H) and formation of new M-H and M-C bonds; the latter together with the preexistent M-C bond builds a metallacyclopropane, which is equivalent to a coordinated alkene (“formal” reductive elimination);

5) The metal-alkene bond breaks and the alkene is released, completing the process;

Inhibition of β-elimination

In order to inhibit β-elimination it is possible to act on each of the steps of the intimate mechanism listed above. Consequently, stable compounds can be:

1) Compounds which do not present β-hydrogens;

WMe_6, $Ti(CH_2Ph)_4$, $W(CH_2SiMe_3)_6$, $TaCl_2(CH_2CMe_3)_3$,

$C_2F_5Mn(CO)_5$, $LAuCF_2CF_2Me$, $Pt(C{\equiv}CCF_3)_2L_2$,

$Pt(CH_2COMe)Cl(NH_3)_2$

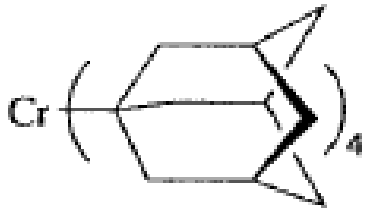
2) Compounds with β-C-H bonds, which are incapable of getting close to the metal due to ligand geometry or to steric congestion:

$PtH(C{\equiv}CH)L_2$, $PdPh_2L_2$, $Cr(CMe_3)_4$, $Cr(CHMe_2)_4$,

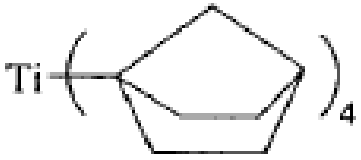
$CpL'_3MoCH{=}CHCMe_3$

Inhibition of β-elimination

3) Compounds in which the β-C-H bonds are incapable of assuming a syn-coplanar conformation with M-C:



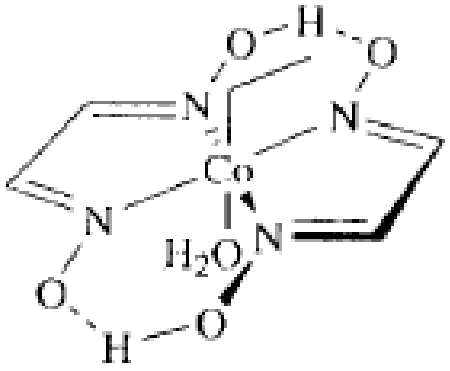
[Cr(1-adamantyl)$_4$]



Ti(6-norbornyl)$_4$

$L_2Pt(CH_2)_3$

4) 18 e- compounds which do not easily dissociate *cis* ligands:



3.4

$Cp(CO)IrPrH_2$

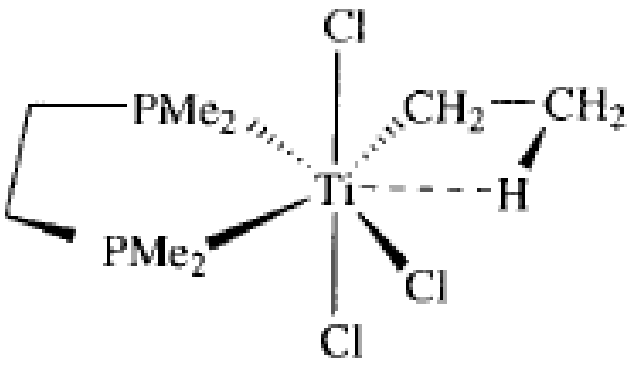
3.5

$[Cr(H_2O)_5I]^{2+}$

3.6

Inhibition of β-elimination

5) Some complexes with the metal in electronic configuration d^0:



3.7

Agostic interaction between the metal centre and the electron density of the σ C-H bond. The interaction can be spotted by structural analysis or by the anomalous chemical shift of the agostic proton in the ^{1}H-NMR, or by the anomalous stretching C-H (at low wavenumbers) in the IR spectrum.

Reactions of TM organometallics with σ M-C bonds

Reactive compounds, which find extensive application as intermediates in very numerous stoichiometric and catalytic reactions of synthetic interest.

Focus will be initially put on reactions which involve intermediates with σ M-C bonds as sole organometallic component.

In this context, the main reaction class is undoubtedly formed by the so-called **cross-coupling reactions**

$$RM + R'X \rightarrow R\text{-}R' + MX$$

RM nucleophile (organometallic reagent, stabilized carbanion)

R'X elettrophile (X= halide, triflate, tosylate etc.)

Metal-catalyzed cross couplings and related reactions; from C-C to C-X

Why «**cross-coupling**» ?

RM + **R'X** → **R**-**R'** + MX

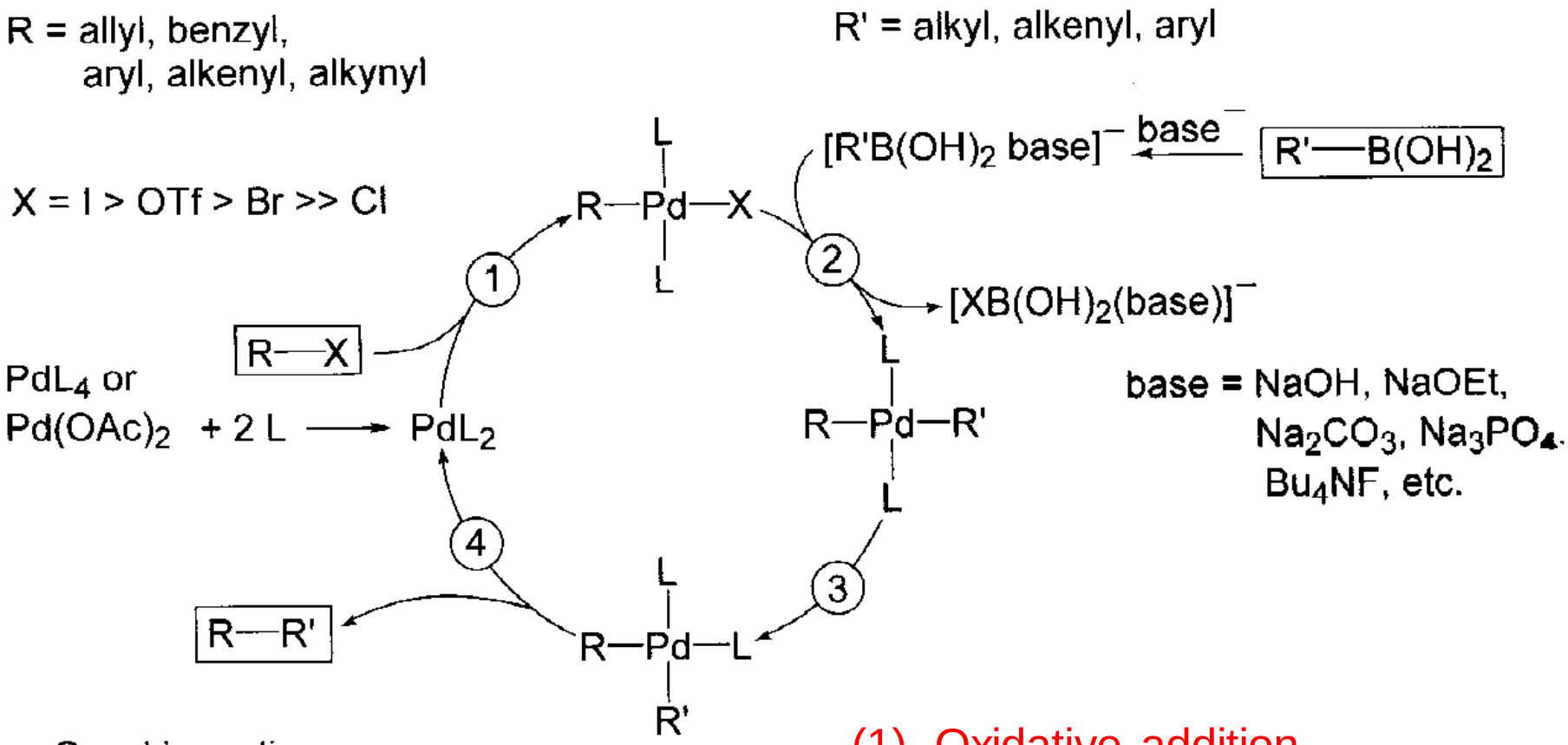
RM **nucleophile** (organometallic reagent, stabilized carbanion)

R'X **electrophile** (X= halide, triflate, tosylate etc.)

Stoichiometry resembles classic nucleophilic substitution

Why do we need a (metal) catalyst?

Cross-coupling reactions (Suzuki)



Suzuki reaction

(1) Oxidative addition
(2) Metathesis (transmetallation)
(3) Rearrangement
(4) Reductive elimination

Cross-coupling reactions

Catalysts based on **Pd, Ni, Cu**, but also Fe, Co, Mn, Au….

Catalysis dominated by **Pd**, due to its ability to efficiently promote all steps in the catalytic cycle; furthermore,

- tolerance to functional groups;

- relatively low sensitivity to air and moisture;

- organometallic (non-radical) reaction mechanisms;

- mechanistic manifold (0/II, II/IV)

- low toxicity;

- low cost compared to other noble metals (Rh, Ir, Pt).

Cross-coupling reactions

Large variety of reactions with different organometallic reagents:

RMgX (Kumada-Corriu coupling): reactive but not very stable, economic, rather slow metathesis;

RZnX, ZnR_2 (Negishi coupling): less reactive than Grignard reagents but still not very stable, quite expensive, fast metathesis;

$RB(OR')_2$, RBF_3K… (Suzuki-Miyaura coupling) very stable, not very expensive, fast metathesis under proper conditions;

$RSiR'_nX_m$ (Hiyama-Tamao coupling) stable, inexpensive, easy to prepare, slow metathesis (it is often necessary to render Si hypervalent with F^-)

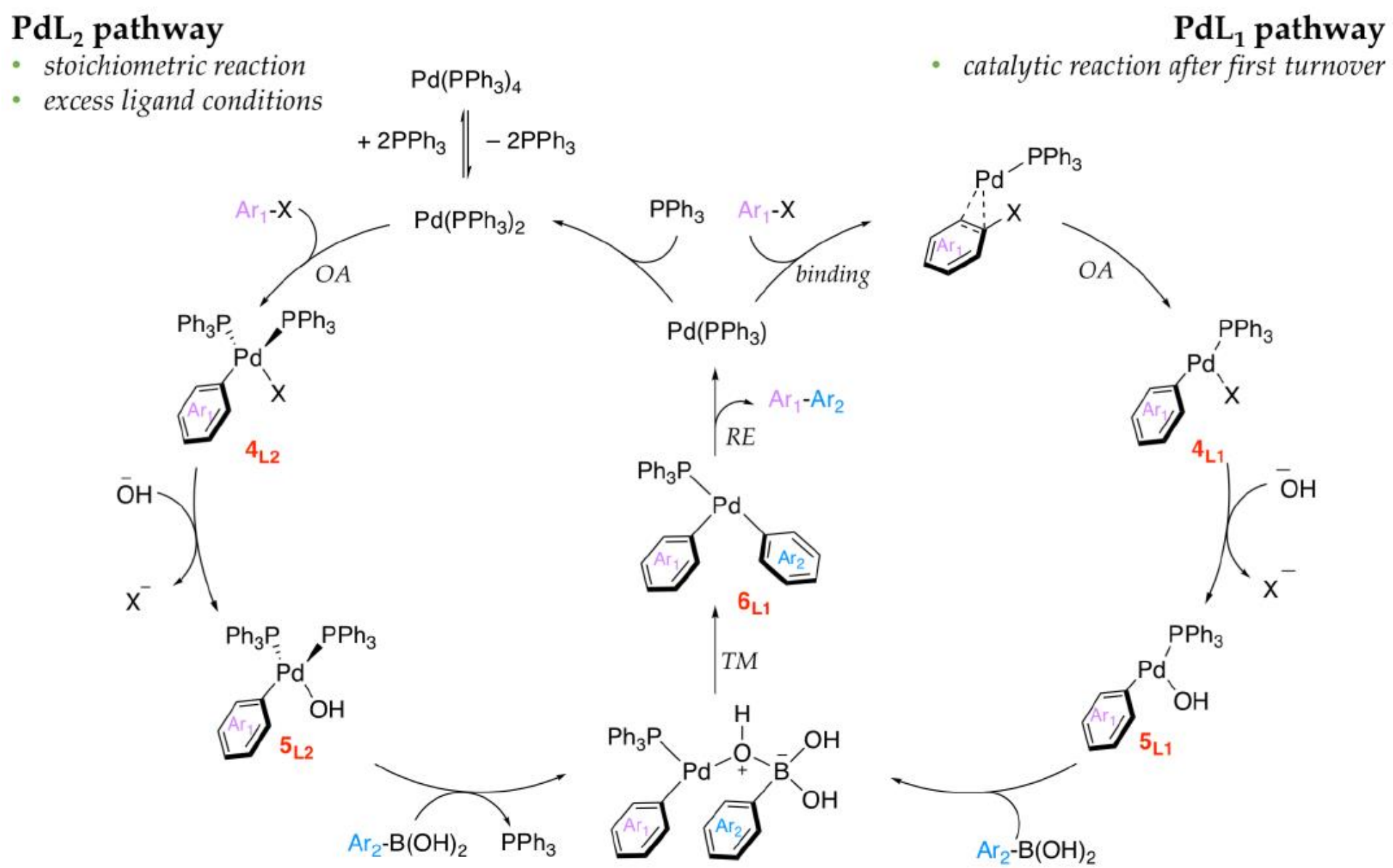
Cross-coupling reactions

$RSnR'_3$ (Stille coupling) stable, inexpensive, easy to prepare, fast metathesis, coprodouct $XSnR'_3$ toxic.

(Cu)-alkynyls (Sonogashira-Hagihara coupling) formed in situ from CuX + terminal alkynes: reactive, economic, also produces homocoupling of two alkynyl fragments (Glaser-Hay coupling).

It is also possible to run cross-coupling reactions using as nucleophile **stabilized carbanions** prepared in situ by deprotonation, such as ketone or ester enolates, terminal alkynyls (Sonogashira reaction “copper-free”).

Cross-coupling reactions (Suzuki)



Cross-coupling reactions - Considerations

Palladium(0) or palladium(II) precatalysts can be employed. The latter must be reduced in situ to palladium(0). As reducing agent the ligands present on Pd, the solvent (or impurities present in the solvent) or the nucleophilic reagent (homocoupling reaction) can be employed:

$$2\ R'M + PdX_2 \rightarrow 2MX + PdR'_2 \rightarrow R'\text{-}R' + Pd(0)$$

Incidentally, this reaction can be employed as synthetic procedure for the homocoupling of two nucleophilic fragments. However, an oxidant is necessary to reoxidize Pd to the +2 oxidation state and close the catalytic cycle ("the oxidant problem", general and still unsolved problem in Pd catalysis).

Cross coupling reaction - Considerations

The reaction starts with the oxidative addition of RX on a Pd(0) complex with 14 (PdL_2) or 12 (PdL) e^-. Strongly donating, bulky ligands L are necessary in order to stabilize Pd(0) against aggregation and promote oxidative addition (electronically unsaturated but electron-rich complexes…).

The reactivity order for RX is I > Br > Cl >> F; OTf > OTs; electron-withdrawing substituents on R favour the reaction, electron donating ones disfavour it.

The rate determining step of the process may be the oxidative addition or the metathesis step. The final reductive elimination is generally fast (faster with R sp^2 or sp).

Cross coupling reactions - Considerations

It is difficult to employ alkyl RX (slow oxidative addition, risk of β-elimination, which is often faster than metathesis), whereas R'M with alkyl R' can be employed (reductive elimination faster than β-elimination). This limitation can however be overcome:

-Use of metal centres on which β-elimination is less efficient (Ni instead of Pd);

- Use of ligands which disfavour β-elimination compared to metathesis and successive reductive elimination (chelating, sterically bulky ligands).

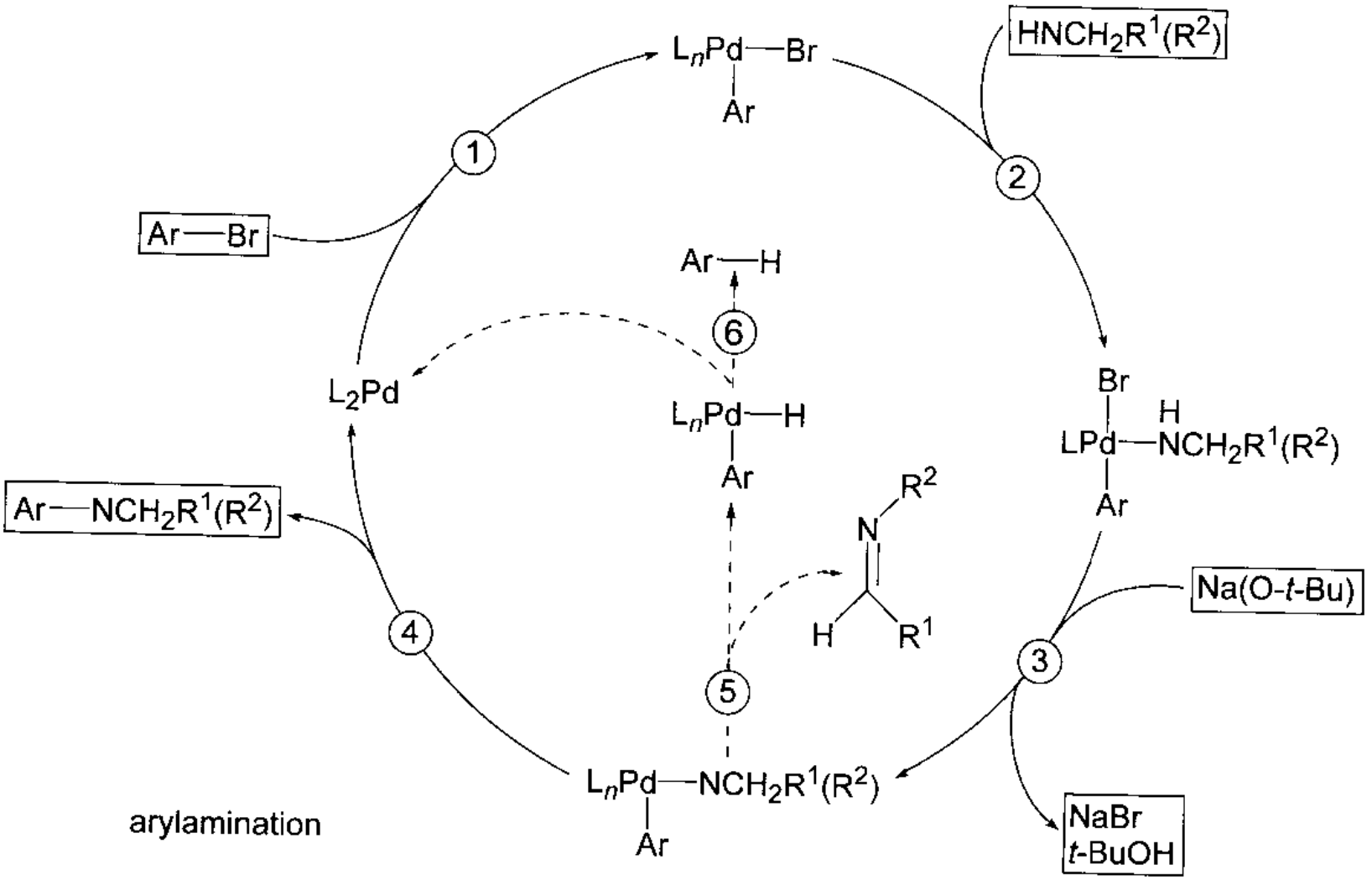
Cross coupling reactions with heteroatom nucleophiles (Buchwald-Hartwig coupling)

The cross coupling catalytic cycle could in principle also lead to the formation of C-heteroatom bonds, by replacing in the reaction the carbon nucleophile R'M with heteroatom nucleophiles (amines, amides, N-heterocycles, other compounds containing N-H bonds, alcohols, phenols, thiols, secondary phosphanes etc.) in the presence of a base to remove the proton.

These reactions are however much more difficult to achieve: reductive elimination is much slower (can become the rate determining step of the process) and consequently decomposition reactions, such as β-elimination from the coordinated heteroatom nucleophile, can take place.

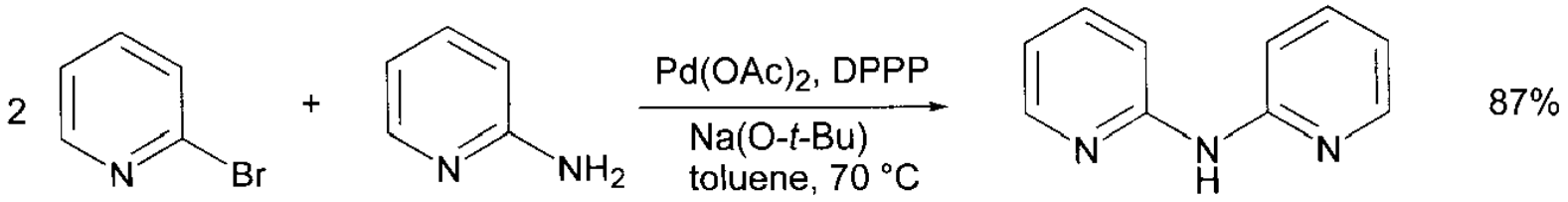
Also in this case, a judicious choice of the ligands and of the reaction conditions can overcome these difficulties.

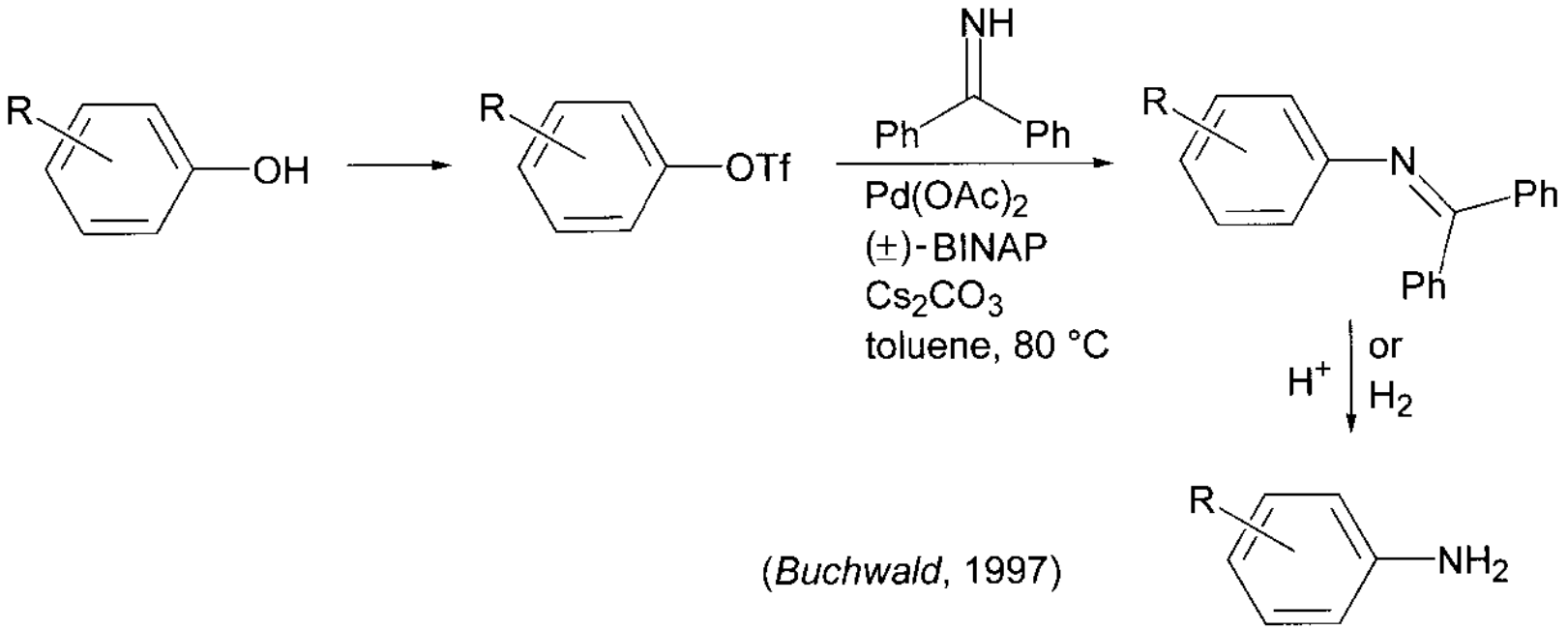
Buchwald-Hartwig coupling



Rif. J. F. Hartwig, Nature 455 (2008) 314

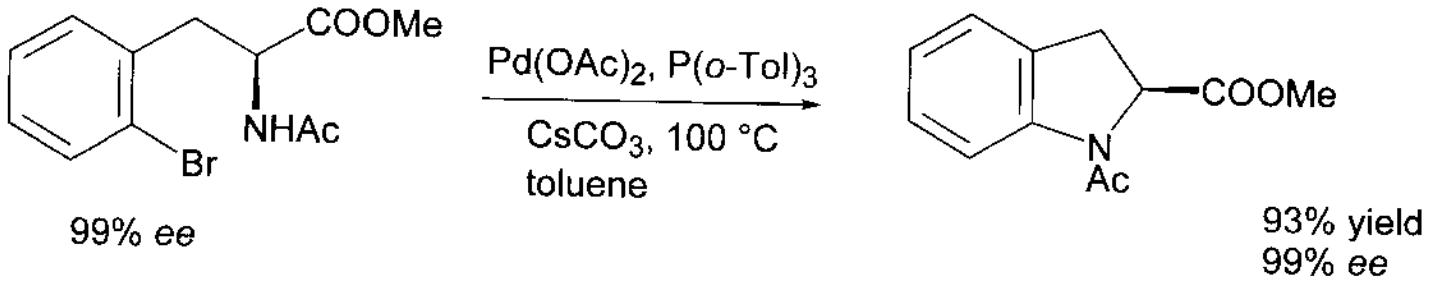
Buchwald-Hartwig coupling

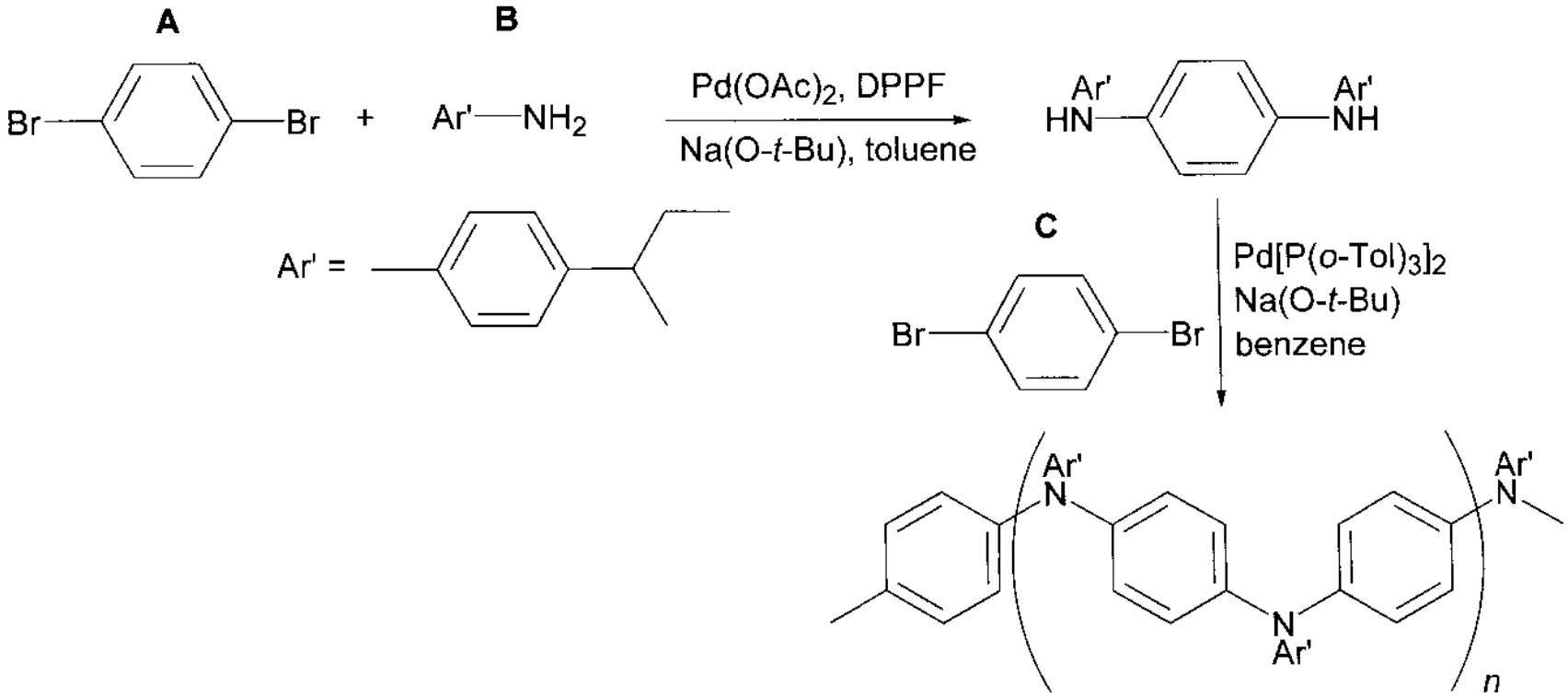




(*Buchwald*, 1997)

Buchwald-Hartwig coupling





Cross-coupling C-X with Cu

Reactions analogous to Buchwald-Hartwig couplings can be performed also using Cu(I) species as catalysts.

Such reactions originally belong to the arsenal of classic organic chemistry (Ullmann reaction, Goldberg reaction….) but only in the last two decades these reactions has been made catalytic in Cu and much more efficient (e.g. feasible at relatively low T).

The reactions can be performed with simple Cu(I) salts, but generally a chelating ligand (N-N, N-O or O-O) is added.

As organic halide, iodides or bromides are routinely employed, much more rarely chlorides.

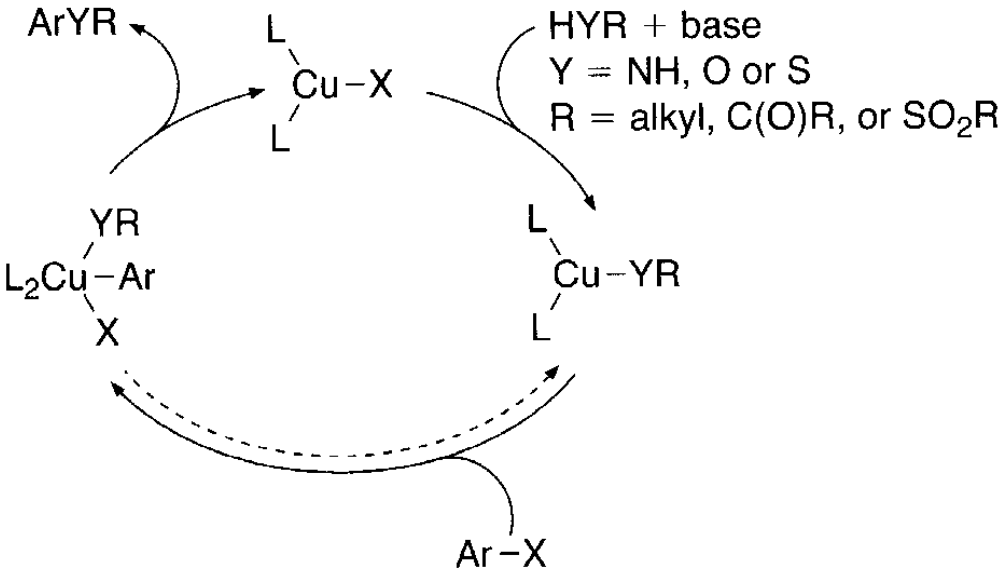
Cross-coupling C-X with Cu

The nucleophiles that can be employed in this reaction efficiently complement those utilized in Buchwald-Hartwig coupling (NH-heterocyclies, phenols). Some stabilized carbanions (e.g. β-diketonates) can also serve as nucleophiles.

The reaction mechanism has not been completely clarified; it is probable that it can be of different nature depending on the reagents, the catalyst and the reaction conditions. In some cases, significant proof has been collected favouring a mechanism similar to Buchwald-Hartwig and involving the Cu(I)/Cu(III) couple; in other cases a radicalic mechanism or mechanisms of yet another kind can be operative.

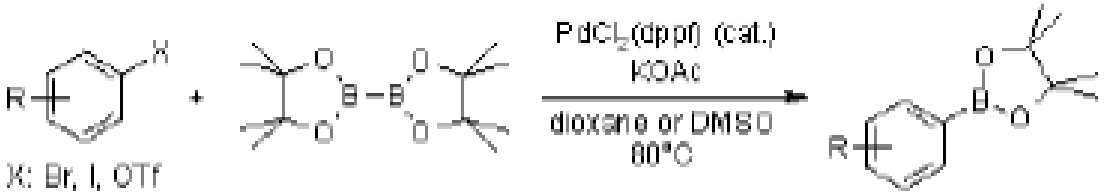
Rif.: F. Monnier, M. Taillefer, Angew. Chem. Int. Ed. 48 (2009) 6954

Cross-coupling C-X with Cu

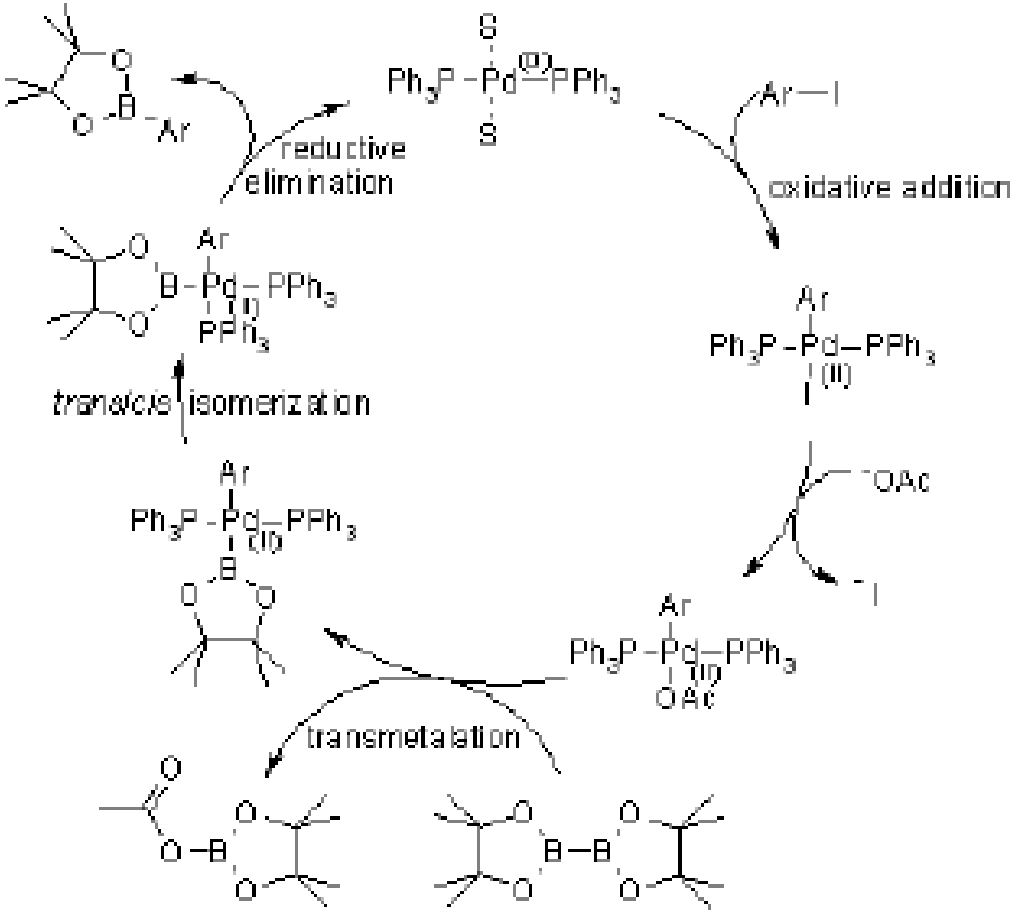


In this case, final reductive elimination is promoted by reaching first a <u>particularly high (unstable) oxidation state</u> for the metal!.

Cross-coupling C-B: Miyaura borylation



A base is needed which does not strongly coordinate to B (since quaternization triggers the consecutive Suzuki reaction) and helps B to access the Pd coordination sphere. KOAc is widely employed as reagent for this purpose.



Borylation through C-H activation

Very efficient reaction (< 1% cat., room T), tolerant to functional groups on Ar (even halides!), selectivity governed by steric and electronic factors (attack to the C-H in meta- o para-, not in ortho- with respect to the already present substituents), preferential attack to the most electron-poor C (most deshielded in ^{13}C-NMR).