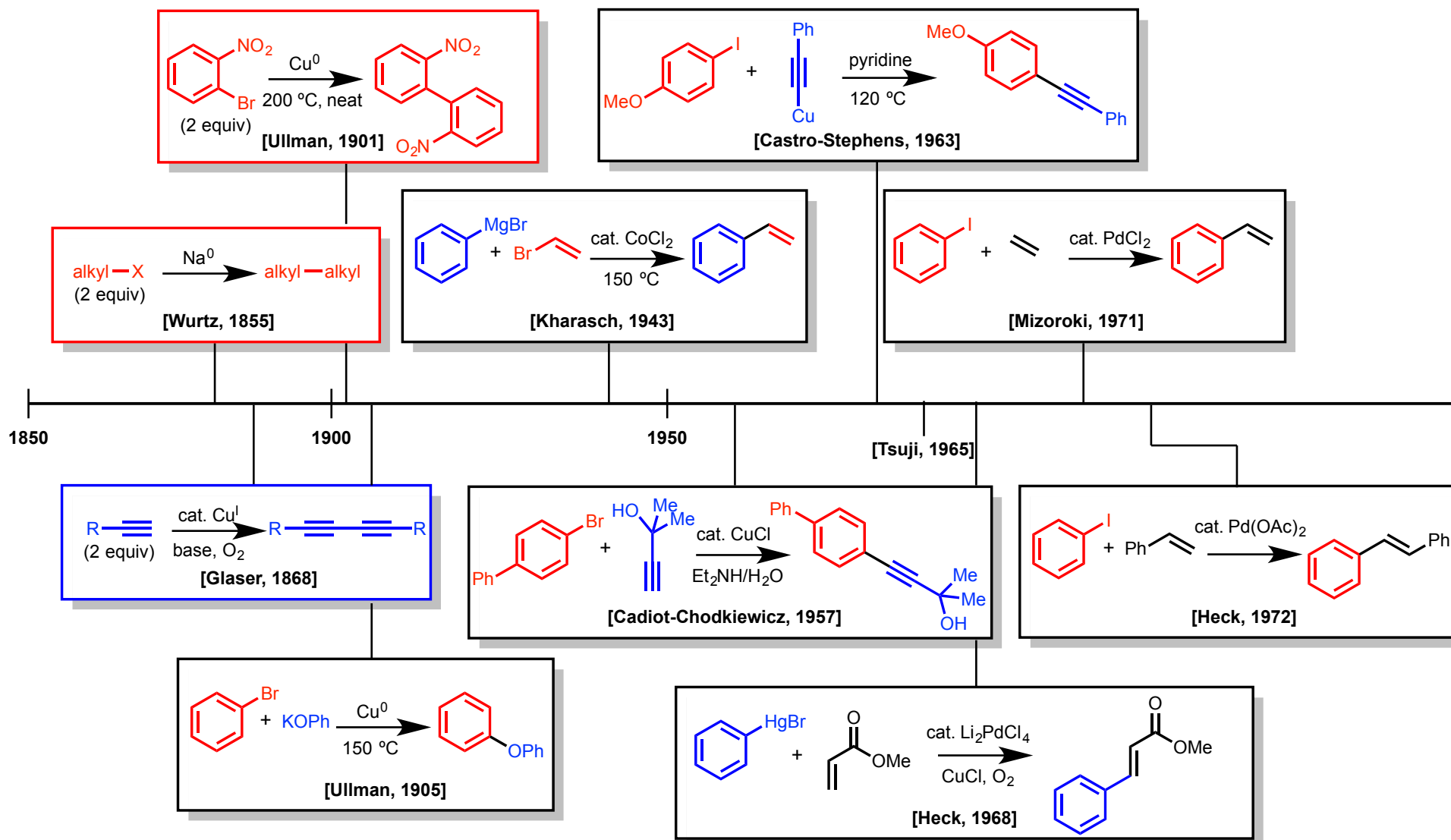
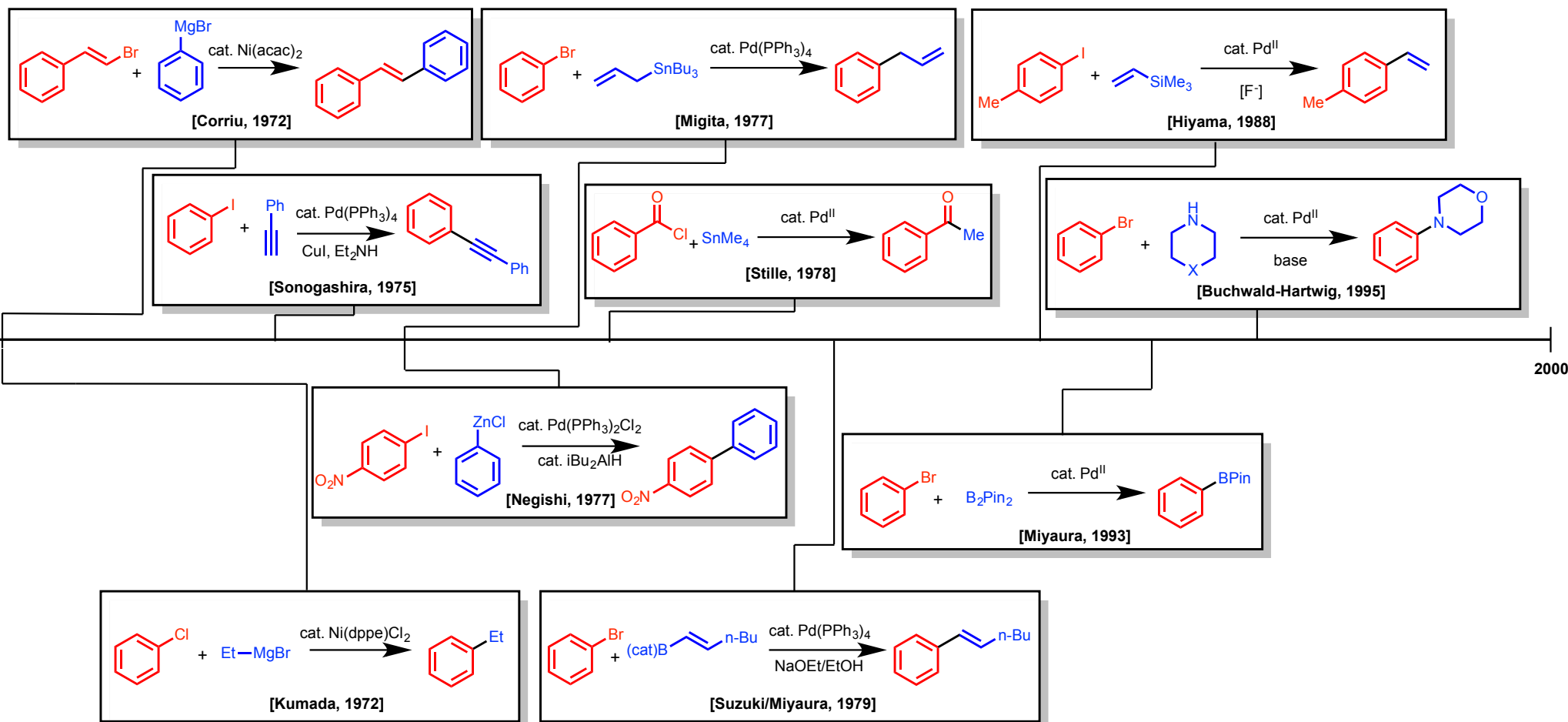


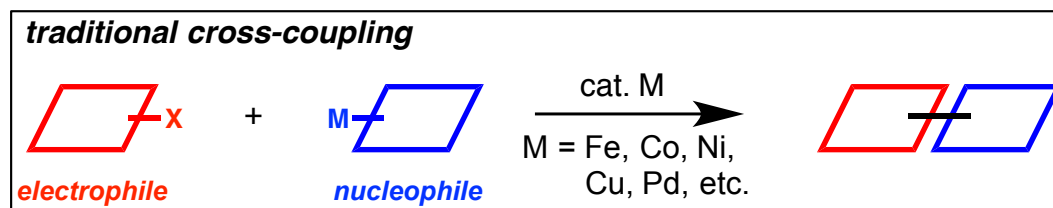
Timeline of Cross-coupling



Timeline of Cross-coupling

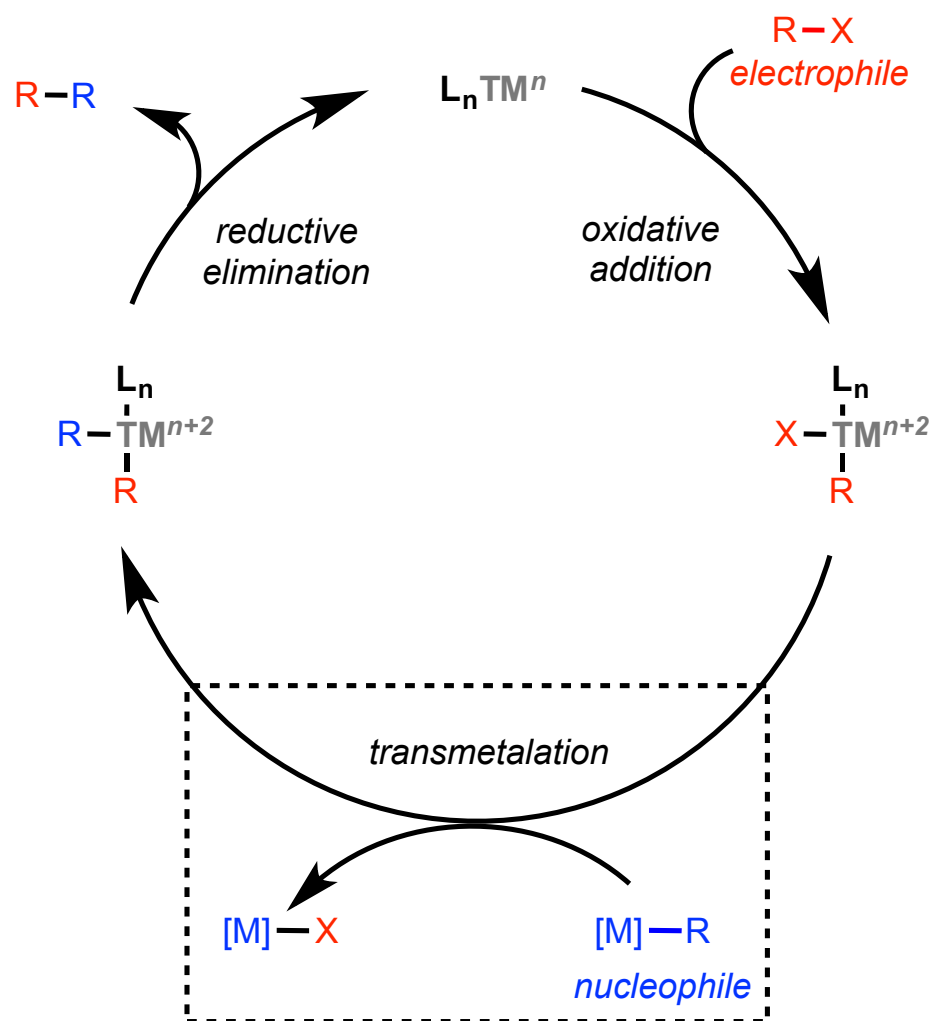


Traditional Cross-coupling



- The term “traditional” refers to the formation of a new bond between a pair of electrophile and nucleophile starting materials.
- In general, most “traditional” transition-metal-catalyzed cross-coupling reactions utilize three main elementary steps for productive catalysis: **(1) oxidative addition**, **(2) transmetalation**, and **(3) reductive elimination**.
- Cross-coupling reactions are differentiated by the *transmetalating agent* (i.e. Suzuki = B, Stille = Sn, etc.) and not by the active catalyst (i.e. Pd, Ni, Fe, etc.)

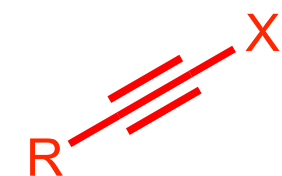
Traditional Cross-coupling: General Catalytic Cycle



$R-[M]$ <i>nucleophile</i>	Name <i>"X coupling"</i>
$R-MgX$	Kumada-Corriu
$R-SnR'_3$	Stille-Migita
$R-ZnX$	Negishi
$R-B[(O)R']_2$	Suzuki-Miyaura
$R-SiR'_3$	Hiyama-Denmark
$R \equiv Cu$ (<i>in situ</i>)	Sonogashira
<i>other nucleophiles:</i>	
$R-BiR_2$	$R-Li$
	$R-AlR_2$

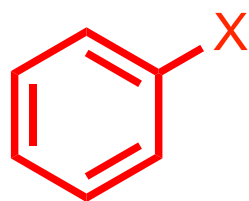
Traditional Cross-coupling: Commonly Encountered Electrophiles

C(sp)



X = I, Br, Cl

C(sp²)

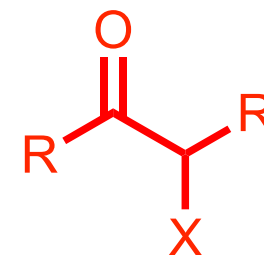


X = I, Br, Cl, F, OR, NR₃⁺, NO₂

C(sp³)

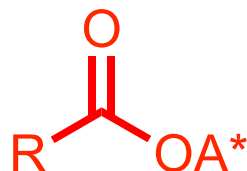


X = I, Br, Cl



X = I, Br, Cl

Other types of electrophiles:



X = Cl, OR, NR₂, SR



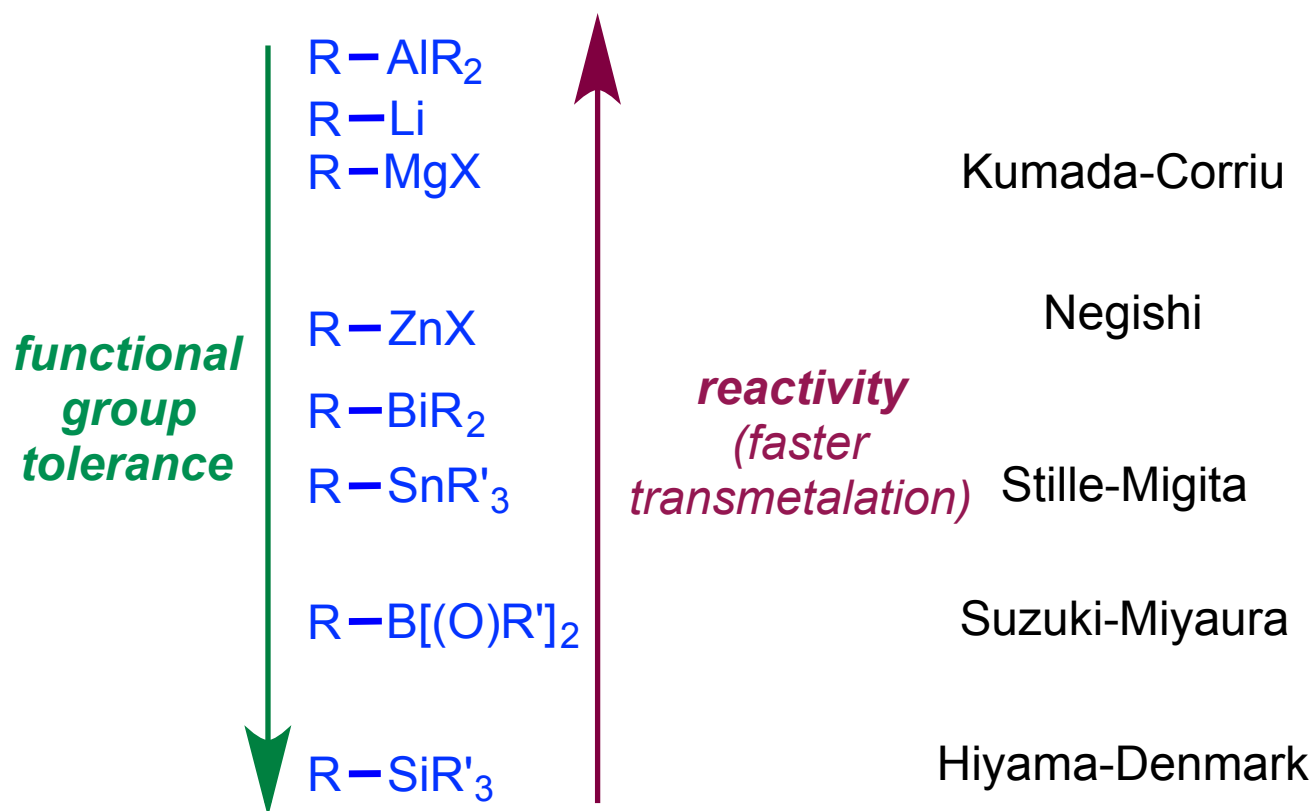
X = I, Br, Cl



X = I, Br, Cl, OR, NR₂, SR

Tsuji-Trost

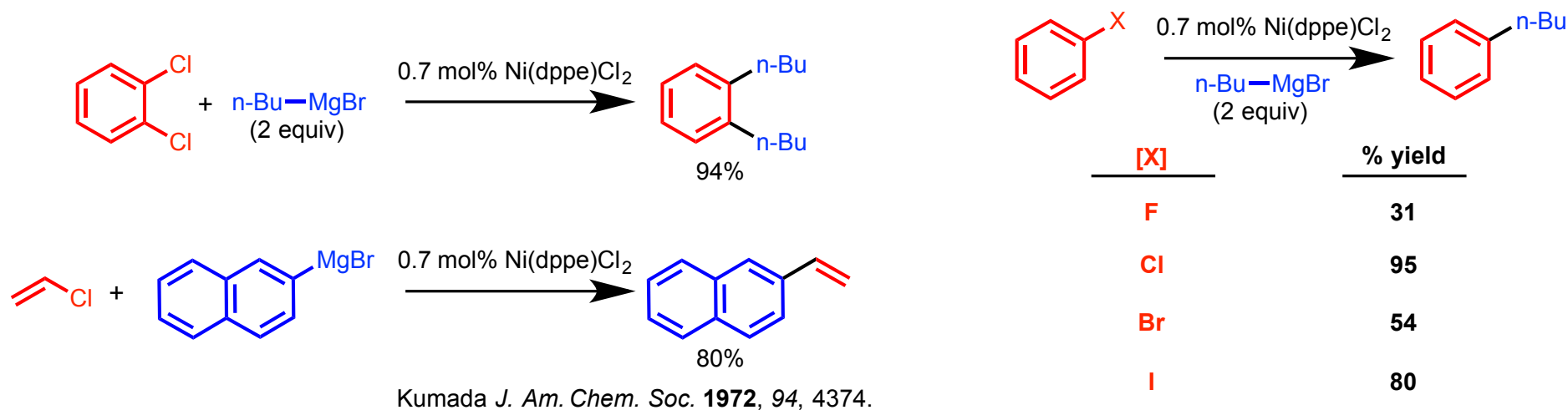
Traditional Cross-coupling: General Trends in Transmetalation



- General trend for transmetalation rates of specific carbogenic fragments is as follows:

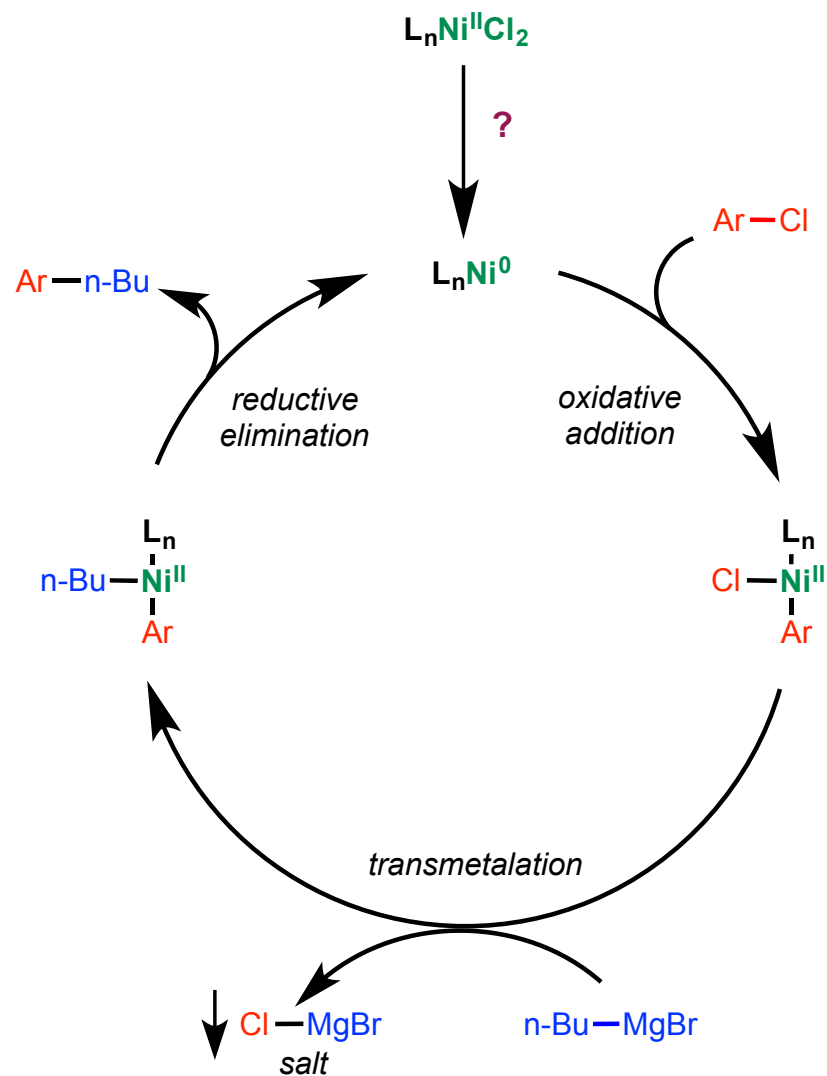


Kumada-Corriu Cross-coupling



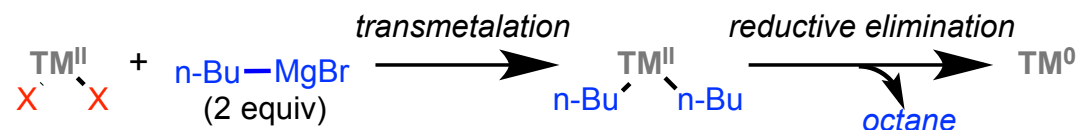
- First reported with a nickel(II) precatalyst to forge both $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ bonds.
- Nickel-catalyzed Kumada couplings generally react more efficiently with $\text{C}(\text{sp}^2)\text{-Cl}$ electrophiles.
- Palladium-catalyzed Kumada couplings were later developed and demonstrated broader substrate tolerance.

Kumada-Corriu Cross-coupling

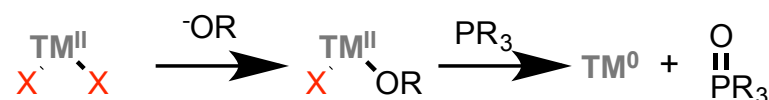


Three most common methods for reducing transition metals to active catalysts:

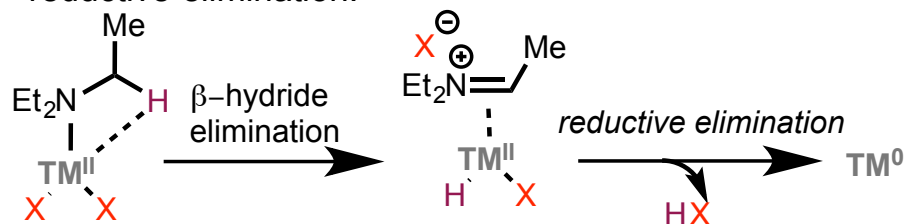
1. Double transmetalation followed by reductive elimination.



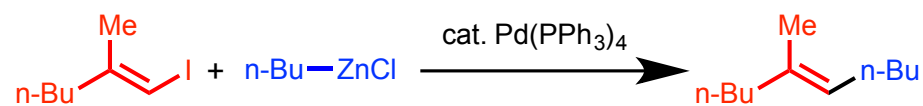
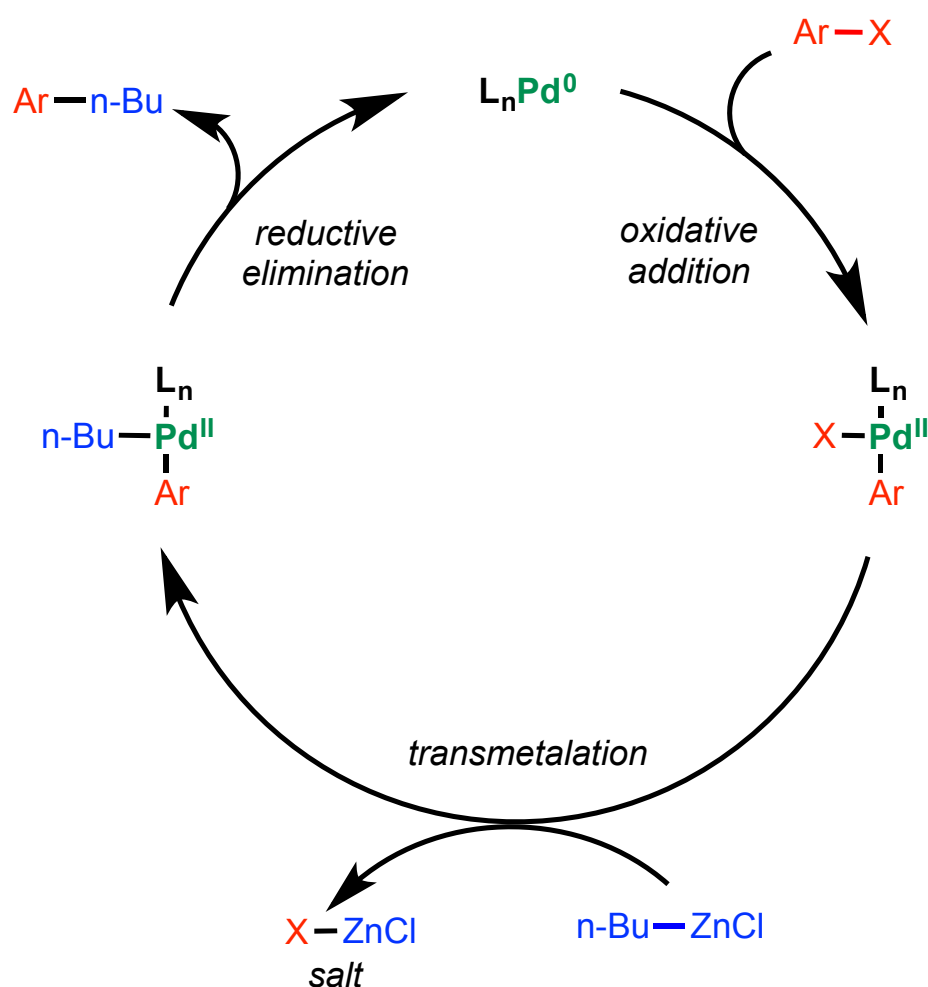
2. Phosphine redox with water or inorganic base.



3. Alkyl amine coordination (L), β -hydride elimination, then reductive elimination.



Negishi Cross-coupling

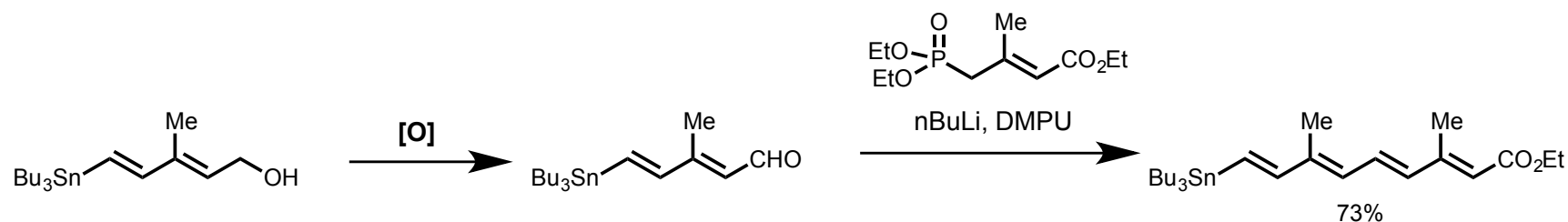


Negishi *J. Am. Chem. Soc.* **1980**, *102*, 3298.

- Organozinc reagents are more tolerant of carbonyl-containing compounds, rendering Negishi couplings attractive alternative to Kumada couplings.
- Though organozinc reagents are robust transmetalating agents, the transmetalation rate can be enhanced with the addition of a base to form the zinc-"ate" complex.
- Organozinc reagents can be synthesized in two main ways: (1) *transmetalation from Grignard reagents*, or (2) *zinc insertion with alkyl halides*.

Stille-Migita Cross-coupling

- Stille coupling is widely regarded as one of the most effective cross-coupling reactions invented – extraordinarily high functional group tolerance, high reactivity, air- and moisture stable, and can be installed early on in a sequence without decomposition.



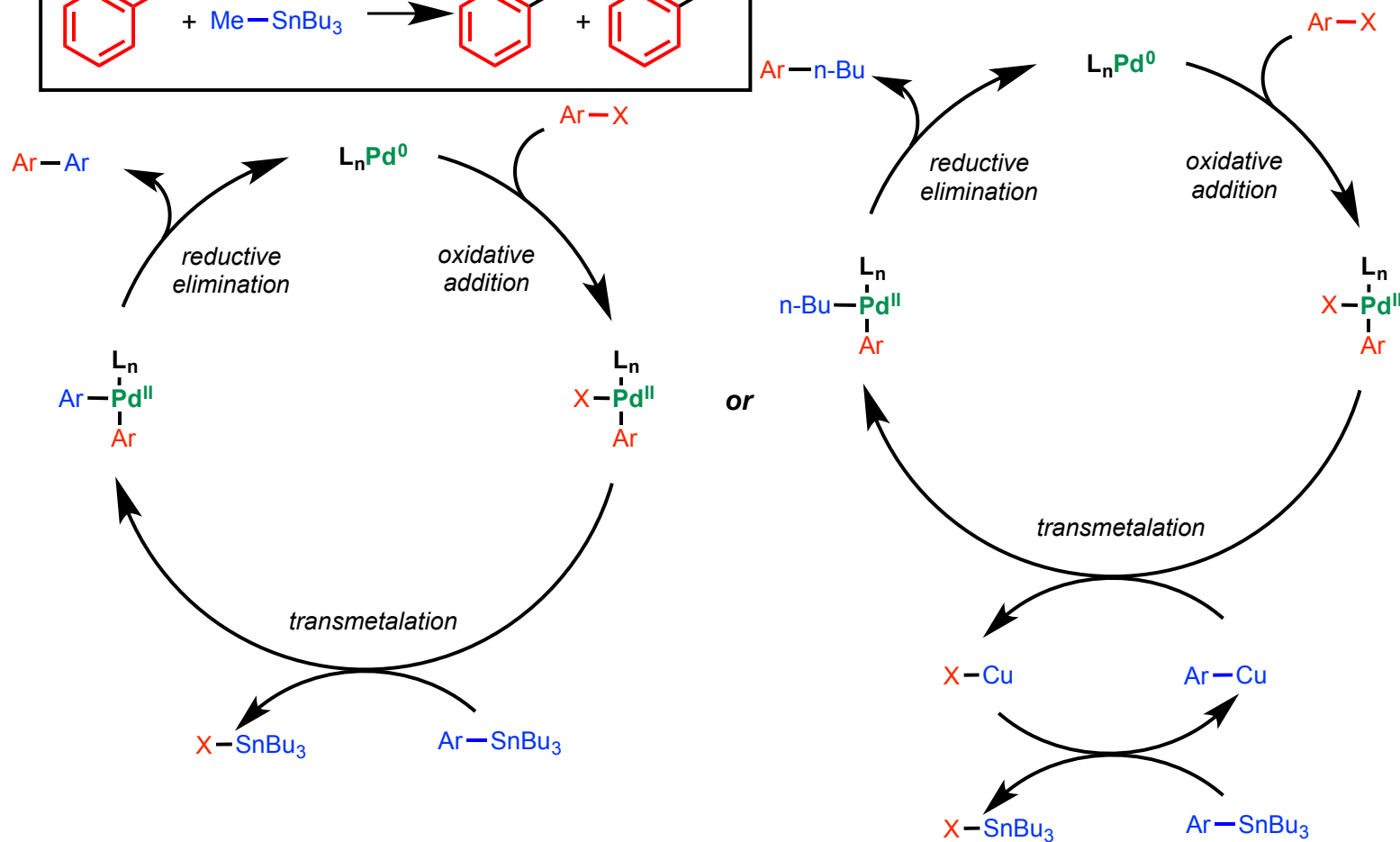
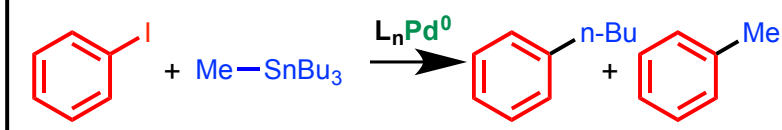
- Despite the appeal of organotin species in organic synthesis from a cross-coupling perspective, they are often mislabeled as being harsh neurotoxins.
- From an atom-economy standpoint, “dummy” ligand alkyl groups on organotin reagents can often be problematic if transferred. (See stannatranes for strategies overcoming this obstacle!)

Stille-Migita Cross-coupling

- In the presence of a copper co-catalyst in palladium-catalyzed Stille couplings, the reaction rate and yield is tremendously increased. Why?
 - *Transmetalation from copper to palladium is more favorable – desired organic fragment is transmetalated to copper and then to palladium.*
 - *CuI can act as a ligand scavenger (mainly phosphines) to free palladium coordination sites.*
 - *Transmetalation to copper slows reversible transmetalation from palladium to tin – tin salts will irreversibly form.*
 - Another strategy (also used in Suzuki-Miyaura couplings) is to add a fluoride base to create insoluble stannous fluoride and drive transmetalation equilibrium.
-

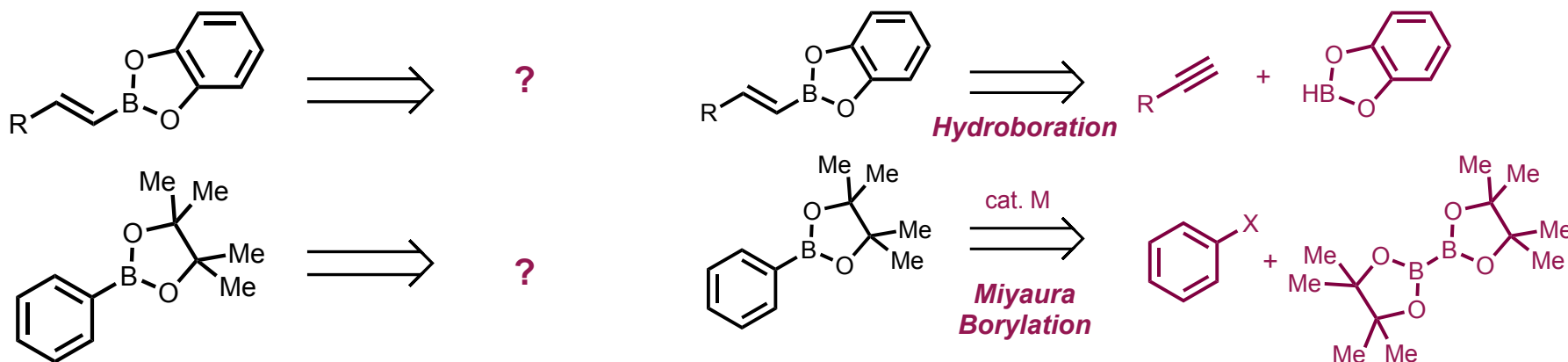
Stille-Migita Cross-coupling

Note: One of the greatest limitations of alkylating Stille couplings is "dummy" ligand transfer.



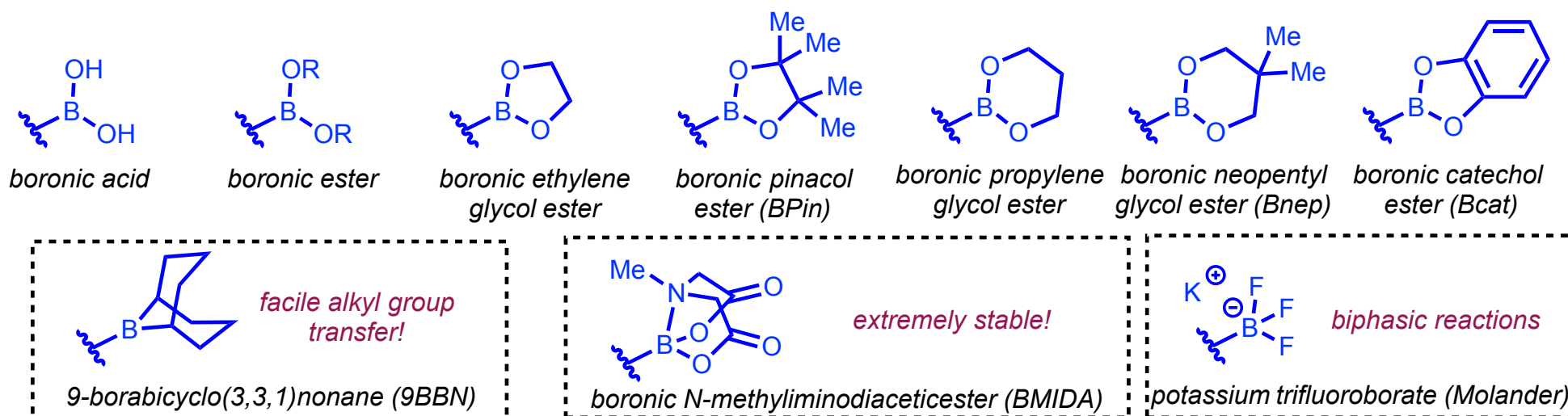
Suzuki-Miyaura Cross-coupling

- Suzuki-Miyaura couplings are considered the most balanced and reliable cross-coupling – most commonly used cross-coupling reaction in industrial setting.
- The high functional group tolerance and relatively non-toxic (though recent studies are proving otherwise) nature of boronic acids in conjunction with their ease of installation makes retrosynthesis involving Suzuki couplings more prevalent.



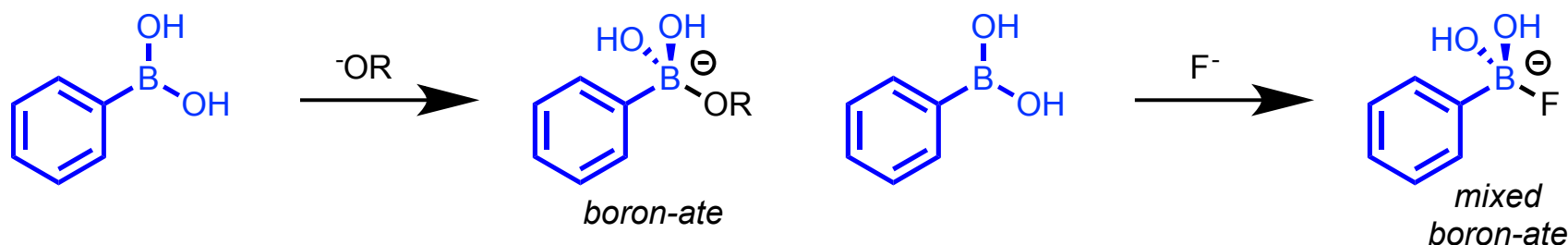
Suzuki-Miyaura Cross-coupling

- A variety of boronate esters can be used in the Suzuki coupling, each with unique properties that most commonly impact the stability of the organoboron reagent.
- In general, electron-rich and unhindered boronates are most reactive. Why?

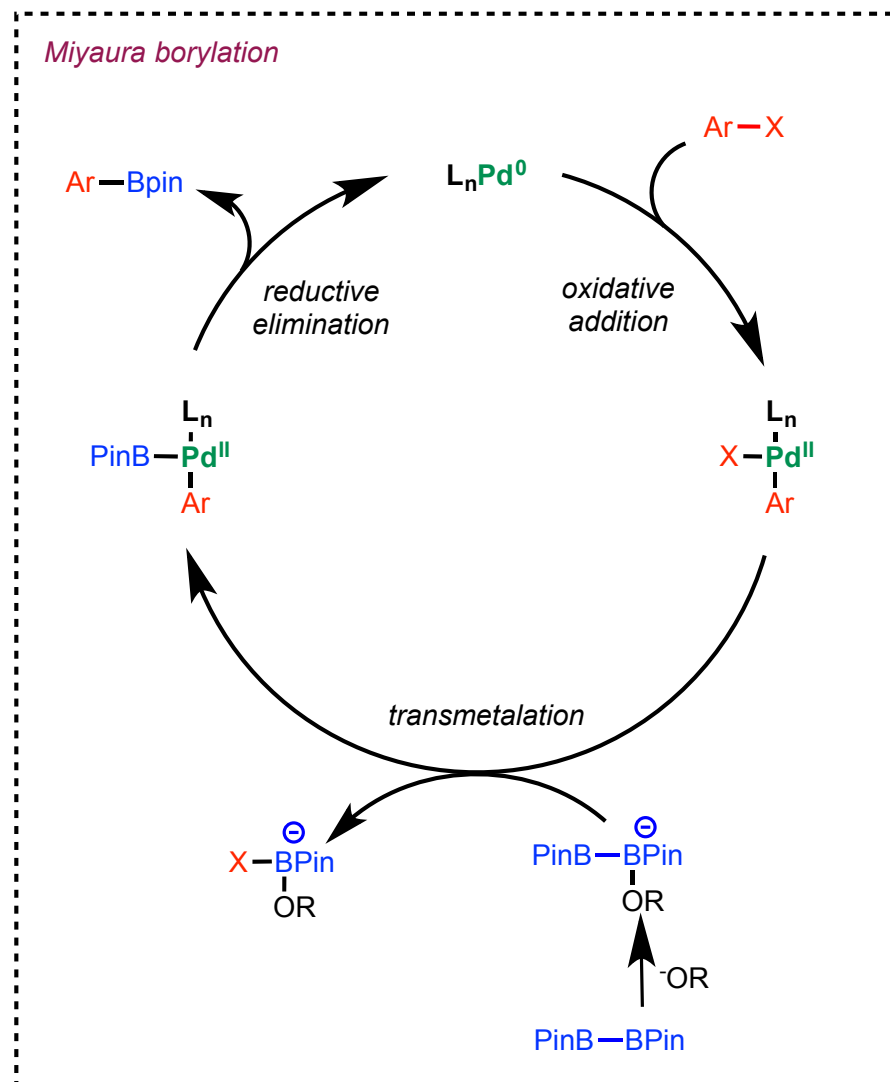
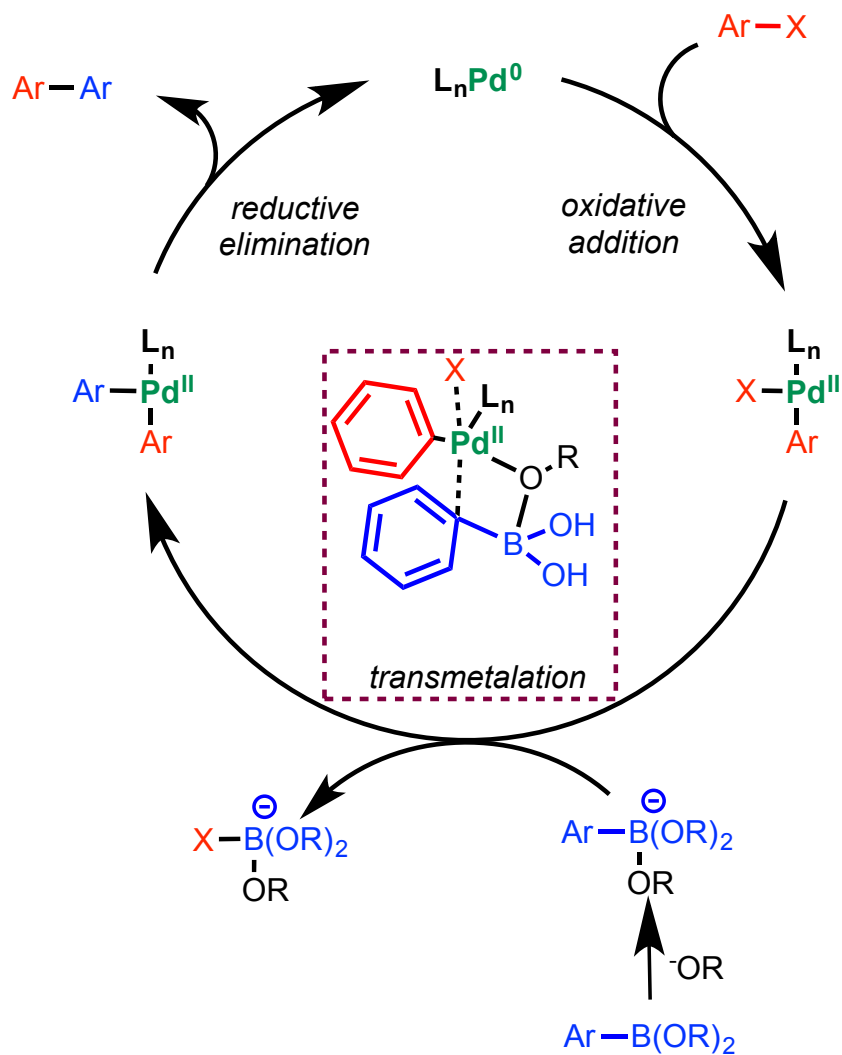


Suzuki-Miyaura Cross-coupling

- In the vast majority of Suzuki couplings, especially those involving a reactive electrophile, transmetalation is the rate determining step. (For more detail in the context of Pd-catalyzed mechanism, see pioneering work by Denmark)
- In nearly all cases, optimized Suzuki couplings require the formation of boron-"ate" complexes using inorganic bases.



Suzuki-Miyaura Cross-coupling

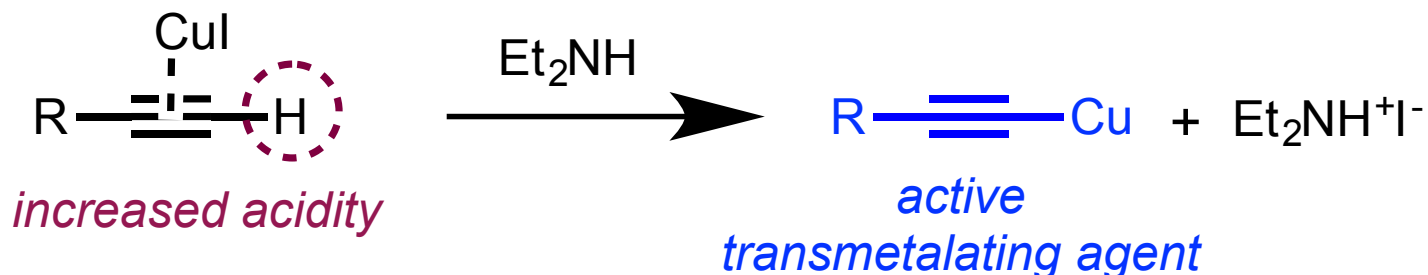


Hiyama-Denmark Cross-coupling

- Hiyama-Denmark couplings are by far the least commonly used cross-coupling reaction; however, it benefits from full functional group tolerance.
- Similar to the Suzuki coupling, organosilicon reagents *must* be activated (silic-“ate”) using fluoride anion for the transition-metal-catalyzed process to proceed.

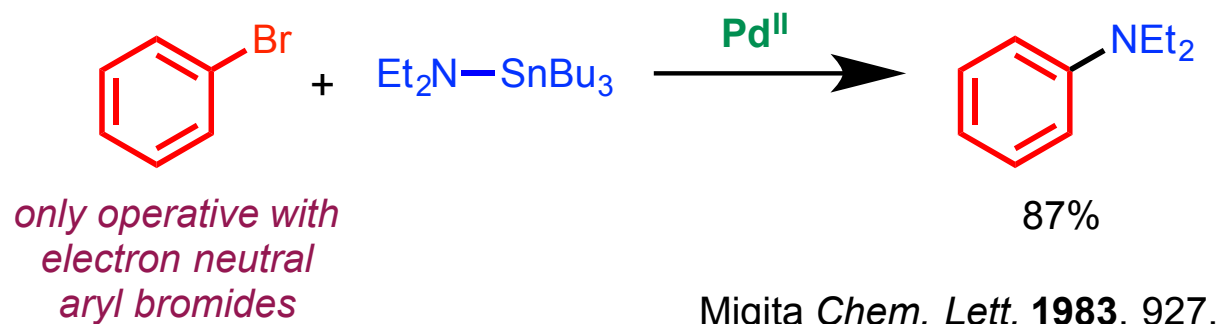
Sonogashira Cross-coupling

- Sonogashira coupling is one of the most widely utilized methods for C(sp)–C(sp²) bond formation with high functional group tolerance.
- Mainly limited to C(sp²) electrophiles, though alkyl-Sonogashira reactions are being studied.
- It is the only cross-coupling reaction that initially used an *in situ* generated transmetalating species through deprotonation/metalation.



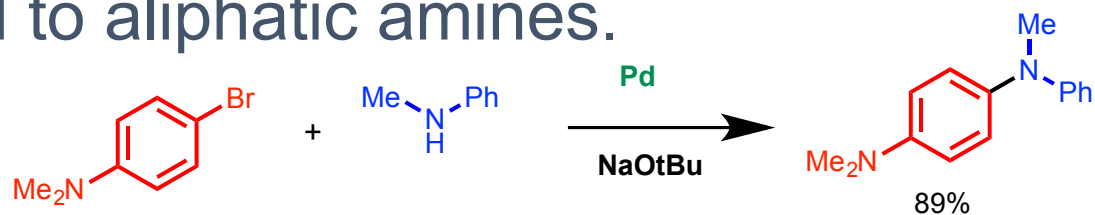
C–X bond forming Cross-coupling

- Based on the catalytic cycles of cross-coupling reactions, it became clear that pre-formed transmetalating nucleophiles could be replaced with classical nucleophiles.
- Stille and Migita demonstrated C–N bond formation using tin amides, relying on the preparation of toxic stannanes.

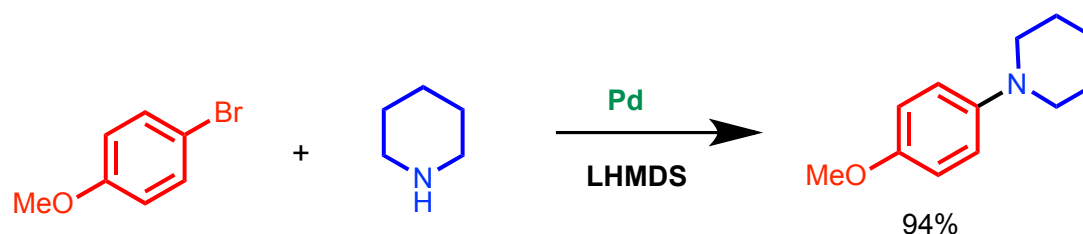


Buchwald-Hartwig Amination

- Concurrently, Buchwald and Hartwig developed C–N bond forming palladium-catalyzed reactions using a “soft deprotonation” approach.
- In this reaction, aryl electrophiles could be effectively coupled to aliphatic amines.

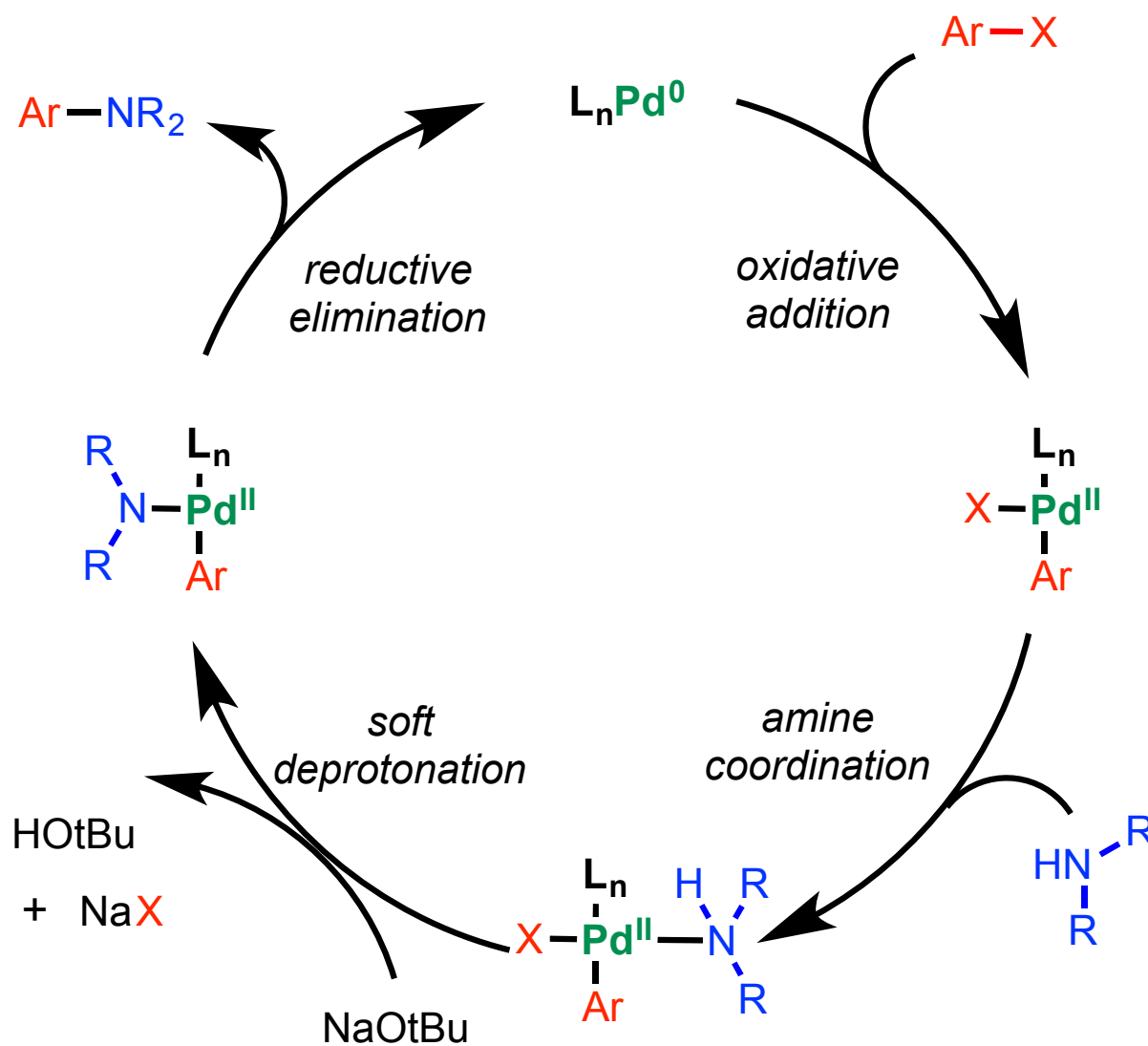


Buchwald *Angew. Chem. Int. Ed.*, **1995**, 34, 1348.



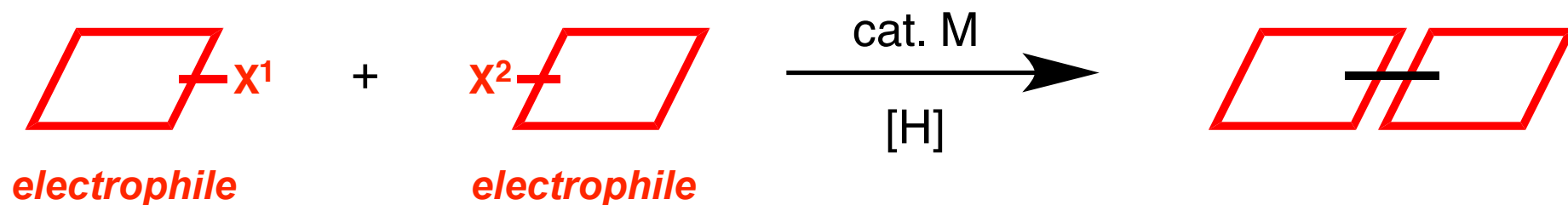
Hartwig *Tetrahedron. Lett.* **1995**, 36, 3609.

Buchwald-Hartwig Amination



Further exploration: Oxidative and Reductive Couplings

reductive cross-coupling



oxidative cross-coupling

