

Lecture 12

Inorganic chemistry

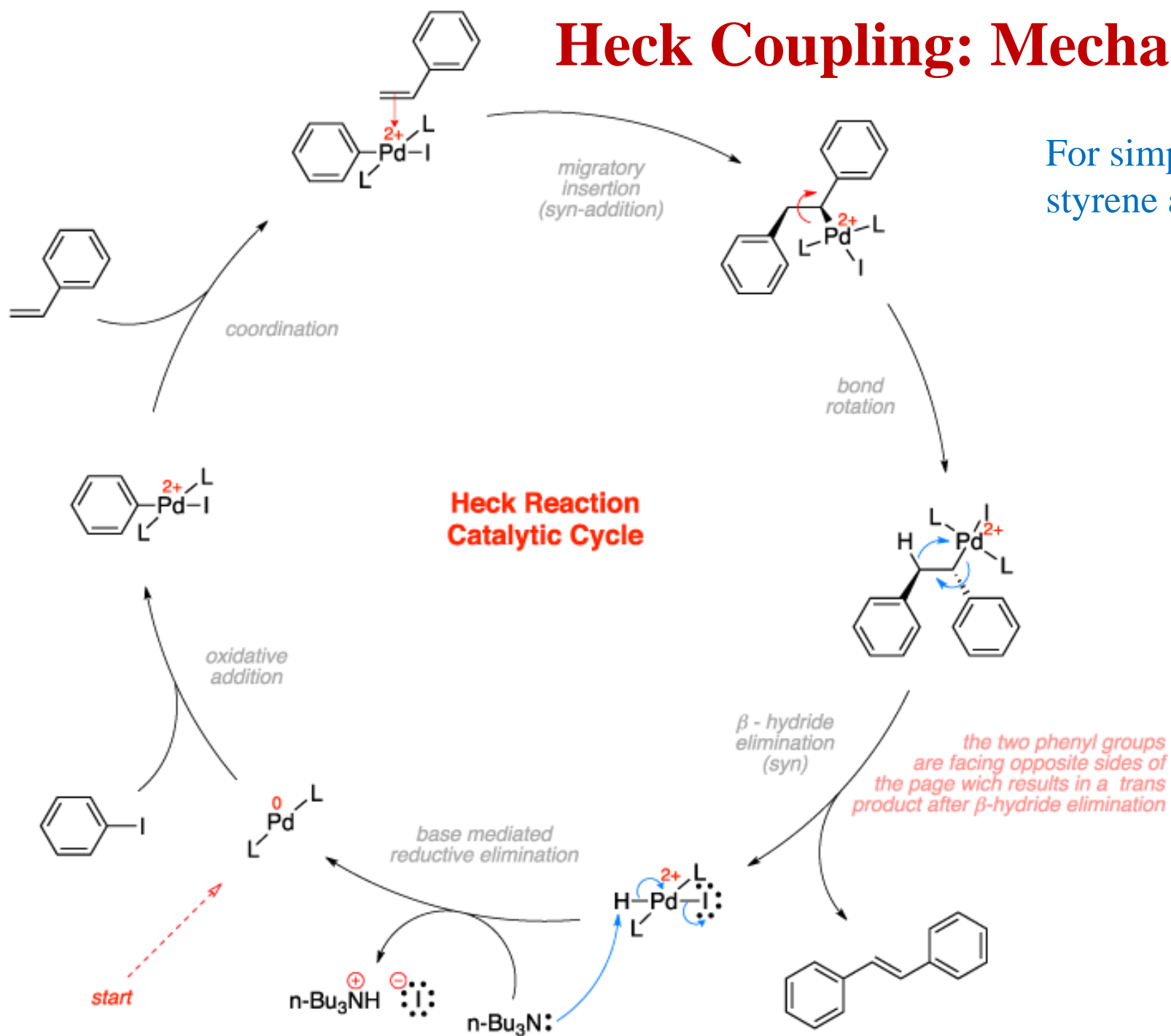
Homogeneous catalysis: Pd catalyzed C–C bond formation reactions for organic synthesis

Heck coupling
Suzuki coupling
Sonogashira coupling

Negishi Coupling
Buchwald–Hartwig amination

Heck Coupling: Mechanism

For simplicity, in this mechanism PhI, styrene and R_3N is used

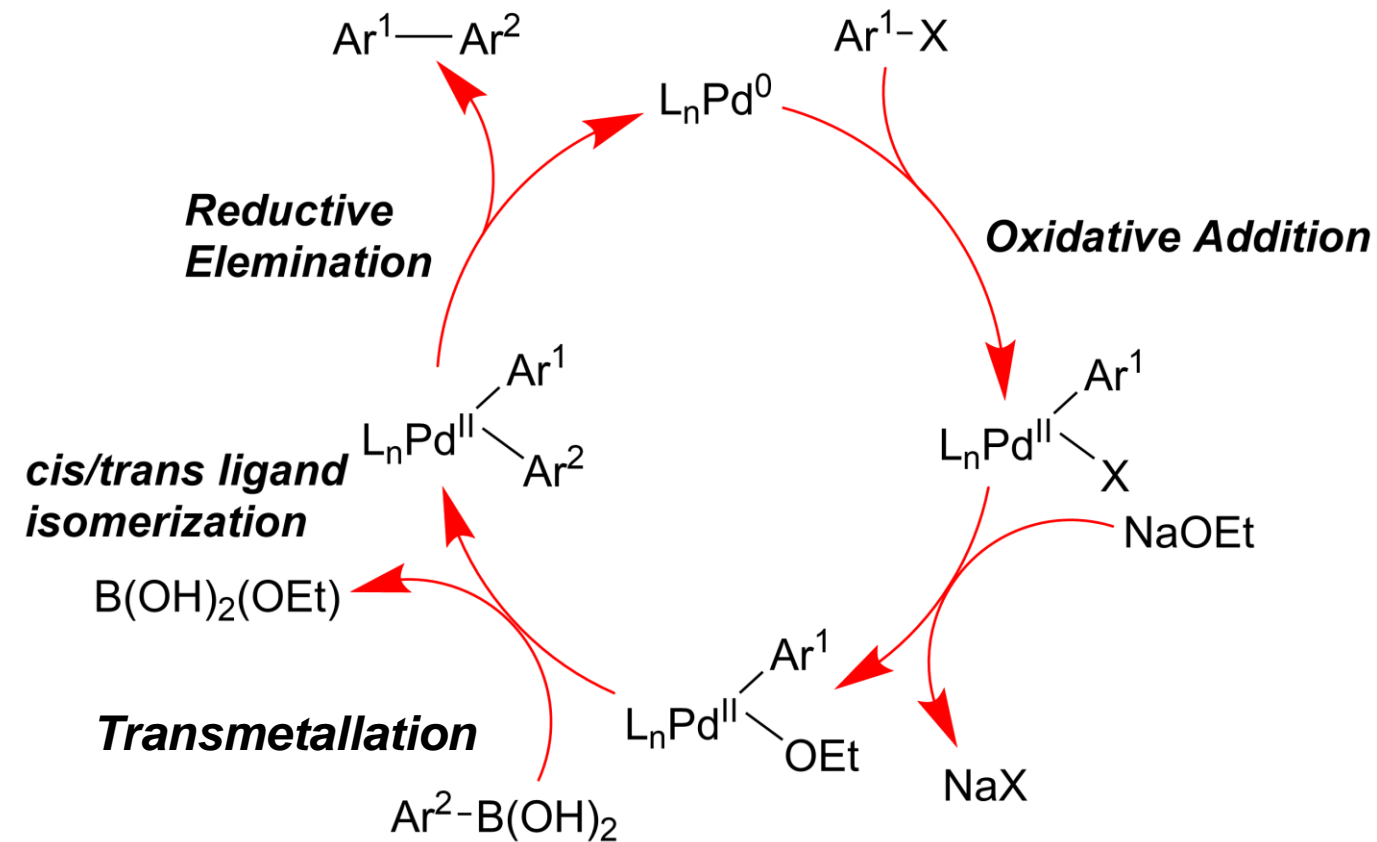


What are the fundamental requirements of a redox cycle catalyst?

Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, 37, 2320–2322.

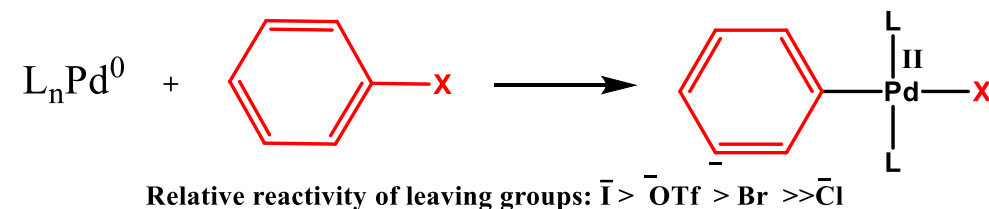
Suzuki–Miyaura Coupling: Mechanism

Mechanism



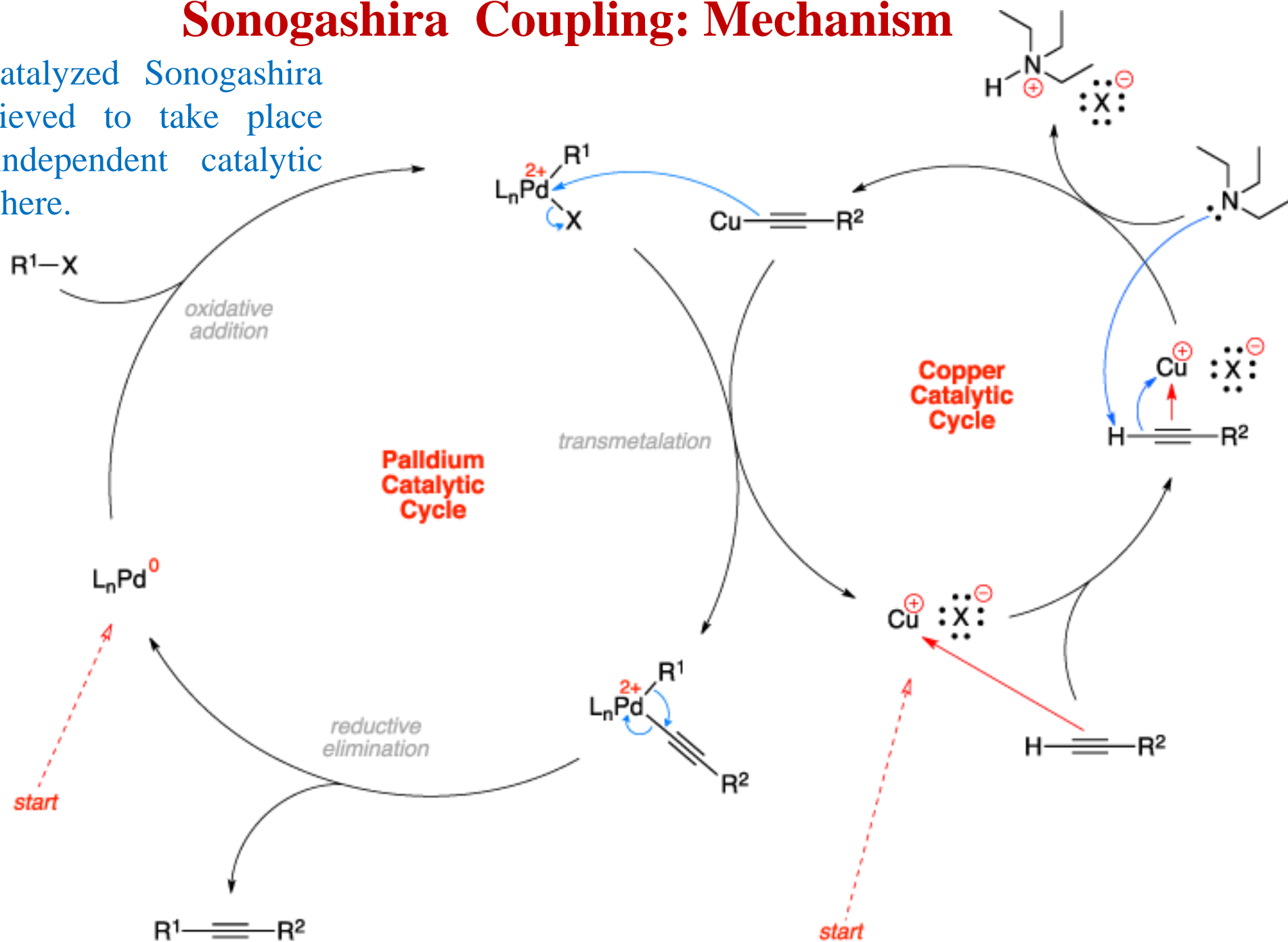
Electronic effects of Oxidative Addition

- The order of reactivity is in good agreement with substituent effect in the oxidative addition of aryl halides to the palladium(0) complex

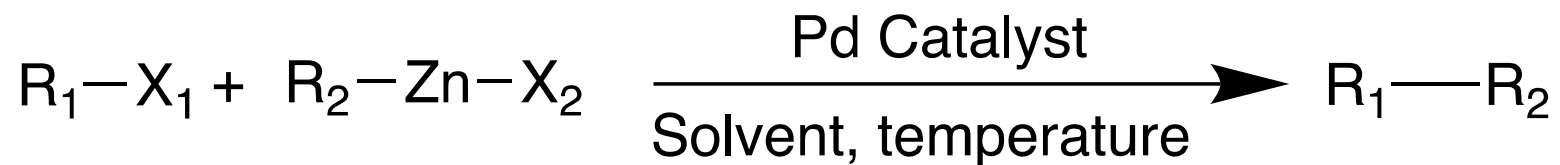


Sonogashira Coupling: Mechanism

The copper-cocatalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles as shown here.



Negishi Coupling



$\text{X}_1 = \text{I, Br, Cl, OTf}$

$\text{X}_2 = \text{Br, I}$

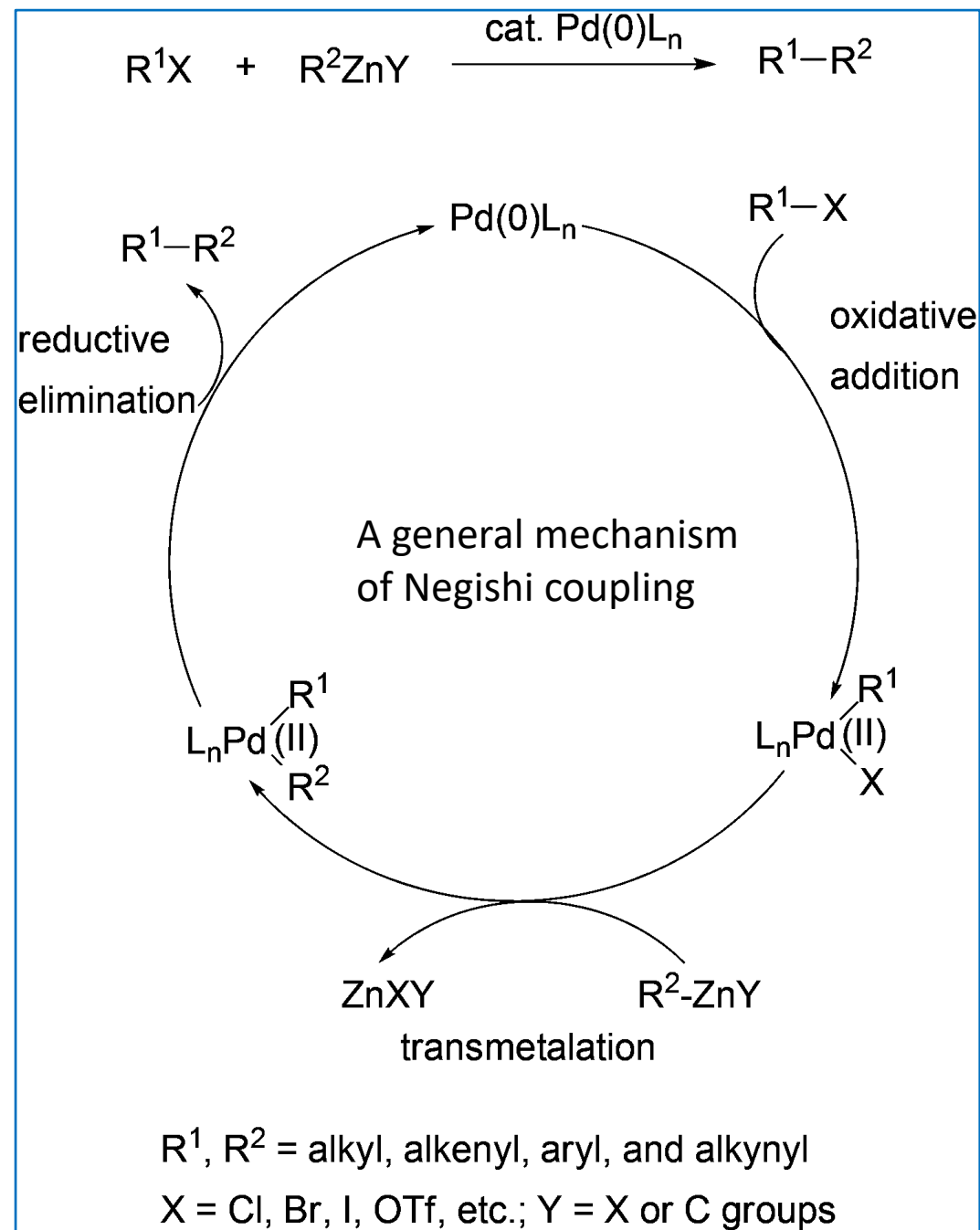
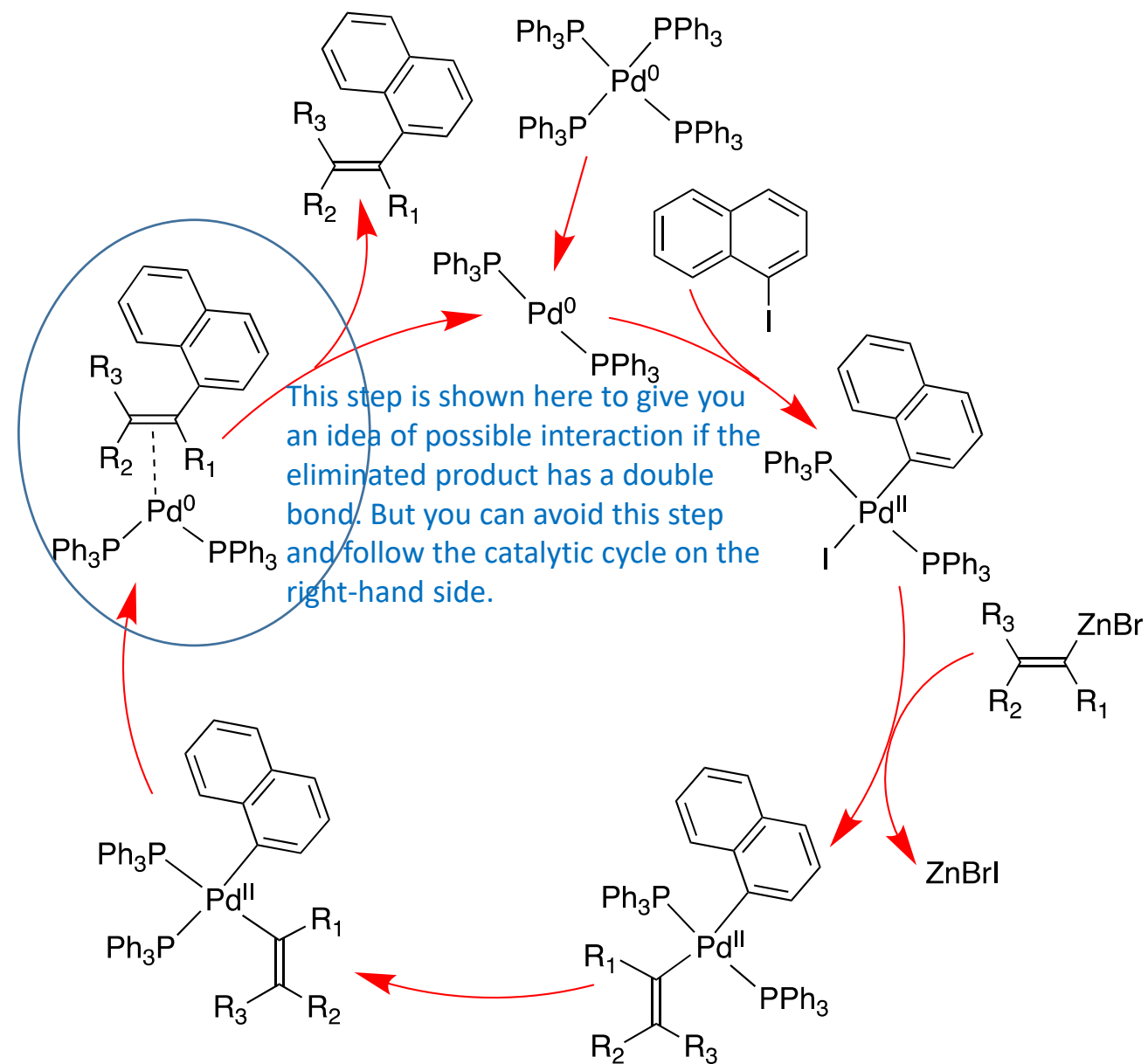
Pd Catalyst: $\text{Pd(PPh}_3)_4$, $\text{PdCl}_2(\text{PPh}_3)_2$, (Pd(OAc)_2) , etc.

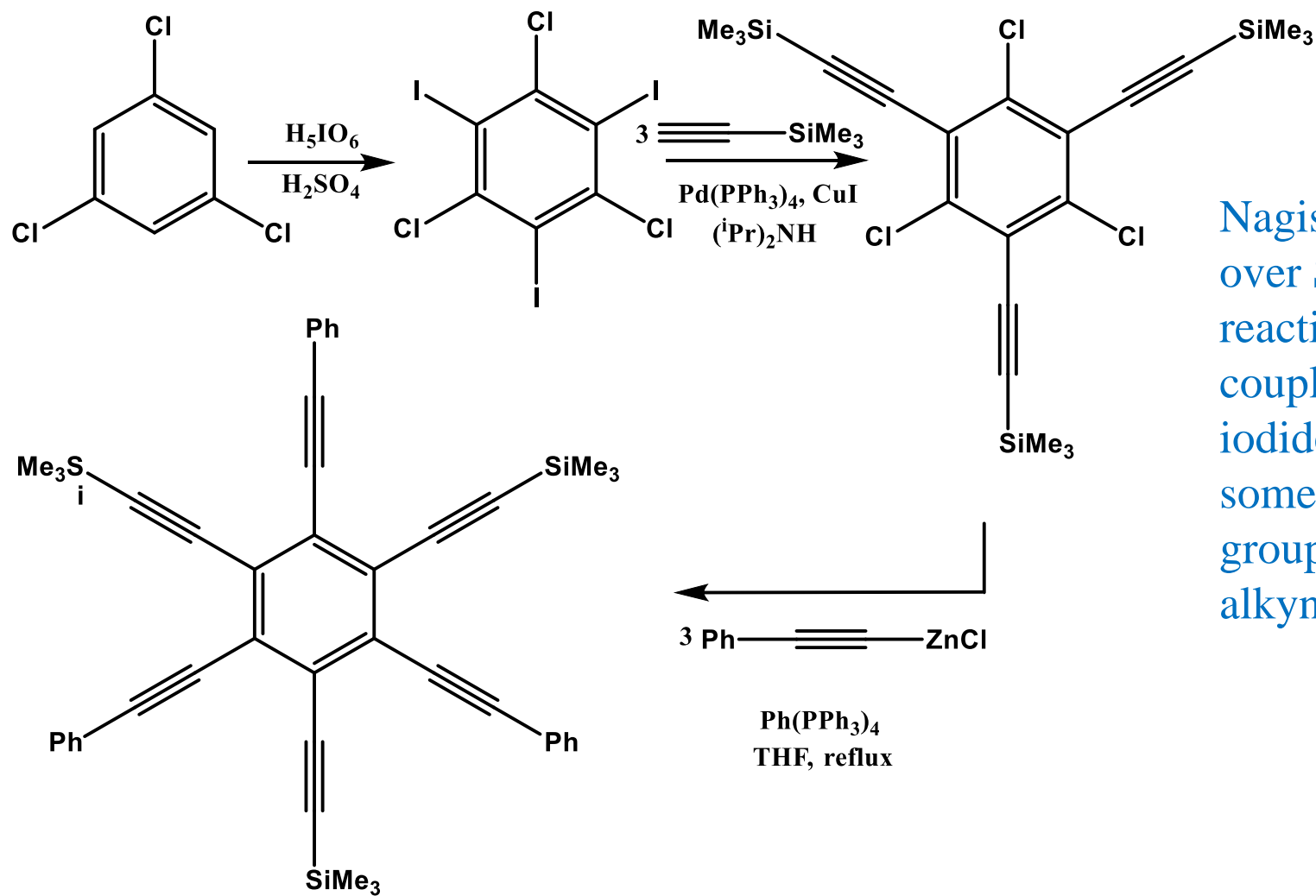
$\text{R}_1 = \text{aryl, acyl, benzyl, vinyl, etc.}$

$\text{R}_2 = \text{aryl, vinyl, alkynyl, alkyl, etc.}$

- The Negishi coupling is a cross coupling reaction that involves an organozinc compound, an organic halide and a palladium catalyst and creates a new carbon-carbon covalent bond.
- The scope of the Negishi reaction is broad, similar to that of Suzuki cross-coupling. The reaction seems to work if $\text{R}_1 = \text{aryl, vinyl, alkynyl, acyl, allyl, benzyl, or even primary alkyl}$, and if $\text{X} = \text{I, Br, or OTf}$ (Cl works, but often sluggishly). Correspondingly, $\text{R}_2 = \text{aryl, vinyl, alkynyl, allyl, benzyl, and primary alkyl}$. The organozinc reagent may either be used as a preformed compound, such as R_2Zn or RZnX ($\text{X} = \text{I, Br, or Cl}$), or RZnX may be generated *in situ* by first allowing R--X to react with Zn dust.

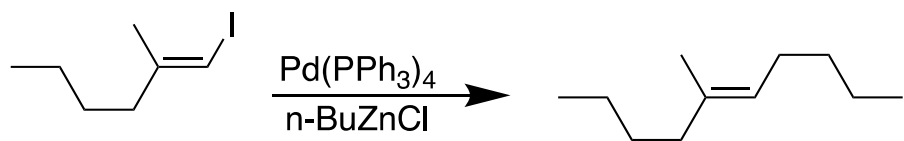
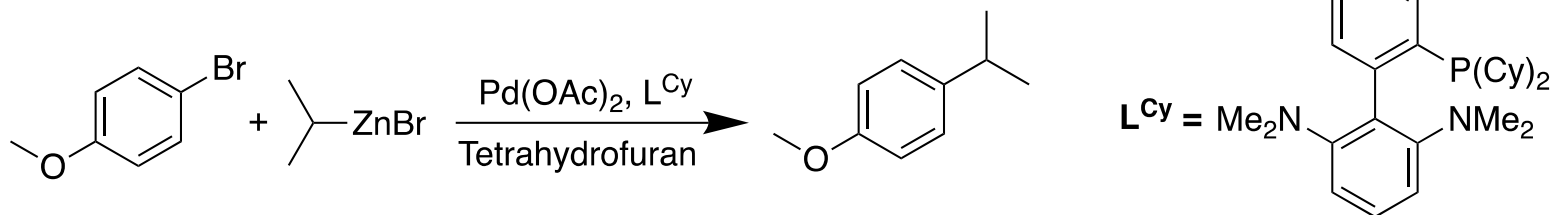
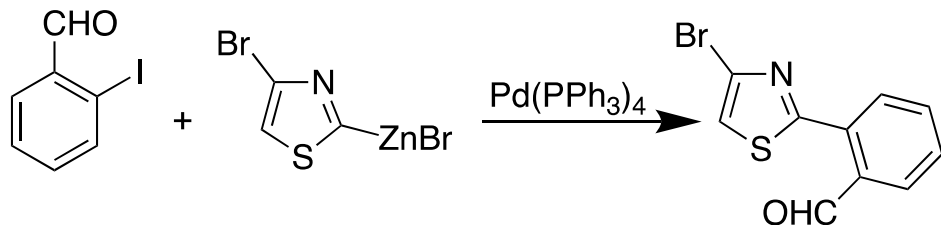
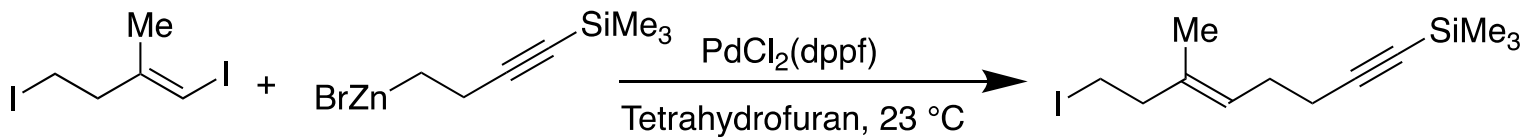
Negishi Coupling: Mechanism



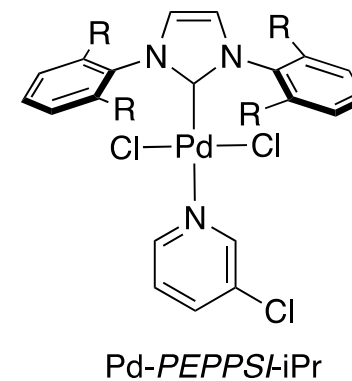
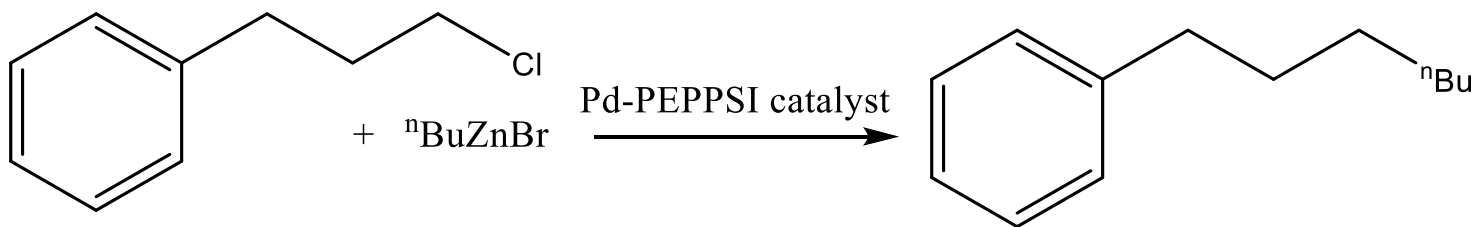


Nagishi coupling also has an upper hand over Sonogashira coupling in many reactions. For example, Sonogashira coupling occurs preferentially on aryl iodides but aryl chlorides (activated to some extent by the substituted alkynyl groups) can be made to undergo further alkynylation under Negishi condition.

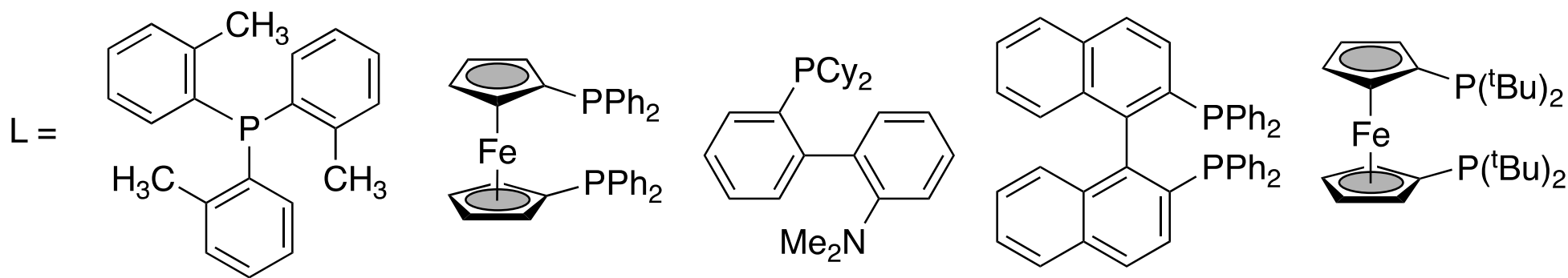
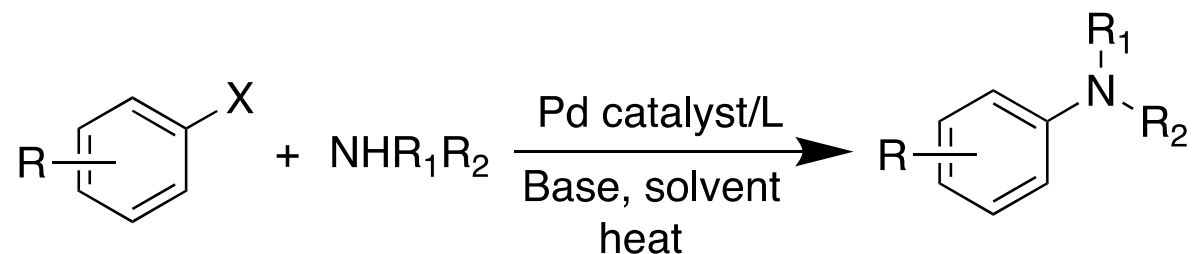
Negishi Coupling



pyridine-enhanced precatalyst
preparation stabilization and initiation



Buchwald–Hartwig amination

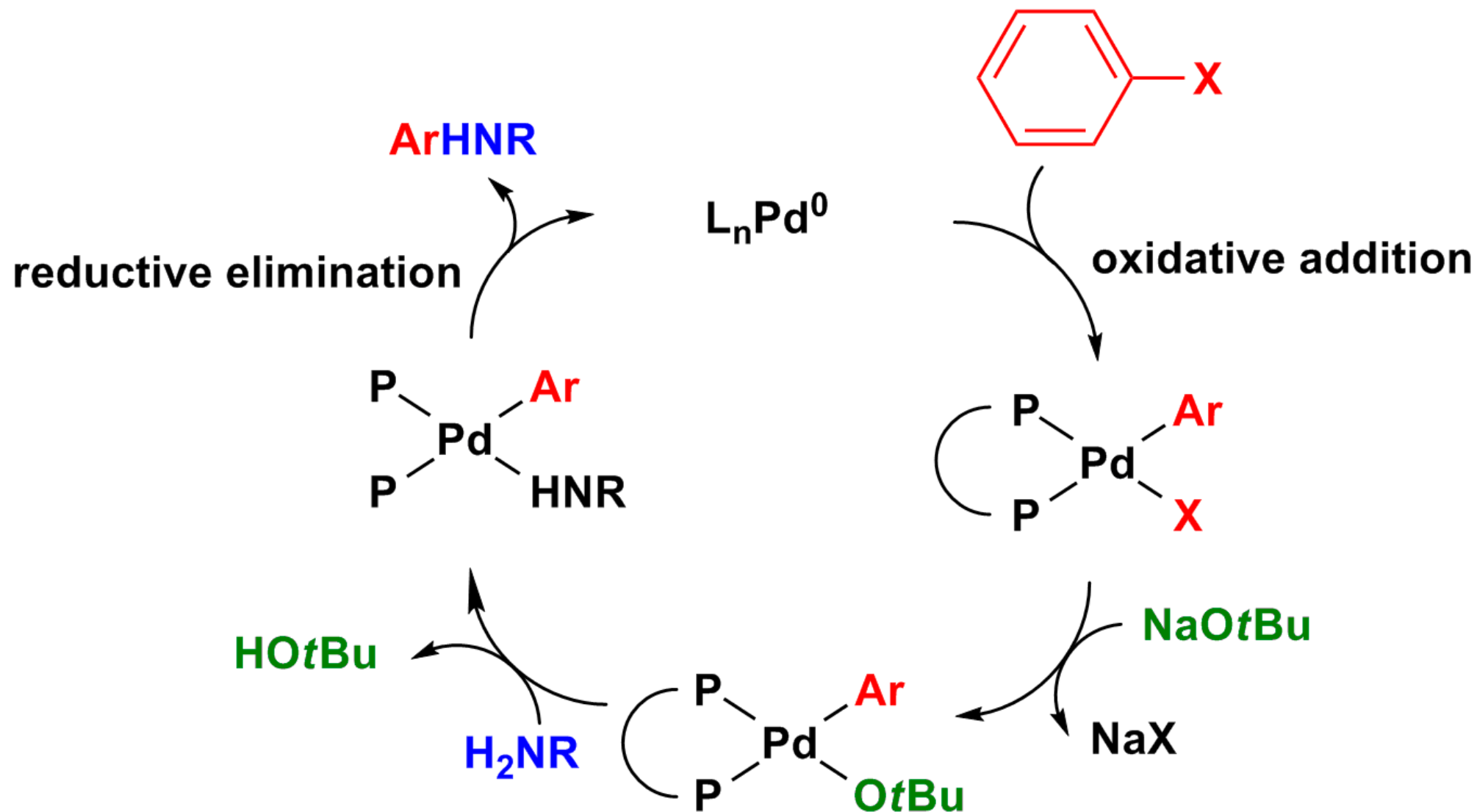


X = Br, I, Cl, OTf, OTs, etc.

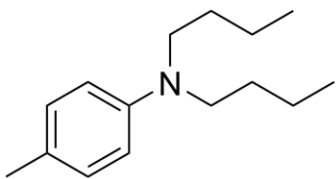
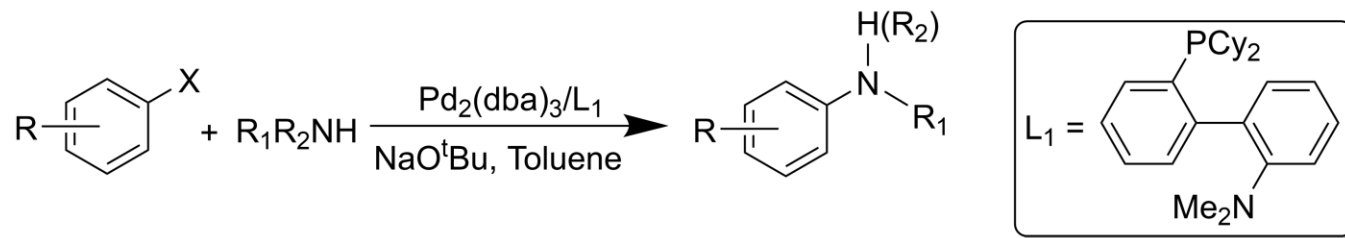
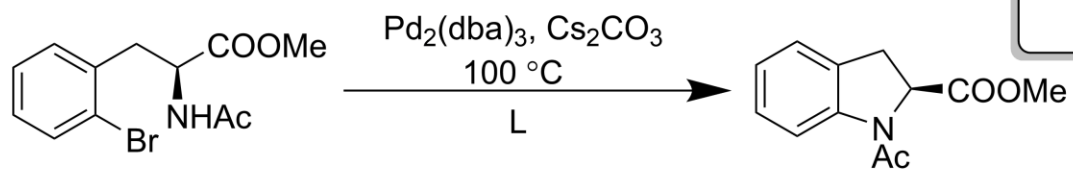
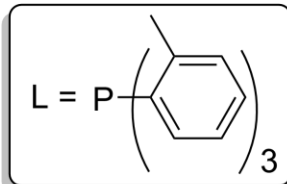
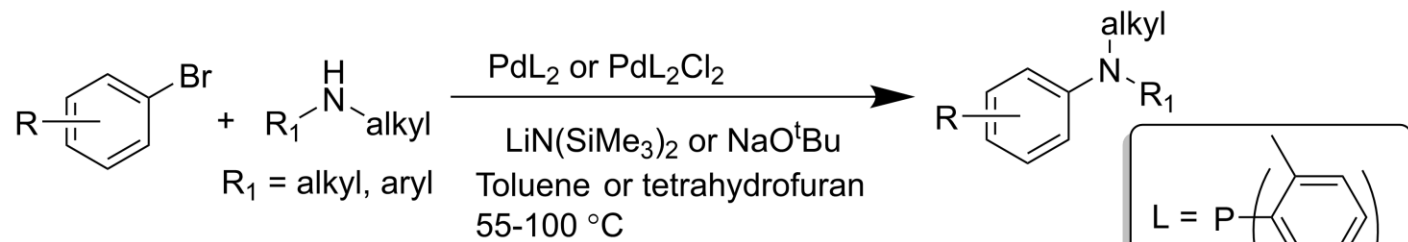
Amine Substrates: HNR_1R_2 , H_2NR_1 , NH_3 , $\text{HN}=\text{CPh}_2$, etc.

Coupling of an aryl halide with an amine forms aromatic amines. This reaction was made practical by Pd based catalytic systems and was developed almost simultaneously by Stephen L Buchwald and John F Hartwig of Yale University in 1995. Before this method no general reaction for the conversion of aryl halides into aromatic amines was available. This reaction has a profound effect on drug discovery as many drugs are aromatic amine derivatives. Although initially worked with aryl bromides and iodides, the use of bulky phosphine made the reaction work well with aromatic chloride as well.

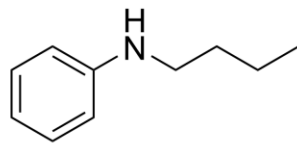
Buchwald–Hartwig amination: Mechanism



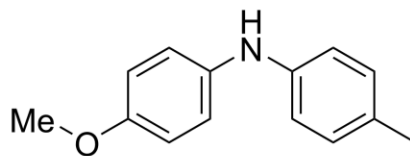
Buchwald–Hartwig amination



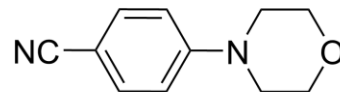
X = Cl, 100 °C, Yield: 95 %
 X = Br, 25 °C, Yield: 96 %



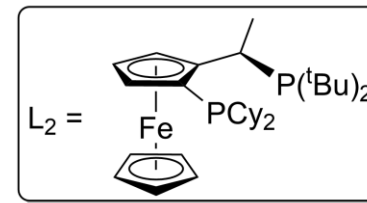
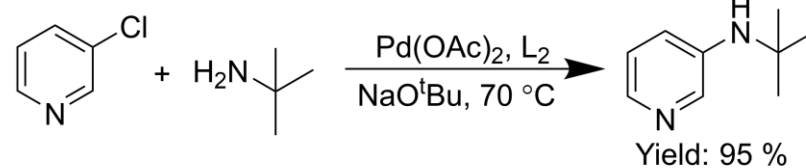
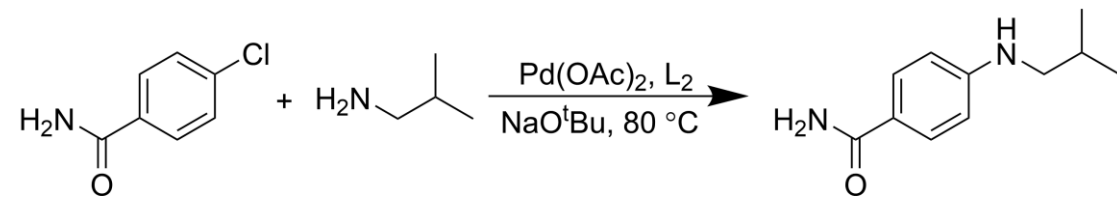
X = Cl, 80 °C, Yield: 99 %
 X = Br, 25 °C, Yield: 88 %



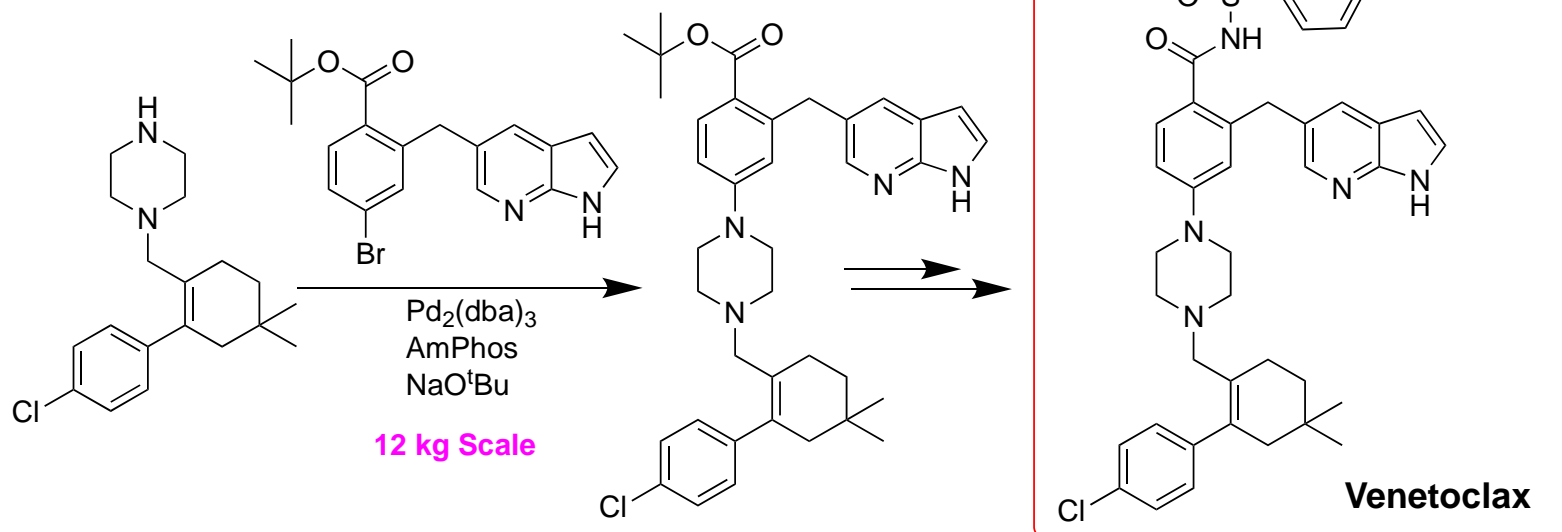
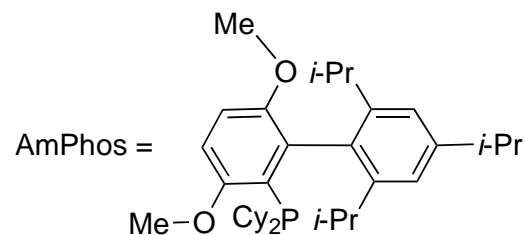
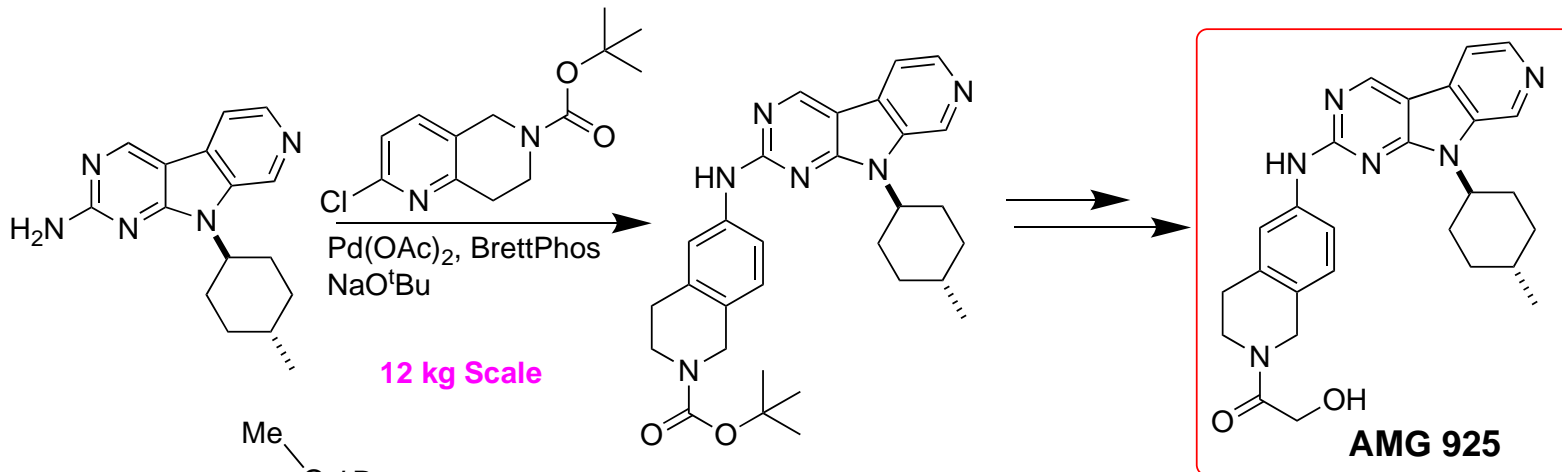
X = Cl, 100 °C, Yield: 93 %



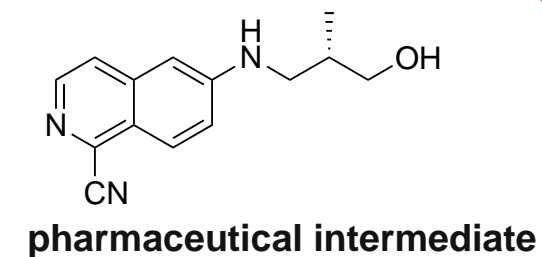
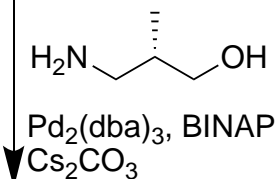
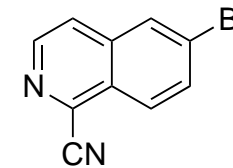
X = Cl, 25 °C, Yield: 96 %



Buchwald–Hartwig amination: Application



A dual FLT3/CDK4 inhibitor with the potential to overcome FLT3 inhibitor resistance in acute myeloid leukemia



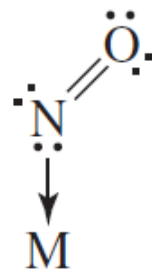
A drug for the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma.

NO Complexes

Linear



Bent



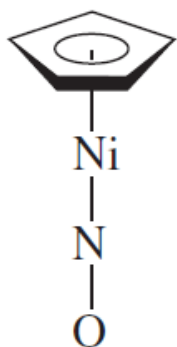
M—N—O angle	165°–180°	119°–140°
ν (N-O) in neutral molecules	1610–1830 cm ⁻¹	1520–1720 cm ⁻¹
Electron donor count	2 (as NO ⁺)	2 (as NO ⁻)
	3 (as neutral NO)	1 (as neutral NO)

The NO (nitrosyl) ligand shares many similarities with CO. Like CO, it is a sigma donor and pi-acceptor and can serve as a terminal or bridging ligand; useful information can be obtained about its compounds by analysis of its infrared spectra. Unlike CO, however, terminal NO has two common coordination modes, linear (like CO) and bent.

NO⁺ is isoelectronic with CO; therefore, in its bonding to metals, linear NO is considered by electron-counting scheme as NO⁺, a 2-electron donor. (Oxidation state method, NO⁺ is 2 electron donor)

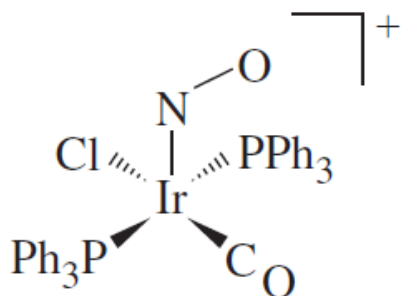
By the neutral ligand method, linear NO is counted as a 3-electron donor (it has one more electron than the 2-electron donor CO).

The bent coordination mode of NO can be considered to arise formally from NO⁻, with the bent geometry suggesting *sp*² hybridization at the nitrogen. By oxidation state method, bent NO is considered the 2-electron donor NO⁻; by the neutral ligand model, it is considered a 1-electron donor.



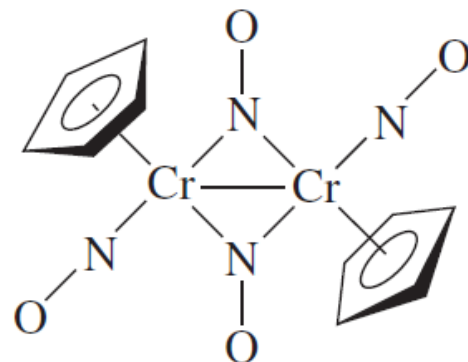
Linear

(A) 18e



Bent

(B) 16e



Bridging

(C) 18e

Thank You