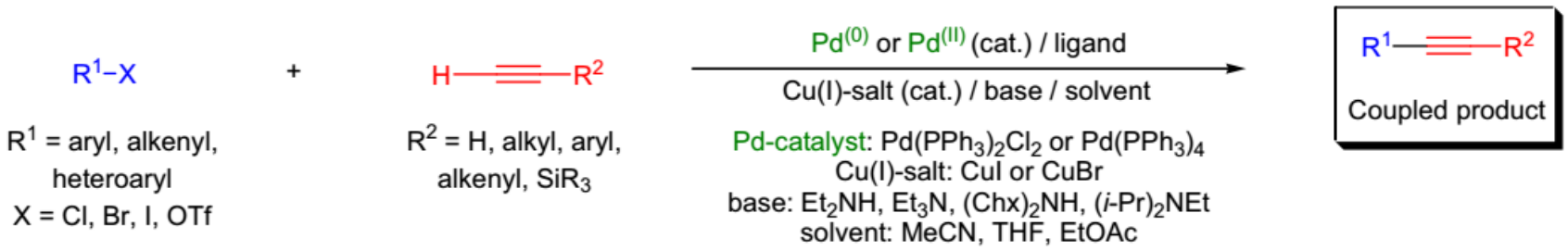
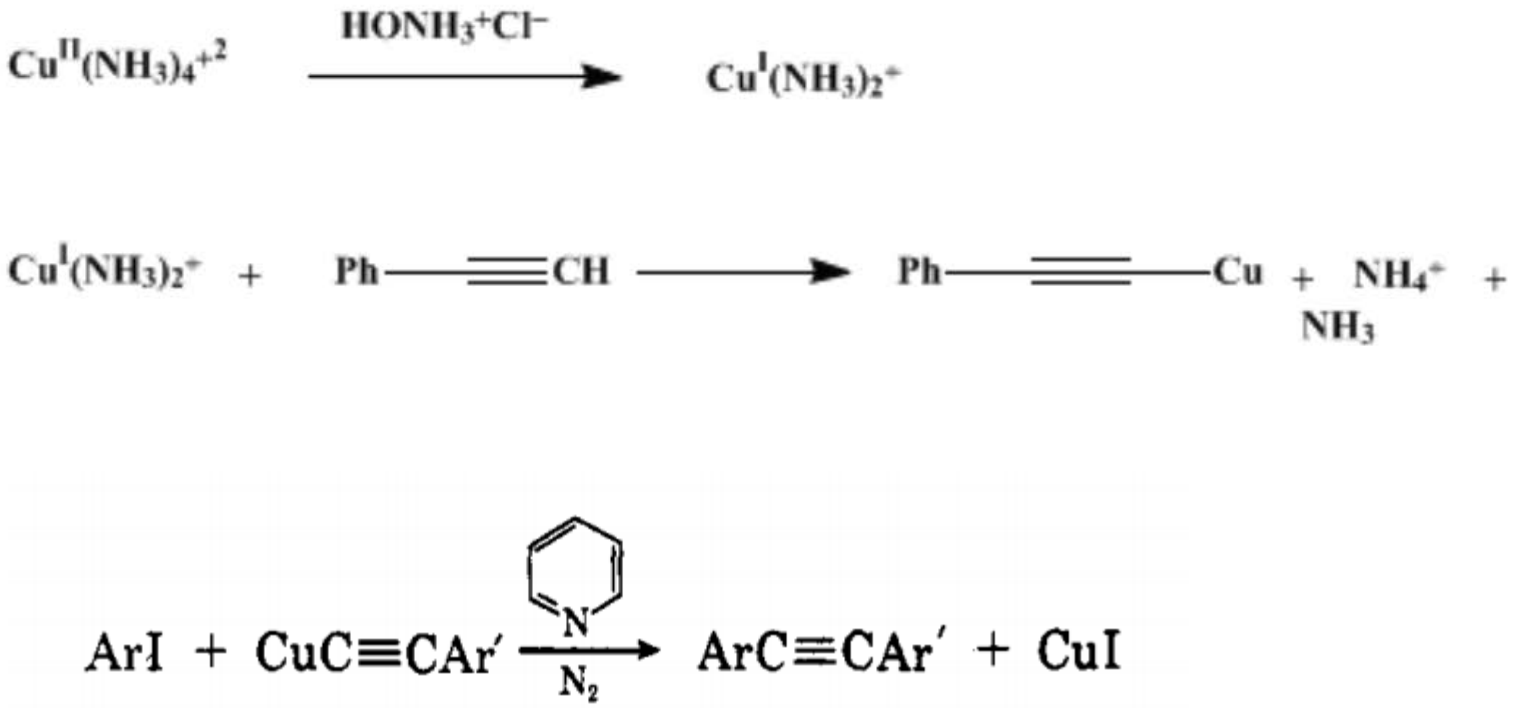
Sonogashira Cross-Coupling

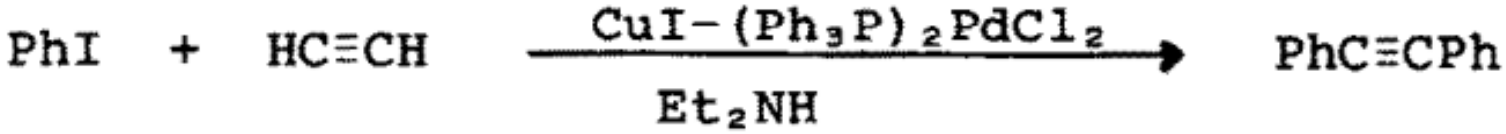


- In 1963, Castro-Stephens coupling



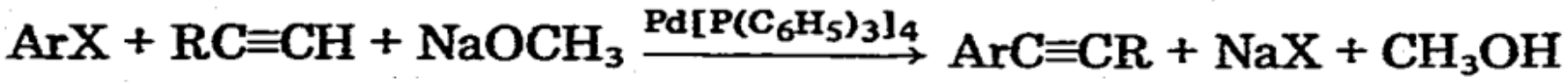
J. Org. Chem., **1963**, *28* (12), pp 3313–3315
Org. Synth. 1972, 52, 128

- In 1975, K. Sonogashira

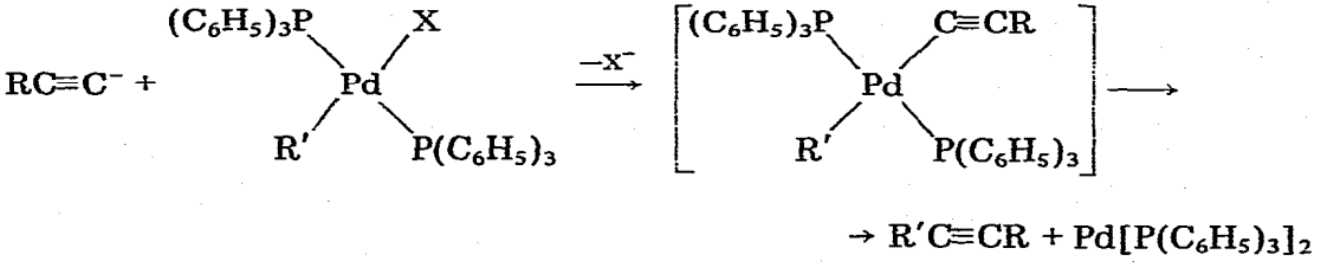


K. Sonogashira *Tetrahedron Lett.* 1975, 4467-4470.

- In 1975, R.F. Heck and L. Cassar

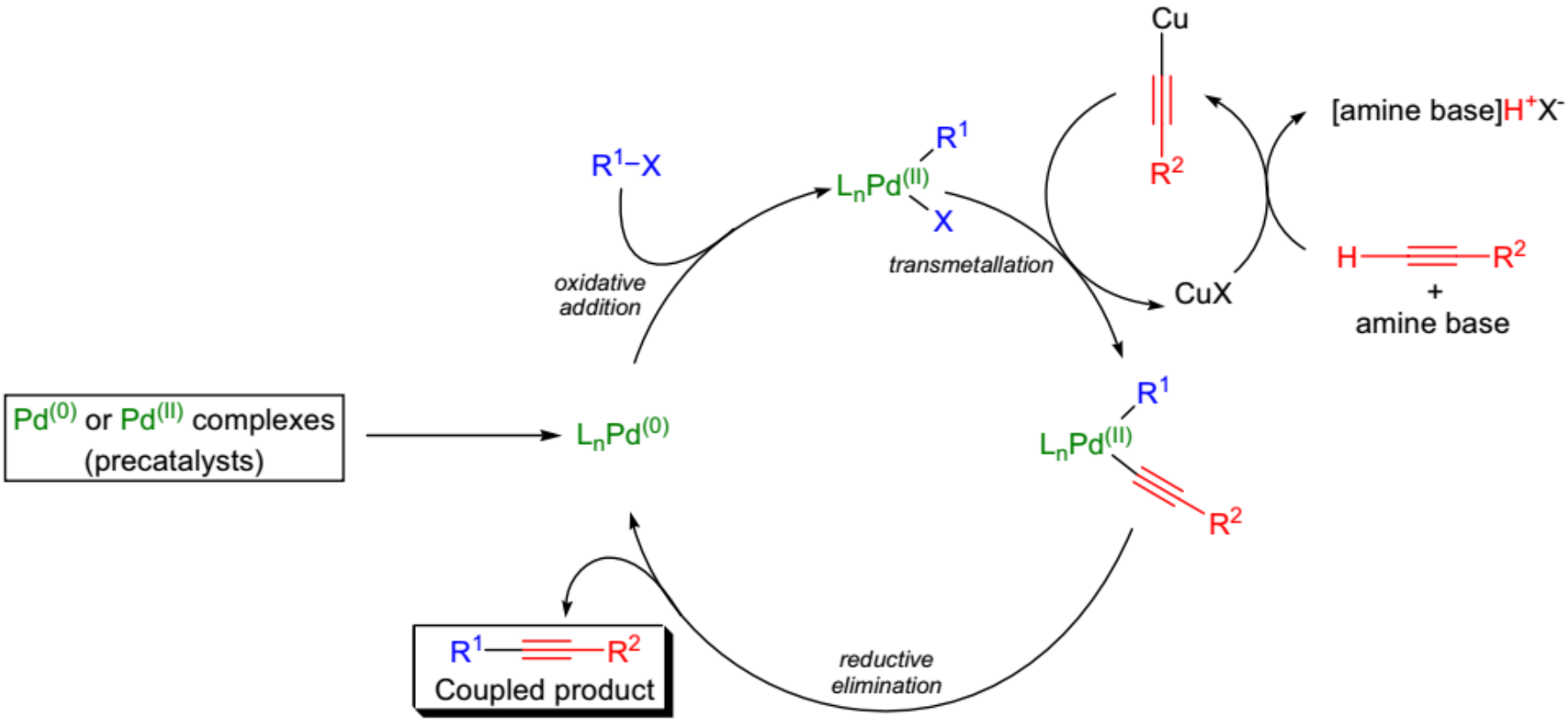


L. Cassar *J. Organomet. Chem.* 1975, 93, 253-257



R.F. Heck *J. Organomet. Chem.* 1975,93, 259-263

Mechanism:

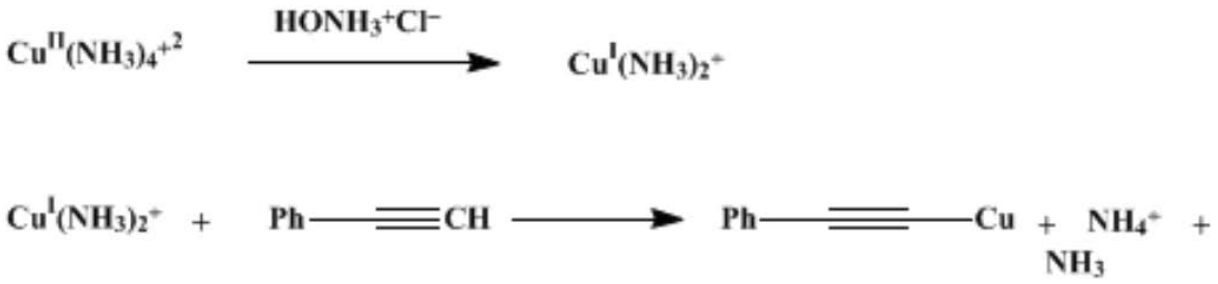

Cu
R2
[amine base]H+X-
R1
R1–X
LnPd(II)
X
oxidative addition
transmetallation
CuX
H
R2
+
amine base
Pd(0) or Pd(II) complexes (precatalysts)
LnPd(0)
R1
LnPd(II)
R2
R1
R2
Coupled product
reductive elimination

Features of Sonogashira cross-coupling reaction:

1) The coupling can usually be conducted at or slightly above **room temperature**

2) The best palladium catalysts are Pd(PPh3)2Cl2 or Pd(PPh3)4

3) The handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I) salt (CuI or CuBr, 0.5-5 mol%)



$$ArX + RC{\equiv}CH + NaOCH_3 \xrightarrow{Pd[P(C_6H_5)_3]_4} ArC{\equiv}CR + NaX + CH_3OH$$

Features of Paterno-Büchi reaction:

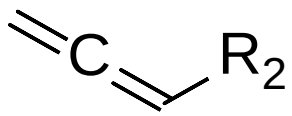
3) The solvents and the reagents **do not need to be rigorously dried**. However, a **thorough deoxygenation** is essential to maintain the activity of the Pd-catalyst.

4) When the **copper co-catalyst** is exposed to air, the copper acetylide undergoes **homocoupling** with itself instead of undergoing the desired cross-coupling with the vinyl or aryl halide compound

5) **Stereochemical** information of the substrates is **preserved** in the products;

6) The order of reactivity for the aryl and vinyl halides is I ≈ OTf > Br >> Cl;

7) Alkynes with conjugated EWG(R2=CO2Me) give Michael addition products ; (R2=CH2CO2Me or NH2, tend to rearrange to allenes)



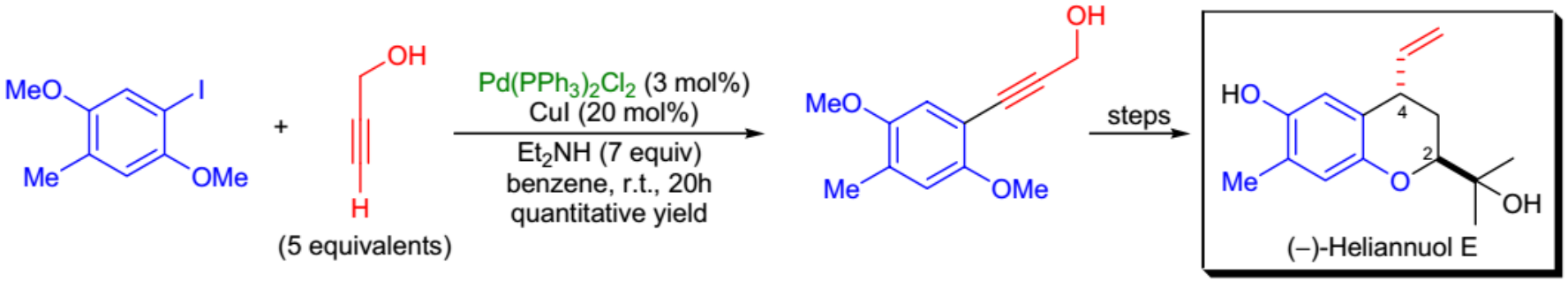
8) Aryl halides and bulky substrates that are not very reactive require higher reaction temperature and at high temperatures terminal akynes undergo side reactions.

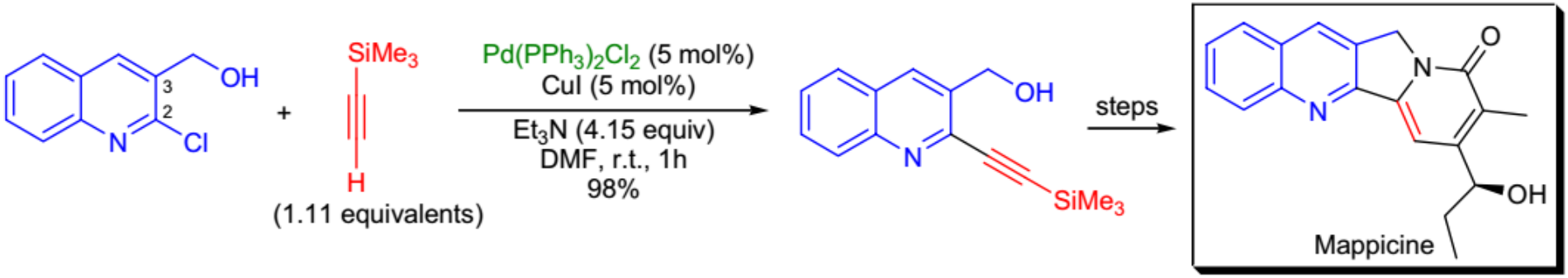
Efforts to Modify Reaction Conditions:

1. The original Palladium catalyst, (Ph3P)2PdCl2, has been occasionally substituted with NaPdCl4, Pd(OAc)2, Pd(MeCN)2Cl2, PdCl2, and PdI2 catalysts.

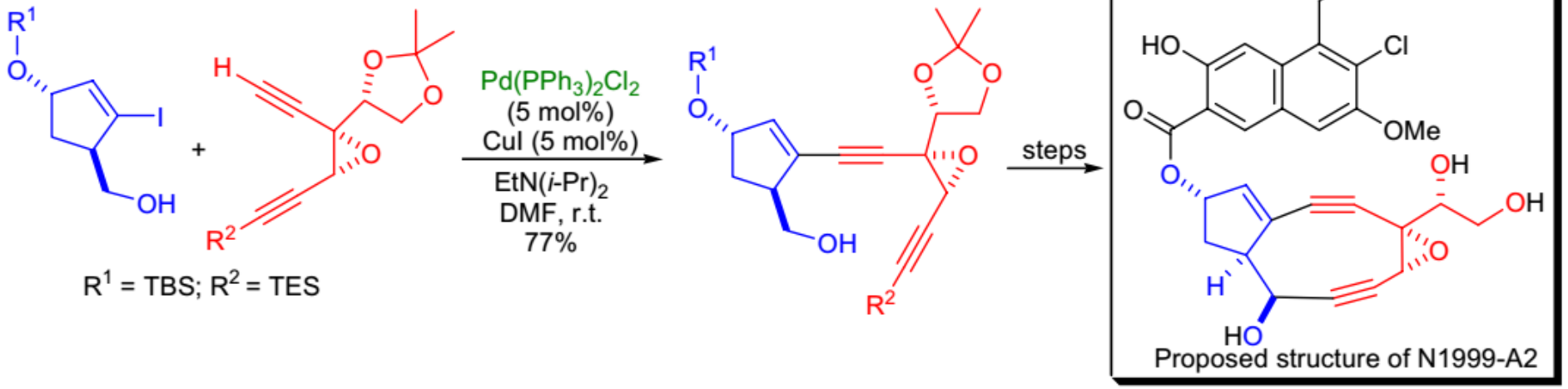
2. The copper co-catalyst has been replaced with other zinc, tin, boron, aluminum.

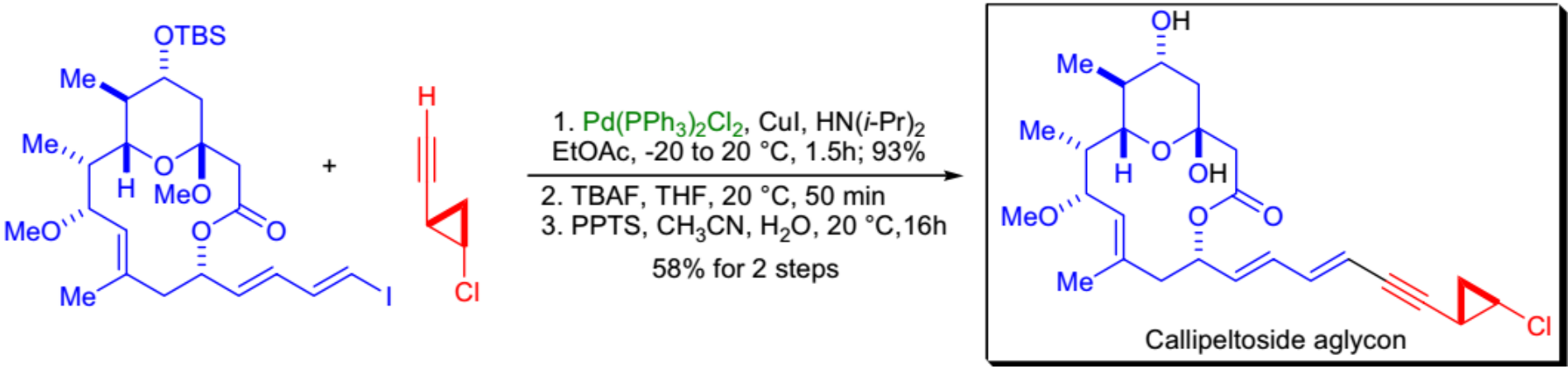
Applications:



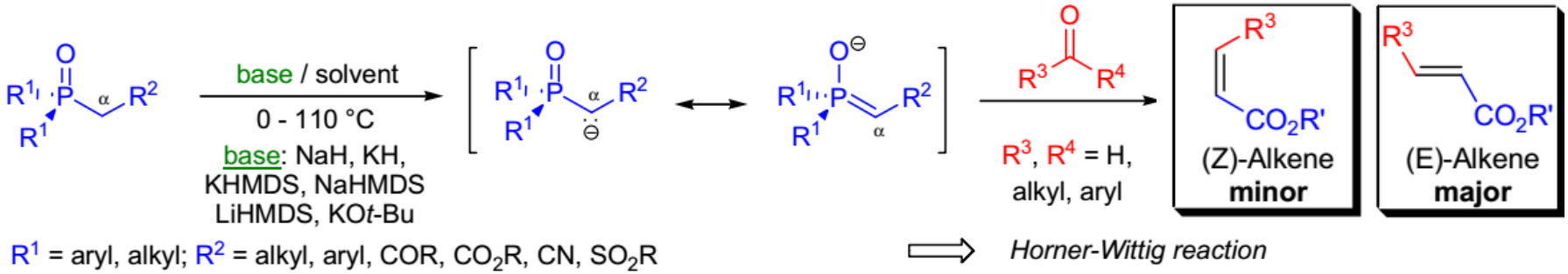


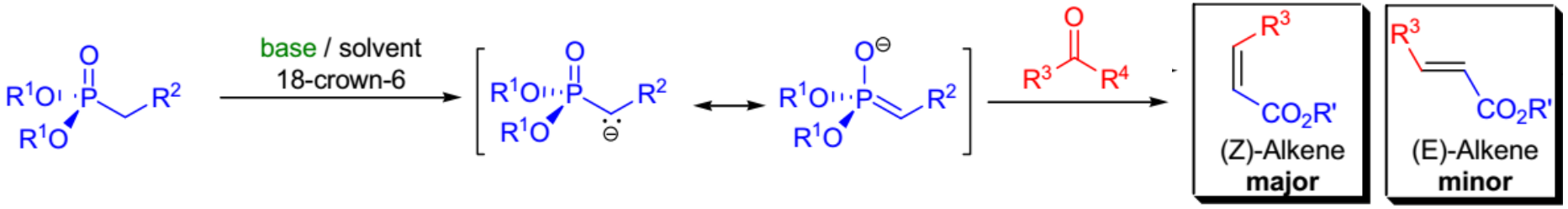
Applications:





1. *Wittig reaction , HWE olefination*





R^1 = CH_2CF_3, trifluoroalkyl; R^2 = COR, CO_2R, CN, SO_2R; $R^{3\text{-}4}$ = H, alkyl, aryl; base = KH, KHMDS