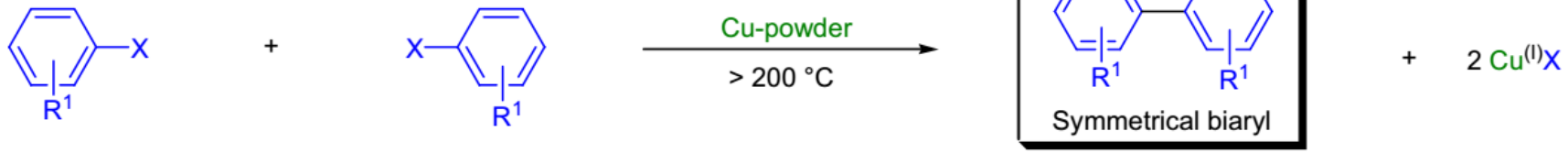
Ullmann Coupling

Ullmann biaryl synthesis (1901, F. Ullmann)

Synthesis of symmetrical biaryls (Ullmann, 1901):



R^1, R^2 = H, CN, NO_2, CO_2R, I, Br, Cl; X = I, Br, Cl, SCN; solvent: DMF, pyridine, quinoline, nitrobenzene, *p*-nitro toluene

Mechanism:

Pathway involving aryl radicals:

Step #1: $Ar-X + Cu^{(0)} \longrightarrow [Ar-X]^{\ominus}_{\bullet} + Cu^{(I)}$

Step #2: $[Ar-X]^{\ominus}_{\bullet} + Cu^{(I)} \longrightarrow Ar\bullet + Cu^{(I)}X$

Step #3: $Ar\bullet + Ar\bullet \longrightarrow \boxed{Ar-Ar}$

Pathway involving arylcopper intermediates:

Step #1: $Ar-X + Cu^{(0)} \longrightarrow Ar-Cu^{(II)}X$

Step #2: $Ar-Cu^{(II)}X + Cu^{(0)} \longrightarrow Ar-Cu^{(I)} + Cu^{(I)}X$

Step #3: $Ar-Cu^{(I)} + Ar-X \longrightarrow Ar-Cu^{(III)}XAr$

Step #4: $Ar-Cu^{(III)}XAr \longrightarrow \boxed{Ar-Ar} + Cu^{(I)}X$

Features of Ullmann Coupling reaction:

1) The Ar-X and Het-X are substrates for the coupling， order of reactivity is I > Br >> Cl, but aromatic fluorides are totally inert;

2) EWG (e.g., NO2, CO2Me, CHO) ortho to the halogen substituent increase the reactivity of the aryl halide

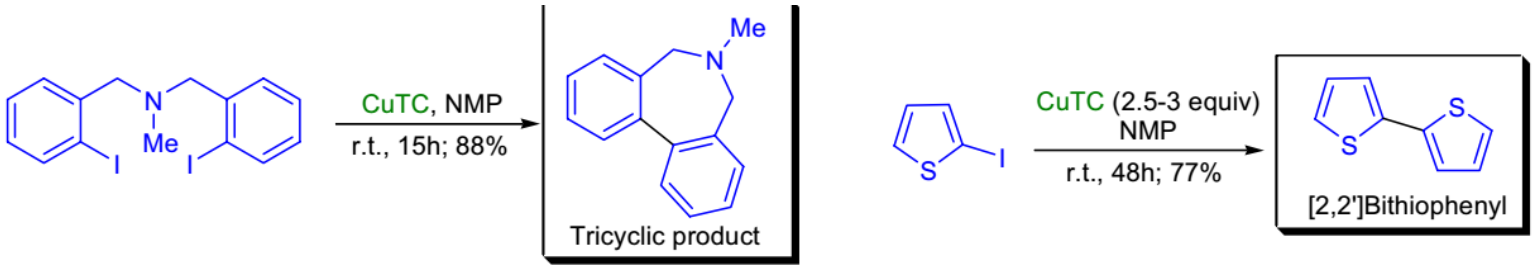
3) Substrates that are very electron rich (e.g., multiple alkyl or alkoxy groups) tend to give lower yield of the biaryl

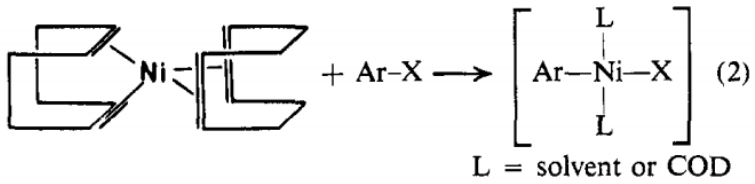
4) Common solvents: DMF, PhNO2 ,p-NO2C6H4CH3

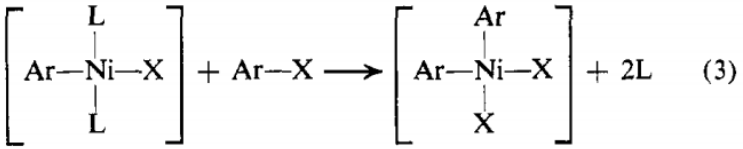
5) Cu(I)-salts (e.g., Cu2O, Cu2S) also mediate the coupling although they are less active than the activated copper metal

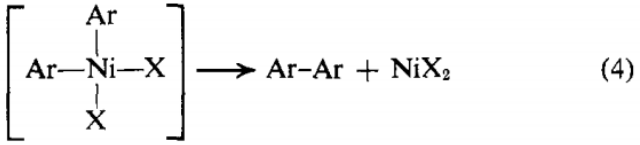
6) Cu(I) thiophene 2-carboxylate (CuTC) was found to be an efficient mediator under mild conditions (usually room temperature) in NMP

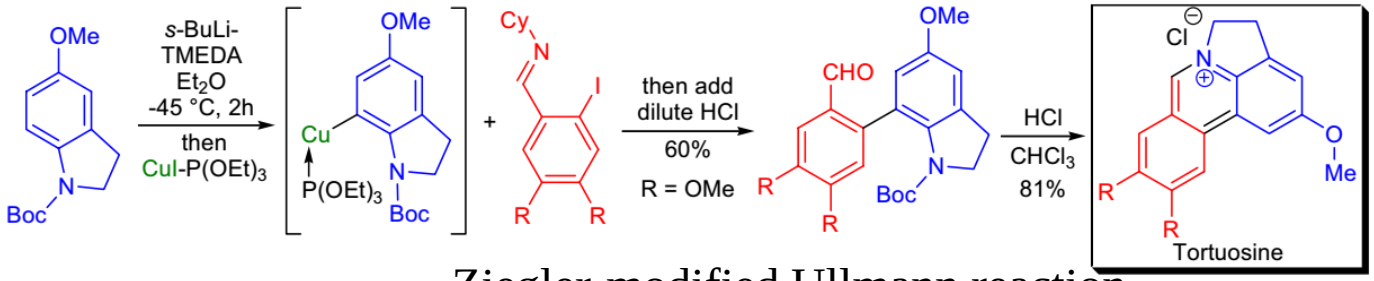
7) Modifications: Ni(0) complexes are used in place of copper metal, Ziegler modification





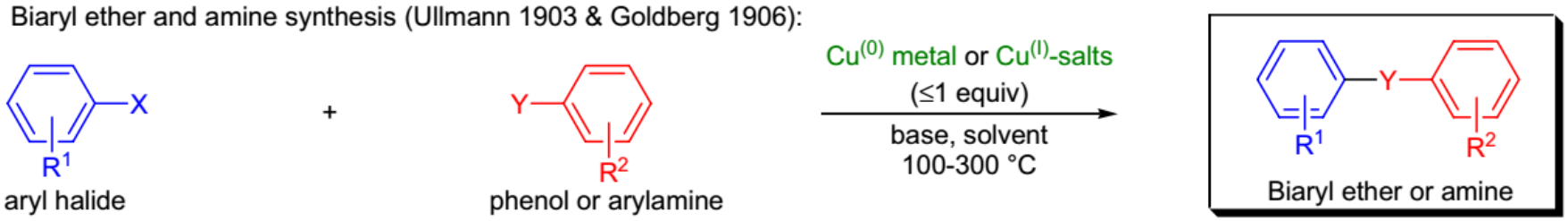


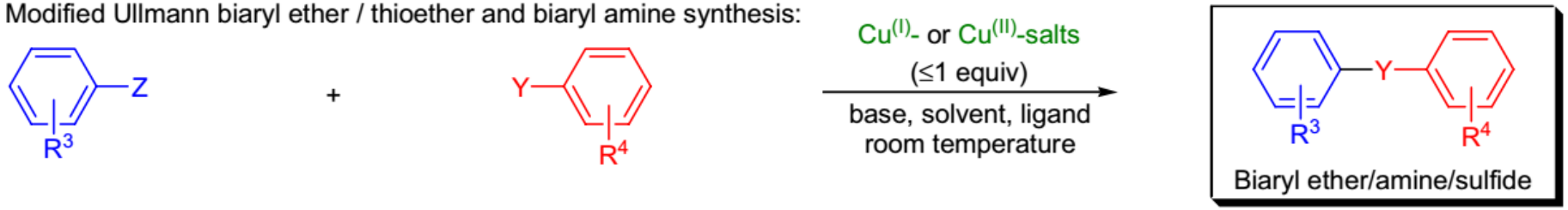




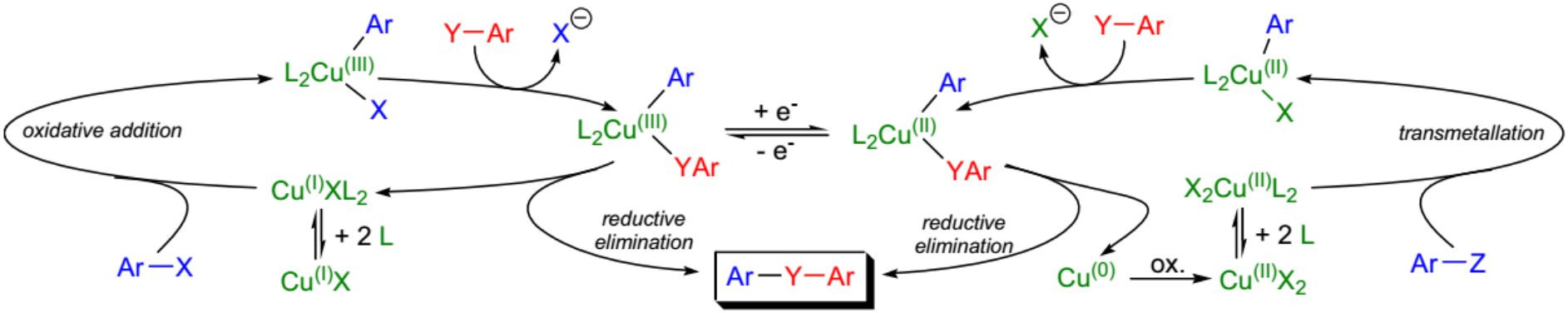
Ziegler-modified Ullmann reaction

Biaryl ether and amine synthesis (Ullmann 1903 & Goldberg 1906)





Mechanism:



Features of reaction:

1) Order of reactivity is I > Br > Cl >> F (uncatalyzed S_NAr reactions);

2) Temperature ranges from 100 to 300°C;

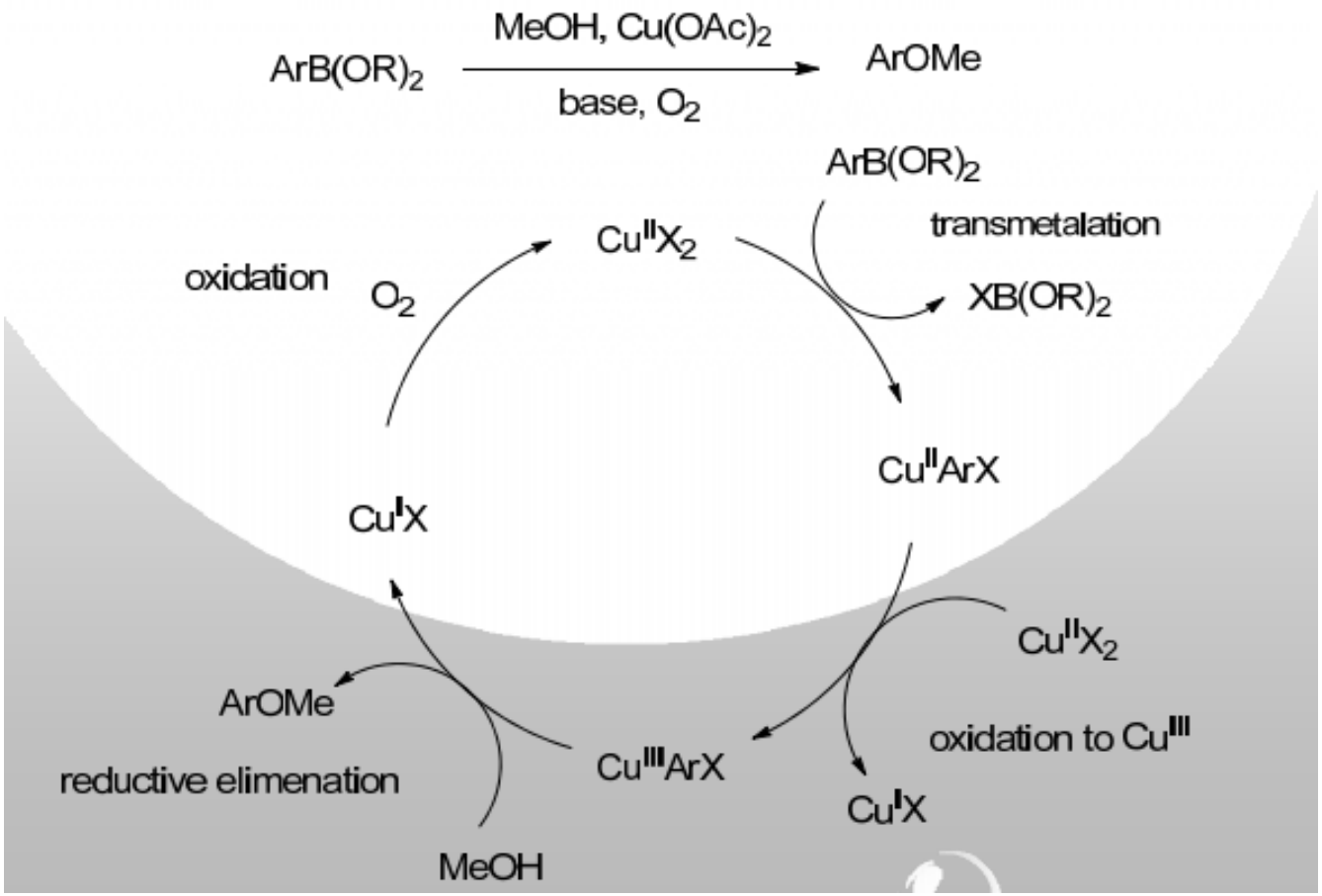
3) A wide variety of solvents work well and most of them contain a heteroatom with a lone pair of electrons, the solvent helps to solubilize the catalytically active copper species

4) since phenols and phenolates are sensitive to oxidation, the use of an inert atmosphere is often required;

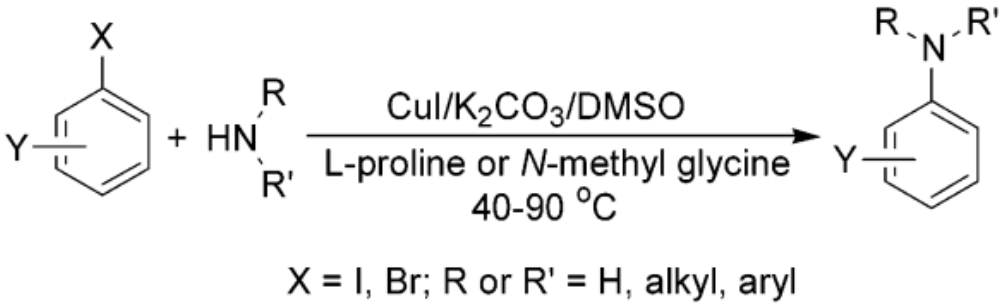
5) Side reactions: reductive dehalogenation, Ullmann biaryl homocoupling, exchange of halogens with the Cu(I)-salt;

6) Modifications: Chan-Evans-Lam reaction, Batey modification ($ArBF_3X$), Beringer-Kang modification ($Ar^1\text{-}I^+\text{-}Ar^2$), Barton plumbane modification (Ar_2Pb), Barton modification ($BiAr_3$), Dawei Ma modification.

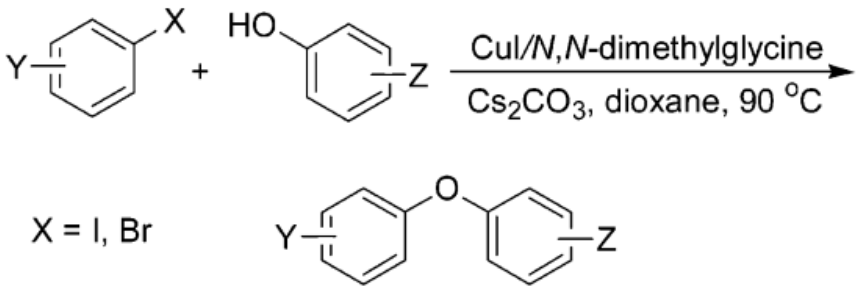
Chan-Evans-Lam reaction



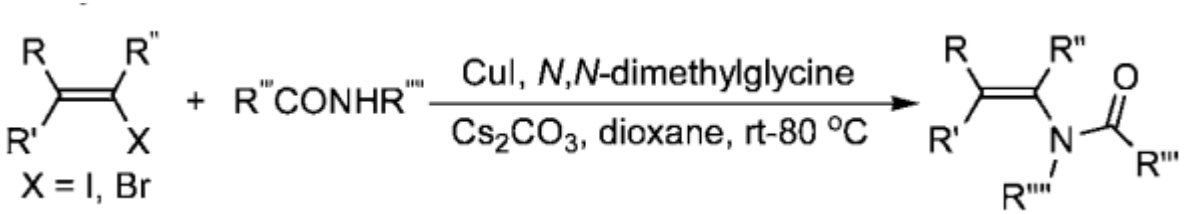
Dawei Ma modification



Org. Lett. **2003**, *5*, 2453

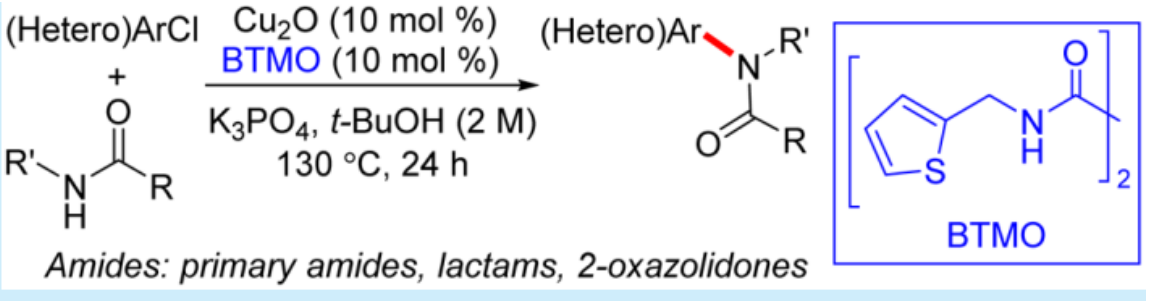


Org. Lett. **2003**, *5*, 3799

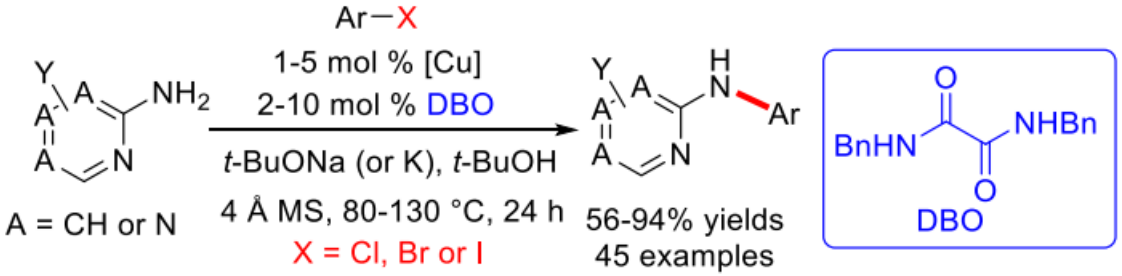


Acc. Chem. Res. **2008,** 41, 1450

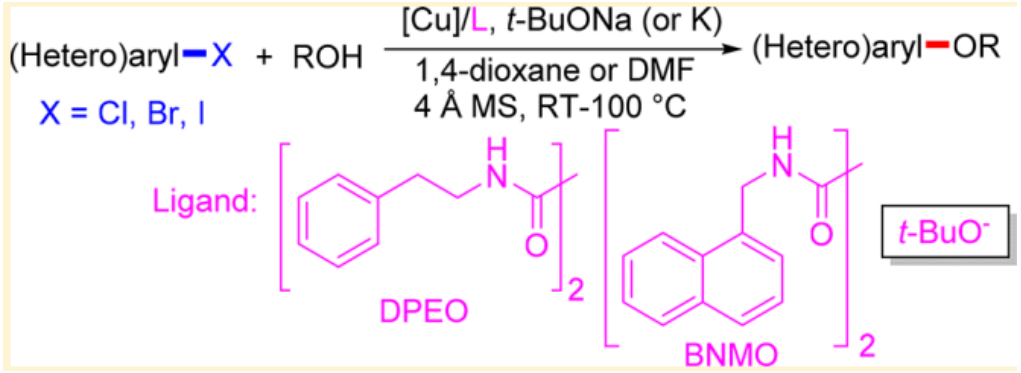
Dawei Ma modification



Org. Lett. **2017**, *19*, 4864

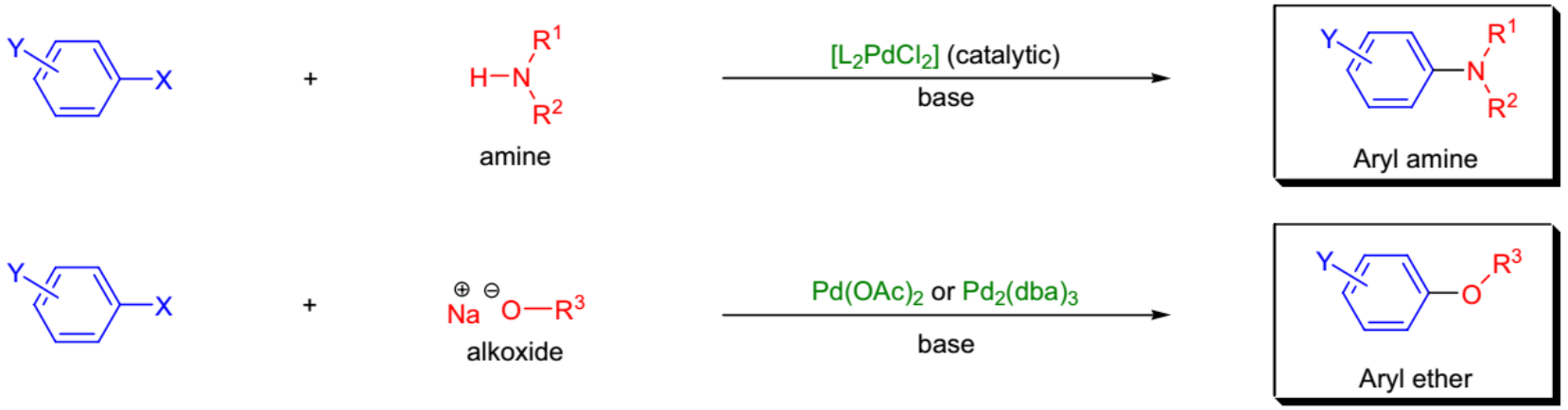


Org. Lett. **2019**, *21*, 6874



J. Am. Chem. Soc. **2019**, 141, 3541

Buchwald-Hartwig cross-coupling



X = Cl, Br, I, OTf; Y = *o, m* or *p*-alkyl, phenacyl, amino, alkoxy; $R^{1\text{-}2}$ = 1° or 2° aromatic or aliphatic; R^3 = 1°, 2°, or 3° aliphatic or aromatic; L = P(*o*-Tol)$_3$, BINAP, dppf, dba; base: NaO*t*-Bu, LHMDS, K_2CO_3, Cs_2CO_3