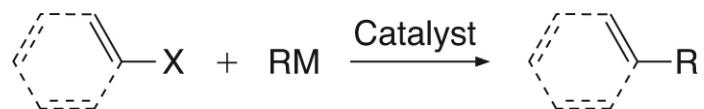


Transition Metal Catalyzed Coupling Reactions

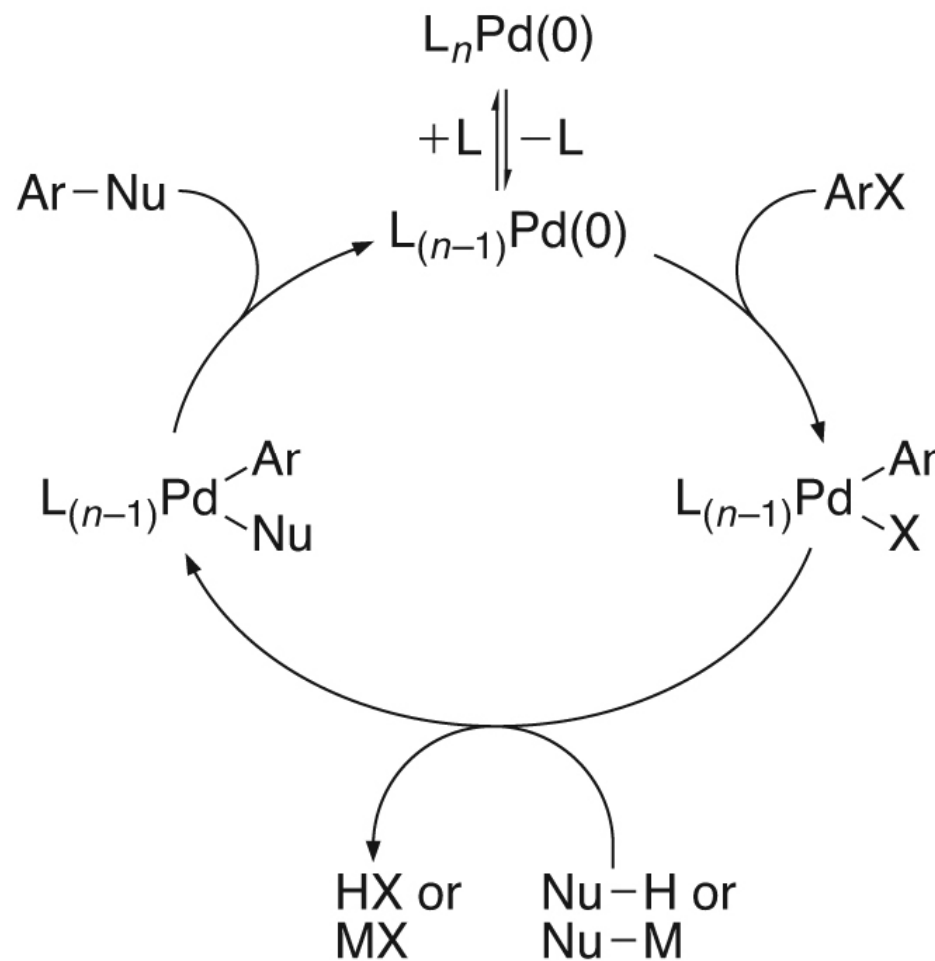
- Catalytic nucleophilic substitution reactions comprise some of the most commonly used catalytic processes in synthetic organic chemistry.



- The original cross-coupling reactions formed C-C bonds, however catalytic carbon heteroatom C-X formation has now been developed where X = N, O, S, P, Si, B.
- A list of well known (*not comprehensive*) C-C and C-X bond forming reactions is given below
 - Ulmann coupling & condensation
 - Kumada
 - Negishi
 - Fukuyama
 - Glaser & Hay
 - Hiyama-Denmark
 - Mozoriki-Heck
 - Stille
 - Suzuki-Miyaura
 - Sonogashira
 - Buchwald-Hartwig
 - Chan-Lam

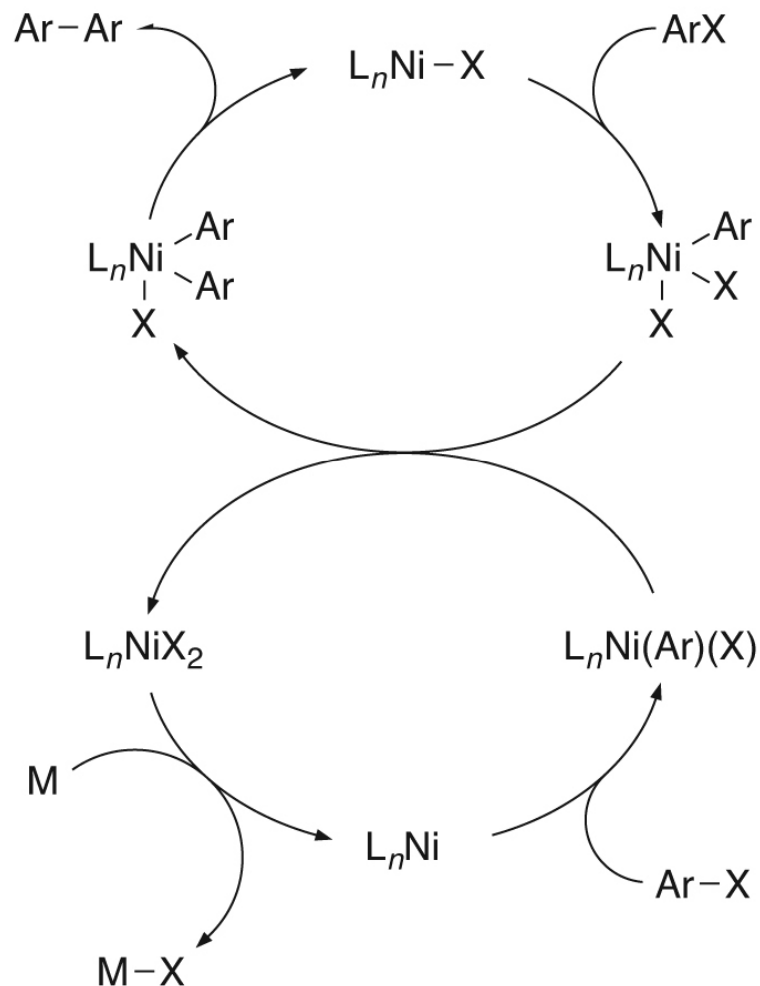
Cross-Coupling Reactions

- The mechanism of the various cross-coupling reactions (with the exception of the Heck reaction) includes three stages:
 - Oxidative addition
 - Transmetalation (*+isomerization*)
 - Reductive elimination
- As we have already covered, oxidative addition and reductive elimination are multi-step as they involve ligand association and dissociation respectively.
- Transmetalation involves the exchange of ligands between two metal centers.



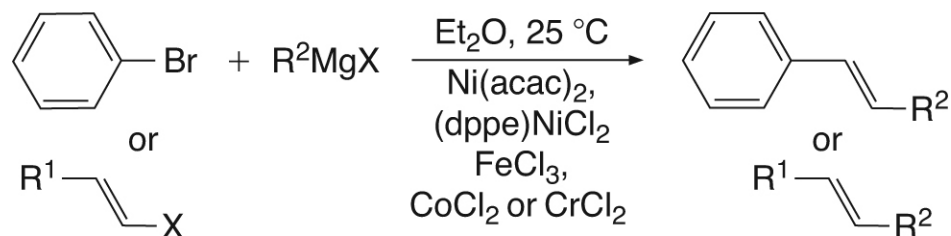
Homo-Coupling Reactions

- Homocoupling is less well studied and thus understood as its cross-coupling analogue.
- Suggested mechanisms have invoked sequential oxidative addition of an aryl halide to produce the $L_nM^{IV}Ar_2Cl_2$ species. Alternatively, one could imagine how disproportionation of the $L_nM^{II}ArCl$ species could lead to $L_nM^{II}Ar_2$. In each case reductive elimination resulting in the symmetrical bisaryl.
- Kochi showed using a stoichiometric reaction involving a Ni reagent that a more complex mechanism is likely taking place involving Ni^I , Ni^{II} and Ni^{III} .

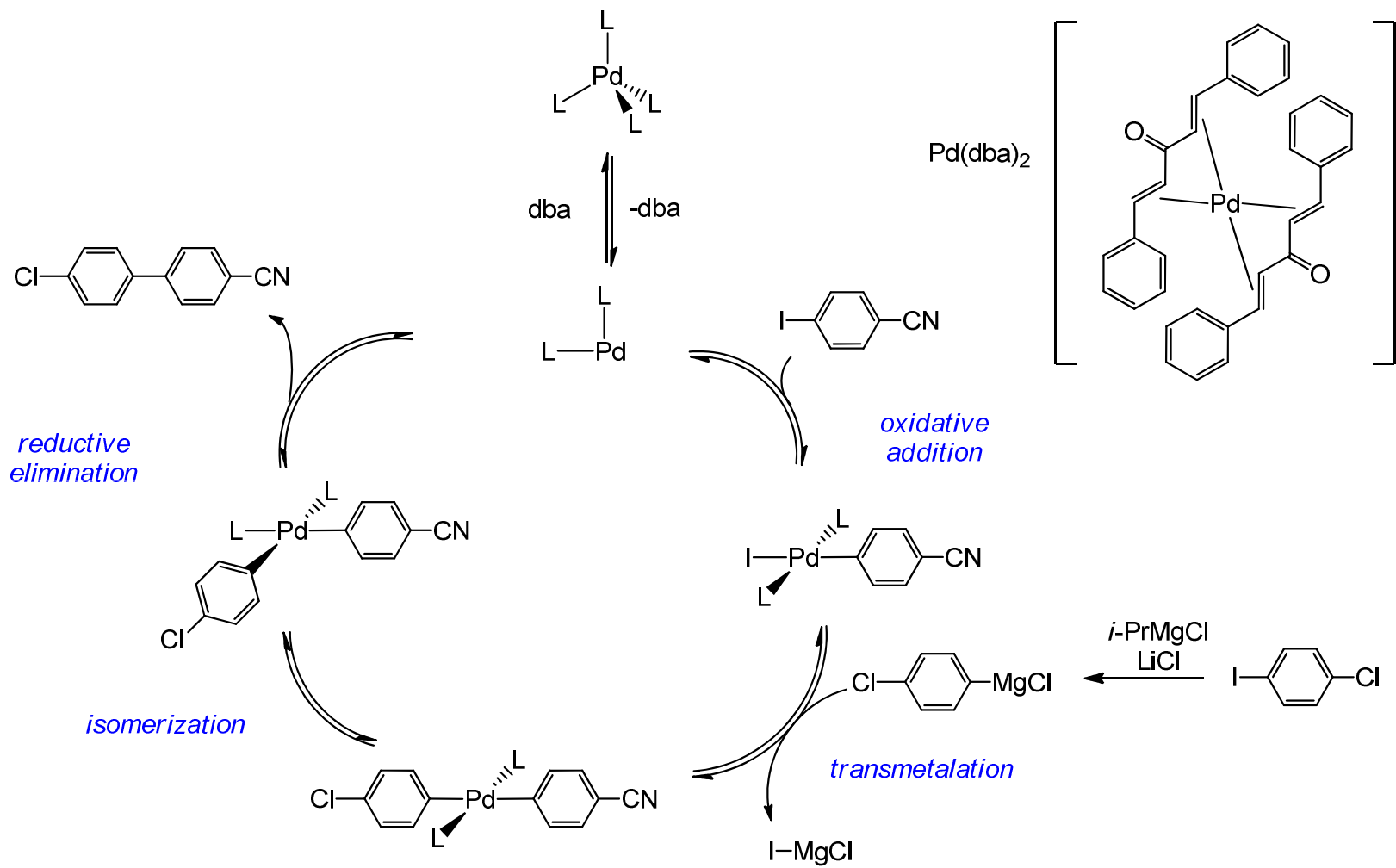


Kumada Coupling

- In 1972 Kumada and Corriu independently reported the first Pd or Ni-catalyzed cross coupling reaction towards C-C bond formation.
- Kumada coupling involves **coupling of a Grignard reagent with alkyl, vinyl or aryl halides** in the presence of a Ni transition metal catalyst providing an economic transformation.
- Less efficient catalysts were reported earlier by Kochi (Fe) and Kharasch (Co & Cr).

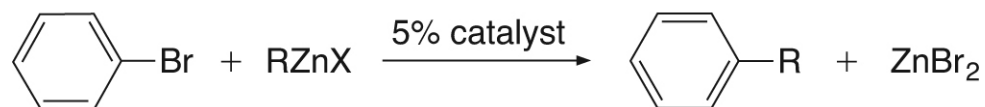


- The reaction is limited to however to halide partners that do not react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives, and the Kumada Coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls.
- The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of Grignard reagents to zinc compounds for the starting materials in the Negishi Coupling.



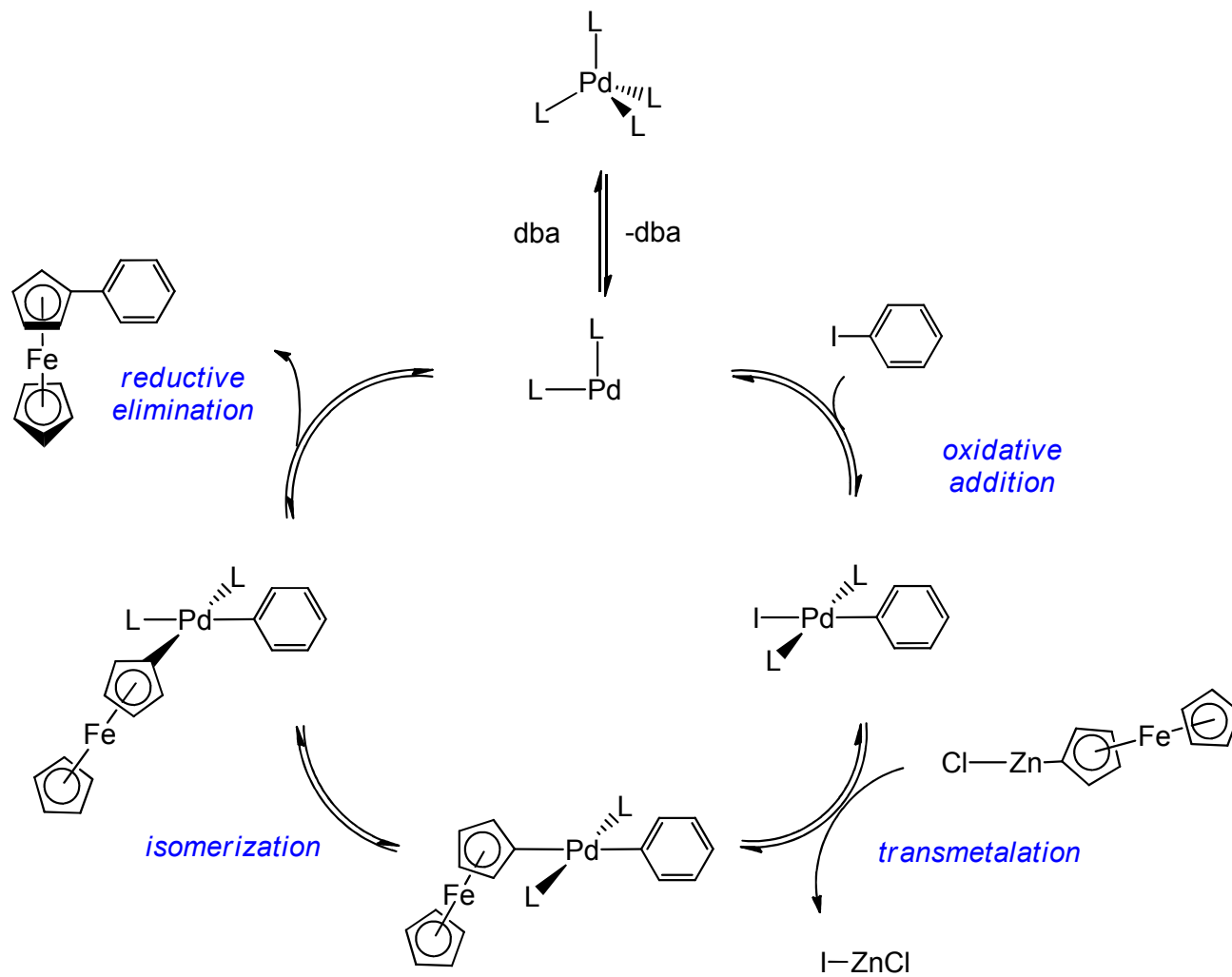
Negishi Coupling

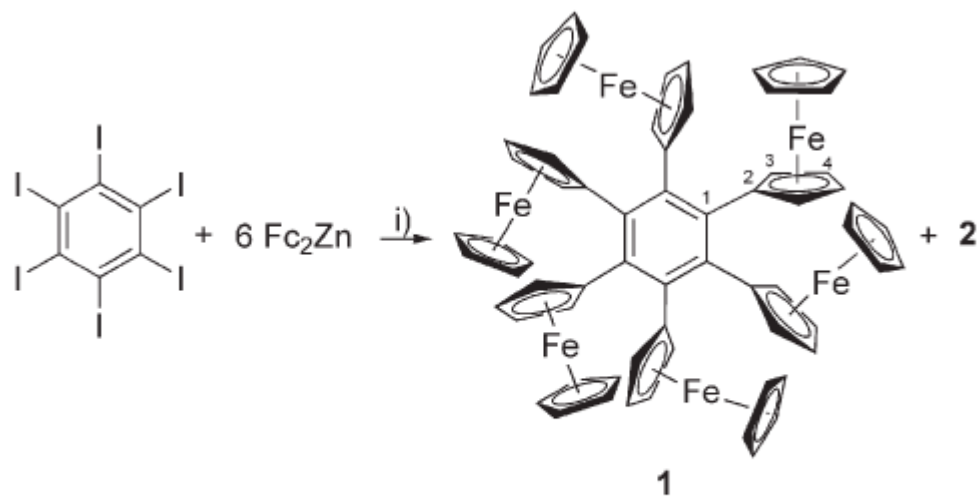
- Since the reports of Kumada and Corriu, many advances have been made in the types of carbon nucleophiles available for cross-coupling processes as alternatives to Grignards reagents.
- Although Grignard reagents are easy to generate, and many are commercially available, they have low functional group tolerance.
- In 1977 Negishi reported the preparation of unsymmetrical biaryls in good yields via nickel- or palladium-catalyzed **coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl)**.



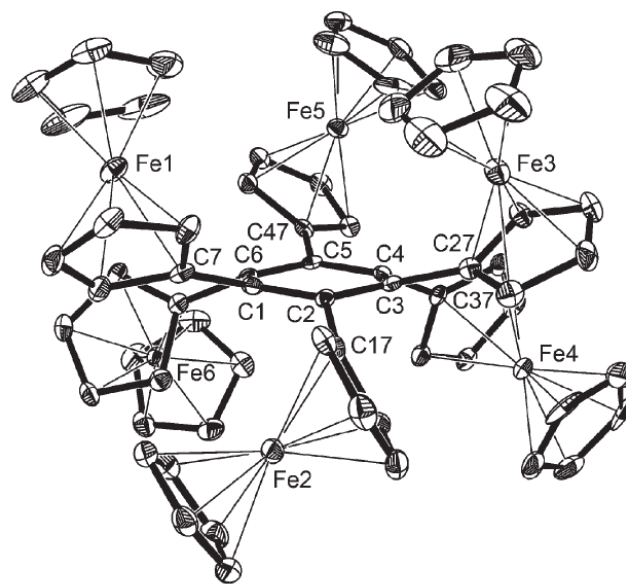
Catalyst = $(\text{PPh}_2)_4\text{Ni}$ from $\text{Ni}(\text{acac})_2/\text{PPh}_3/\text{Bu}^t_2\text{AlH}$
or $(\text{PPh}_3)_2\text{PdCl}_2$ and Bu^t_2AlH

- The Negishi reaction has broad scope, and is not restricted to the formation of biaryls.
- Pd catalysts tends to be less sensitive to oxygen and are believed to be less toxic than their Ni counterparts. Furthermore they tend to react without the intervention of radical intermediates that can lead to side products (e.g. homocoupling, racemization, isomerization).



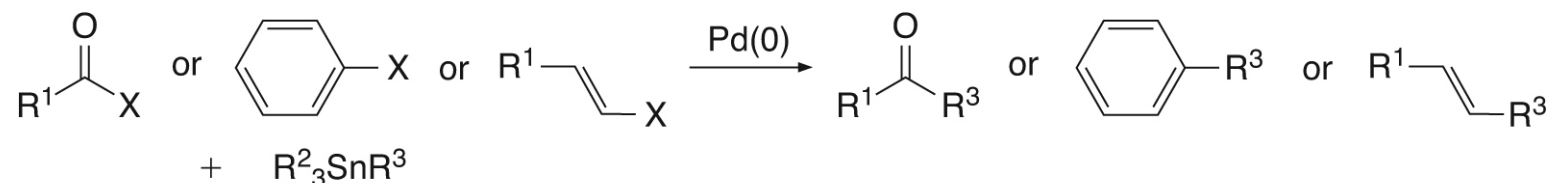


Scheme 1 Synthesis of hexaferrocenylbenzene **1**. *Reagents and conditions:* (i) $\text{Pd}_2(\text{dba})_3$ (30%), THF, 68 °C, 63 h.

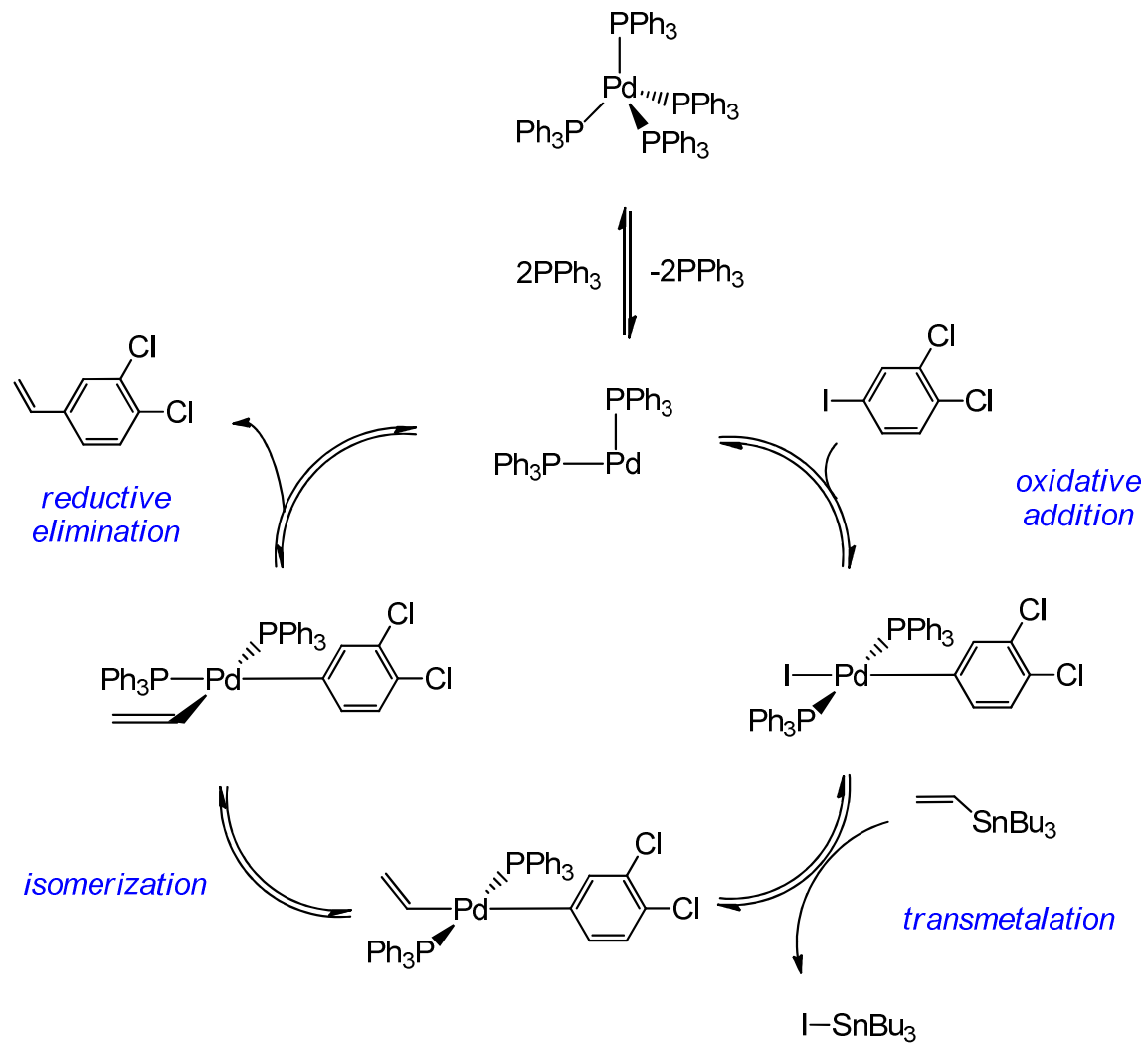


Stille Coupling

- The Stille Coupling is a versatile C-C bond forming reaction between **stannanes** and **halides** or **pseudohalides**, with very few limitations on the R-groups.

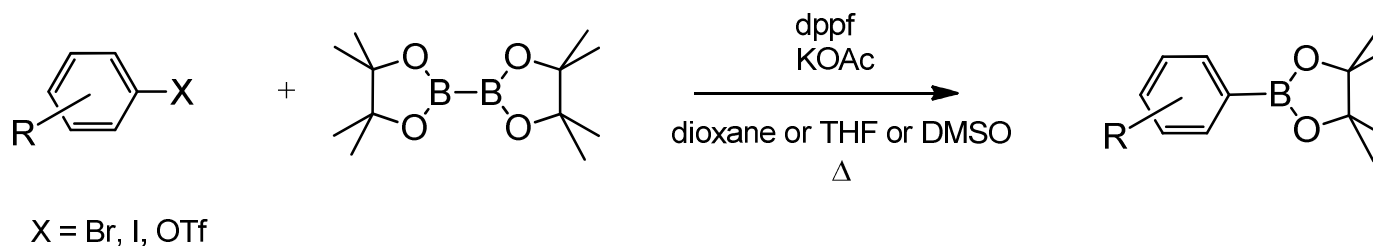


- The main drawback is the **toxicity of the tin compounds** used, and their low polarity, which makes them poorly soluble in water.
- Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki Coupling.
- Improvements in the Suzuki Coupling may soon lead to the same versatility without the safety drawbacks of using tin compounds.

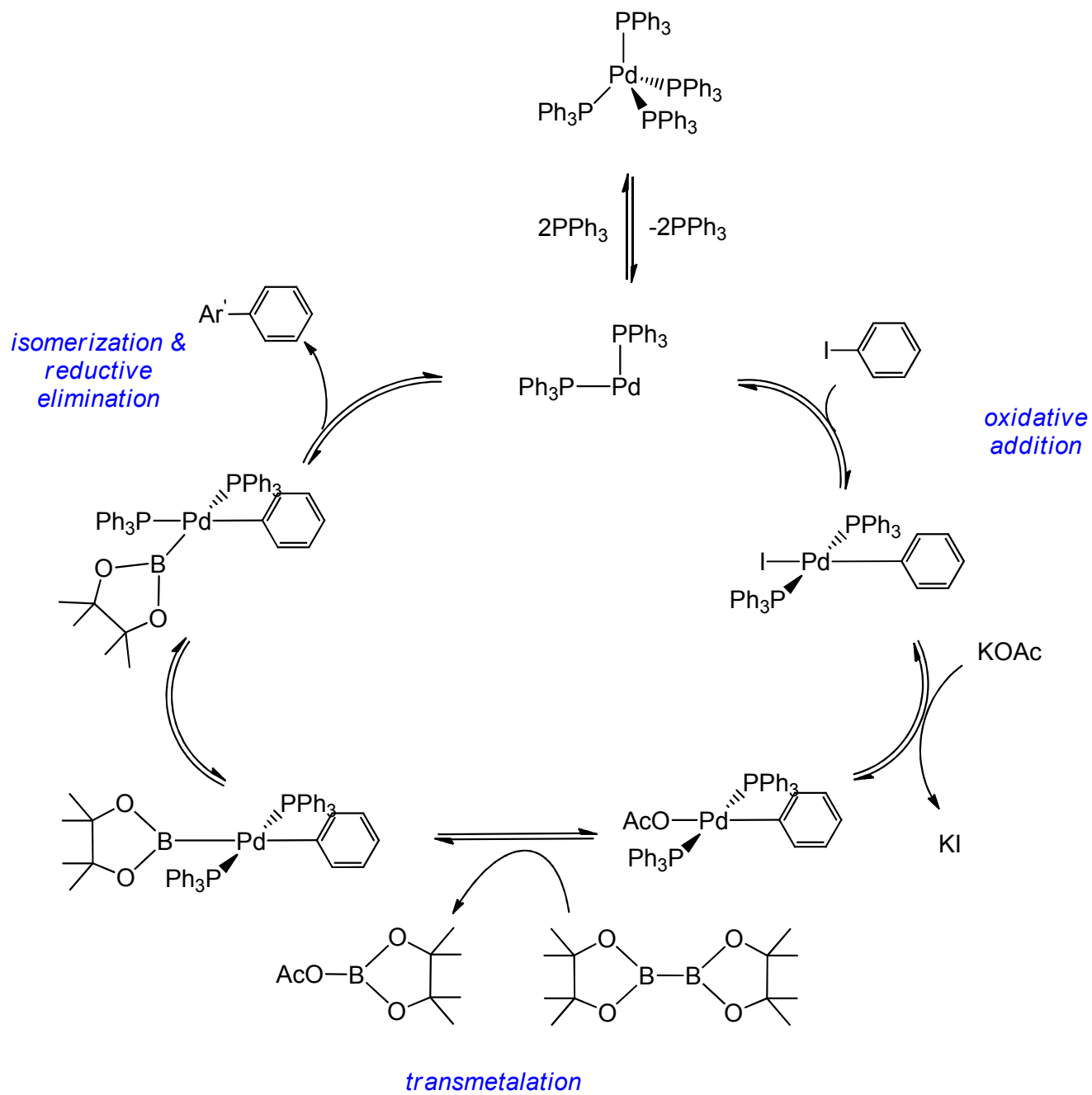


Miyaura Borylation

- The coupling of organoboron reagents has become the most commonly used cross-coupling process. Organoboron reagents are less toxic than organotin reagents and tend to undergo coupling reactions in the presence of a variety of functional groups.
- The Miyaura borylation reaction enables the synthesis of boronates by cross-coupling of bis(pinacolato)diboron with aryl halides and vinyl halides.

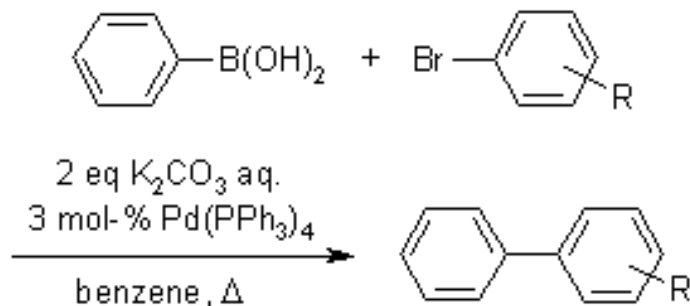


- Borylated products derived from bis(pinacolato)diboron allow normal work up including chromatographic purification and are stable towards air. Pinacol esters are difficult to hydrolyze, but they may serve as coupling partners in the Suzuki Coupling and similar reactions without prior hydrolysis.
- Crucial for the success of the borylation reaction is the choice of an appropriate base e.g. KOAc, as strong activation of the product enables the competing Suzuki Coupling.

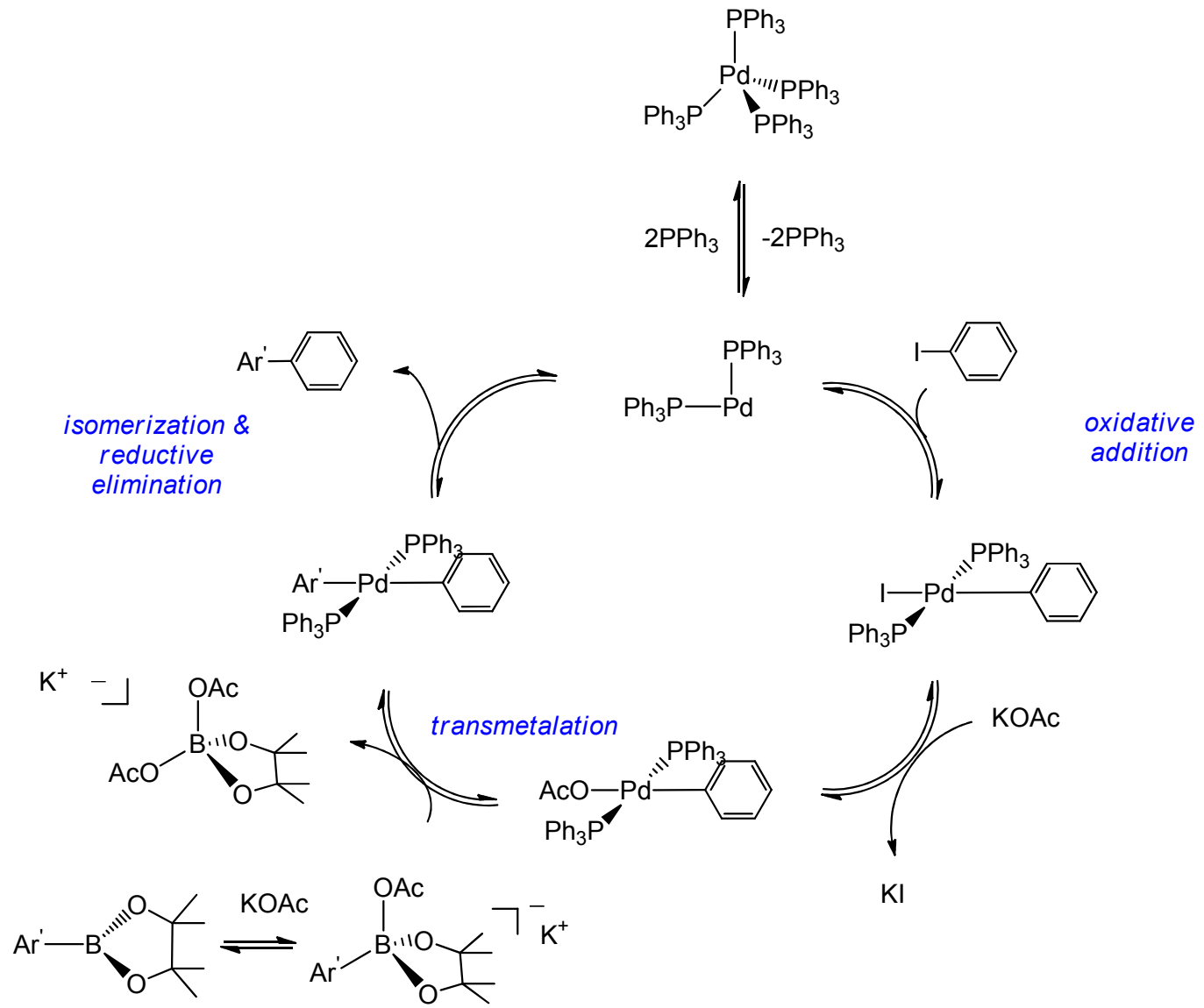


Suzuki Coupling

- The coupling of organoboron reagents has become the most commonly used cross-coupling process. Organoboron reagents are less toxic than organotin reagents and tend to undergo coupling reactions in the presence of a variety of functional groups.
- Like neutral organosilicon groups (Denmark rxn), however, neutral organoboron reagents do not undergo metal-catalyzed cross-coupling without an additive.
- Suzuki showed that addition of a hard base, e.g. OH^- or F^- , causes the organoboron reagent to undergo cross-coupling by generating a four-coordinate anionic organoboron reagent that transfers the organic group from boron to the metal catalyst.
- The scheme below shows the first published Suzuki Coupling, which is the palladium-catalysed cross coupling between organoboronic acid and halides.

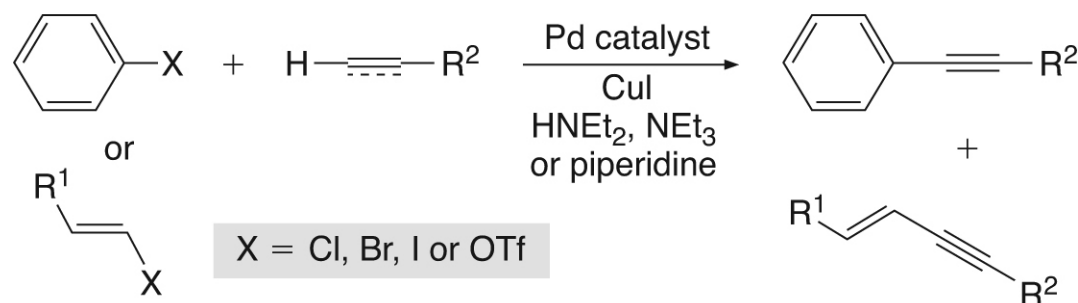


- Recent catalyst and methods developments have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls.
- Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners.
- One difference between the Suzuki mechanism and that of the Stille Coupling is that the boronic acid must be activated, for example with base.
- This activation of the boron atom enhances the polarization of the organic ligand, and facilitates transmetalation.
- If starting materials are substituted with base labile groups (for example esters), powdered KF effects this activation while leaving base labile groups unaffected.

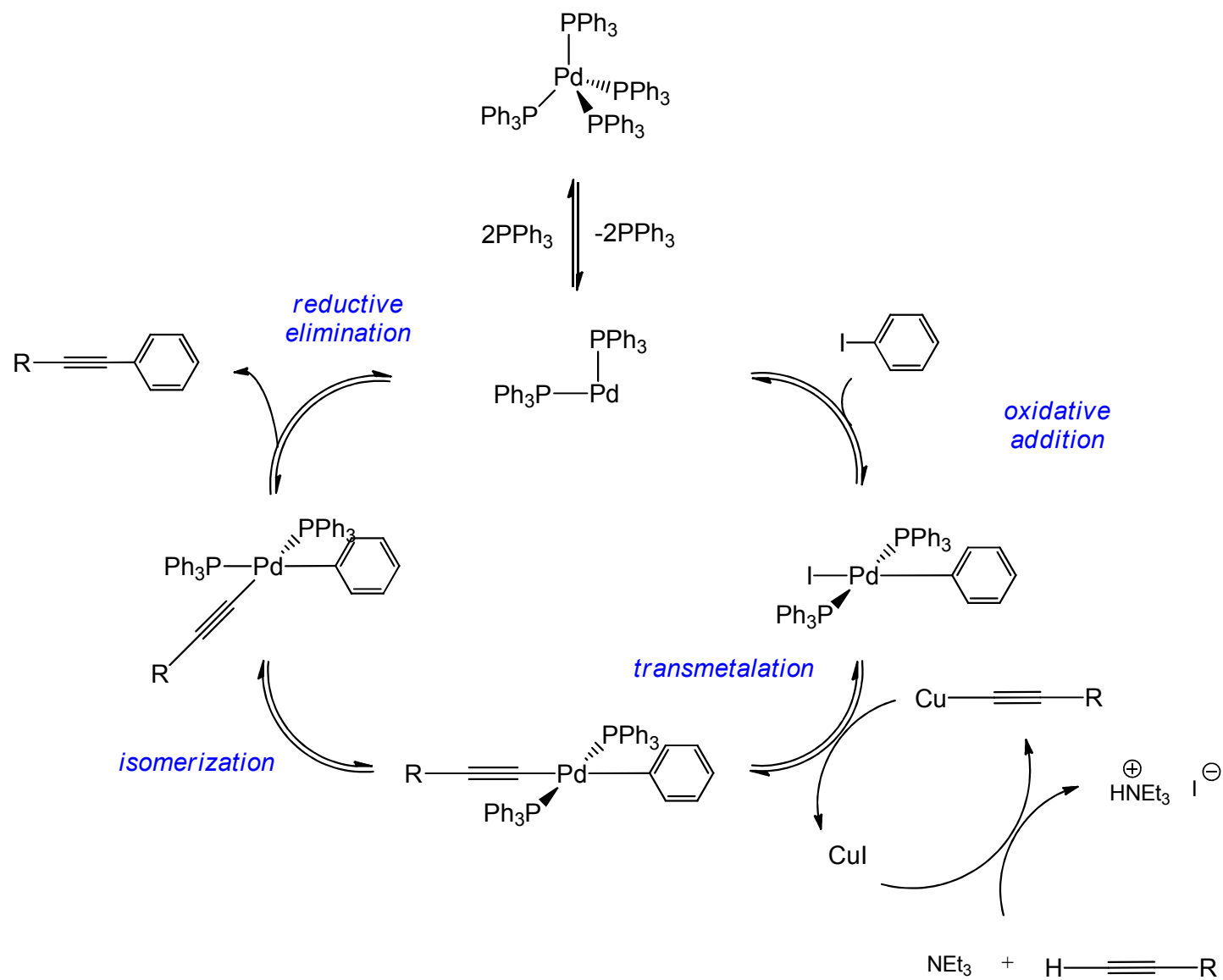


Sonogashira Coupling

- Compounds containing reactive C-H bonds have been shown to undergo cross coupling in the presence of catalyst and base without initial formation and isolation of a main group derivative.
- One classic version of this coupling is the reaction of an aryl halide with a terminal alkyne to form an alkynylarene.
- Although Heck and Cassar independently reported this reaction in 1975 Sonogashira reported that reactions with added copper occur under milder conditions.

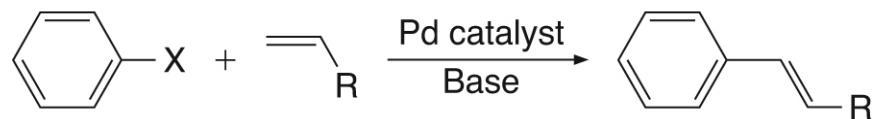


- The copper additive is believed to generate a copper acetylide which then reacts with the Pd catalyst during the coupling process.
- This coupling of terminal alkynes with aryl or vinyl halides is now known as the Sonogashira reaction and is performed with a palladium catalyst, a copper(I) co-catalyst, and an amine base.
- Typically, the reaction requires anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions are not important.



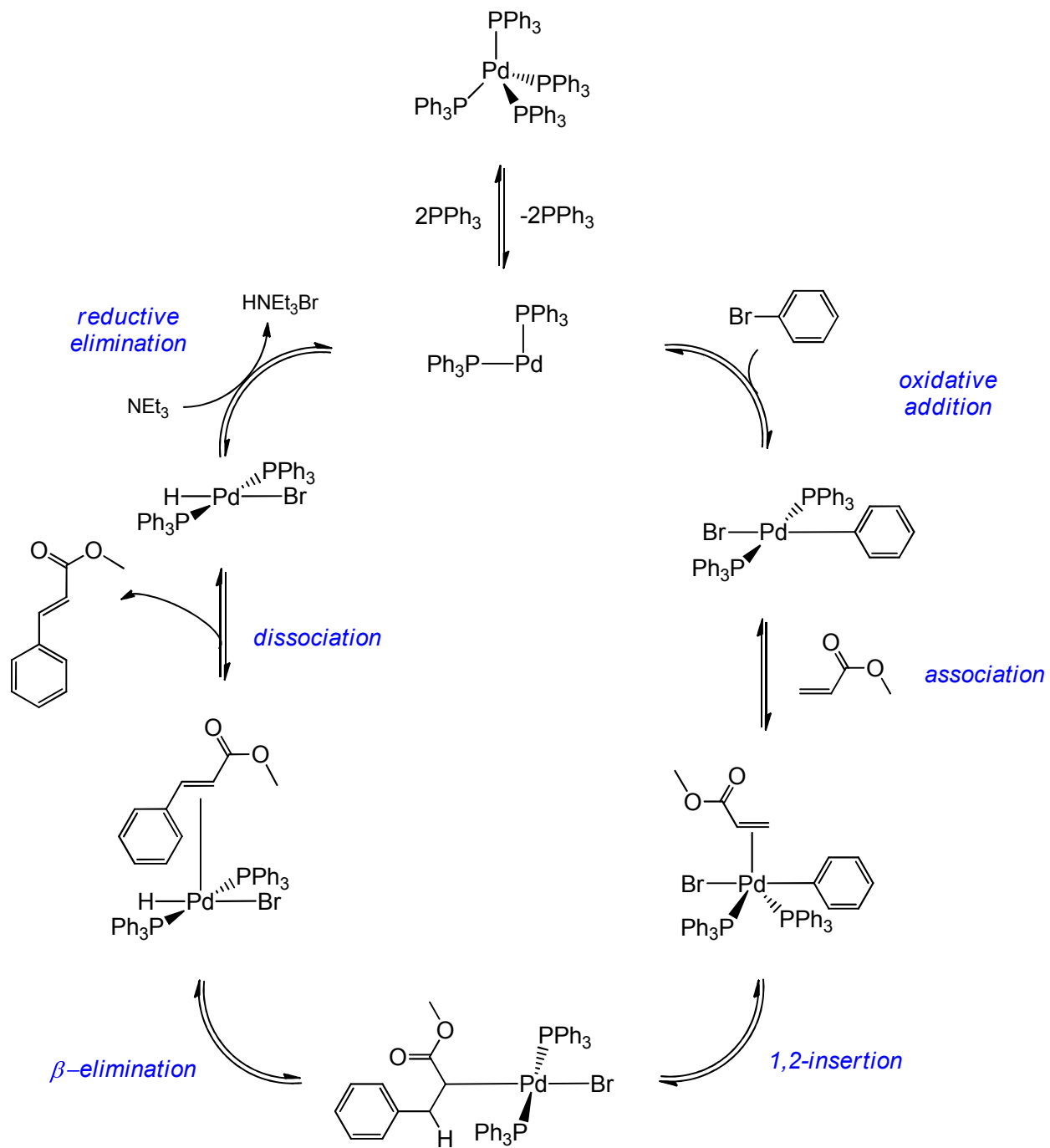
Mizoroki-Heck Coupling

- The Mizoroki-Heck C-C bond forming reaction is coupling of an aryl halide with an olefin to cleave the C-H bond of the olefin and replace it with an aryl group.
- This reaction was first reported by Mizoroki but later developed and optimized by Heck.
- The reaction is most commonly conducted with electron-deficient olefins, such as styrene or acrylate derivatives – the electronic properties of which tend to favor formation of conjugated products.



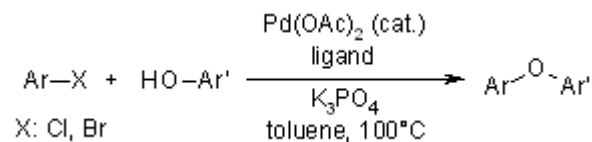
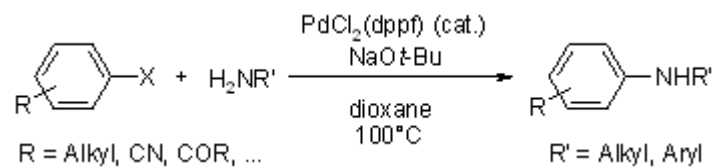
- Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.
- Reaction with aliphatic electrophiles remains rare.
- One of the benefits of the Heck Reaction is its outstanding trans selectivity.

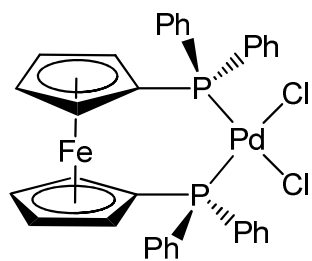
- The Mizoroki-Heck reaction follows a different course from the other cross-coupling reactions after the oxidative addition step.
- The olefin coordinates to the metal center, e.g. Pd^{II}, after oxidative addition of the aryl or vinyl halide.
- This ligand association may occur by associative displacement of a monodentate ligand from the metal center or it may occur by replacement of halide by the olefin to generate a cationic olefin complex.
- In some cases the aryl or vinyl triflate may be used in place of the halide. In this case the olefin readily displaces the triflate to generate a cationic metal-olefin complex.
- 1,2-insertion then takes place to generate a metal-alkyl intermediate. It is this 1,2-insertion step that controls the regioselectivity of the Mizoroki-Heck reaction.
- Subsequently, β -elimination occurs to generate the metal-hydrido-alkenyl product.
- Following dissociation of the product, nucleophilic abstraction by a base removes a proton regenerating the fully reduced metal catalyst.



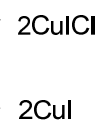
Buchwald-Hartwig Coupling

- Palladium-catalyzed synthesis of aryl amines. Starting materials are aryl halides or pseudohalides (for example triflates) and primary or secondary amines.
- The synthesis of aryl ethers and especially diaryl ethers has recently received much attention as an alternative to the Ullmann Ether Synthesis.
- Newer catalysts and methods offer a broad spectrum of interesting conversions





$\text{PdCl}_2(\text{dppf})$



$\text{Pd}(\text{dppf})$

