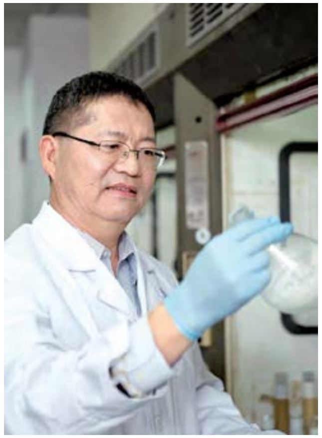
Ullmann-Ma reaction

1895 Received his PhD of the University of Geneva for work with Carl Gräbe.
1905-1913 and 1922-1925 Ullmann taught technical chemistry



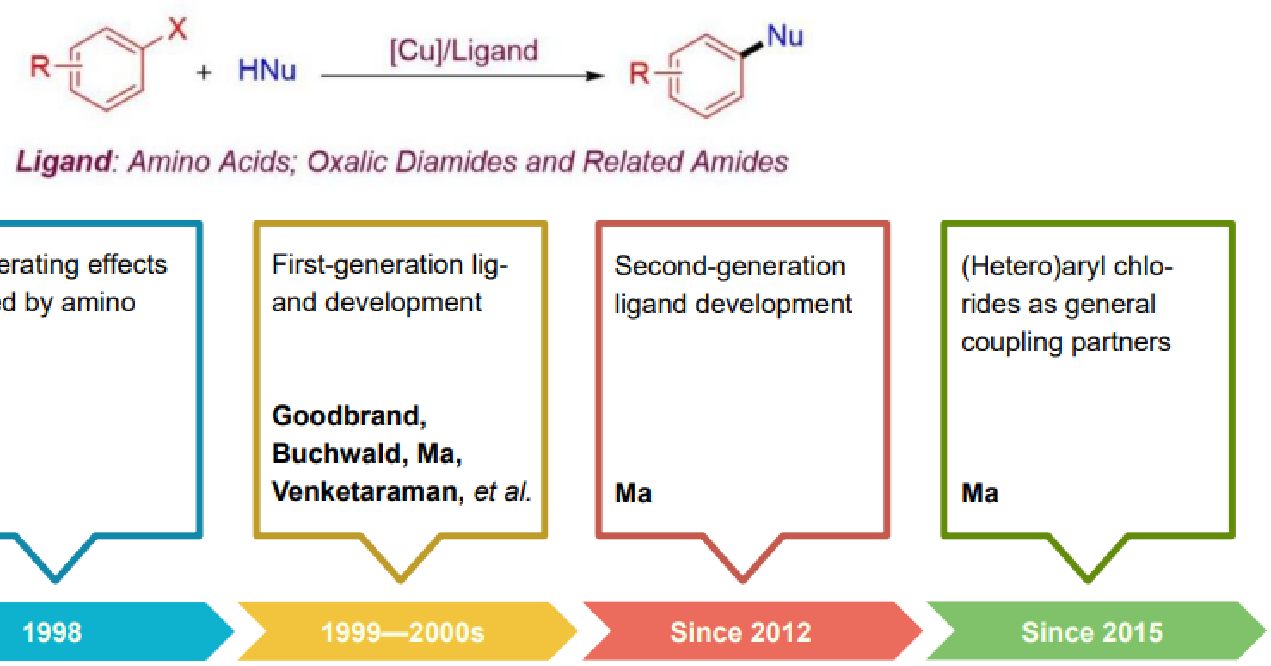
1980.9-1984.7 山东大学化学系学习，获理学学士学位。
1984.9-1989.7 上海有机化学研究所，理学博士，导师：陆熙炎
1990.5 美国匹兹堡大学和梅奥医学中心，进行博士后研究工作。
1994 入选首批中国科学院百人计划，回到上海有机化学研究所工作。
1995.1 中国科学院上海有机化学研究所研究员。
1997 复旦大学长期兼职教授,同年获得国家杰出青年科学基金资助。
2018.9.8 第三届未来科学大奖物质科学奖。
2019.11.22 当选中国科学院院士。

Drawbacks

Narrow substrate scope

Harsh reaction conditions (high temperatures, strong bases)

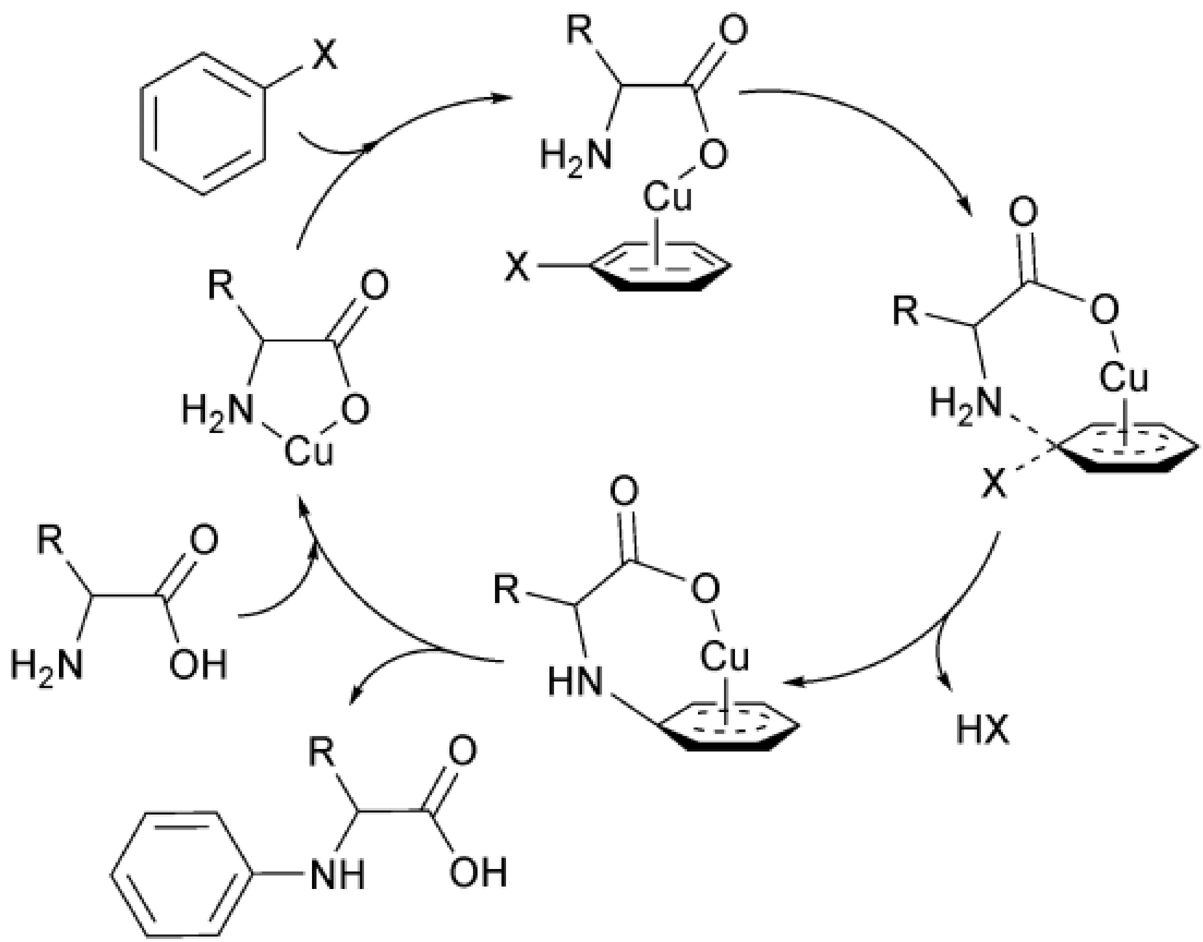
The requirement of stoichiometric amounts of copper reagents



The mechanisms proposed until the 1990s can be conveniently divided into four main classes:

- Aromatic nucleophilic substitution, with Cu(I) p-coordinating to the aromatic ring of the aryl halide to render the aromatic position more electrophilic and susceptible to substitution.
- Mechanisms via Single Electron Transfer (SET) or Halogen Atom Transfer (HAT), involving the redox couple Cu(I)/Cu(II) and radical intermediates.
- Metathesis mechanisms, leading to the formation of fourmembered cyclic transition states, through coordination of Cu to the halogen atom of the aryl halide, making it a better leaving group.
- Mechanisms involving an oxidative addition–reductive elimination cycle with Cu(III) intermediates, either via direct oxidation Cu(I)/Cu(III) or stepwise oxidation Cu(I)/Cu(II)/Cu(III).

Aromatic nucleophilic substitution, with Cu(I) p-coordinating to the aromatic ring of the aryl halide to render the aromatic position more electrophilic and susceptible to substitution.



Mechanisms via Single Electron Transfer (SET) or Halogen Atom Transfer (HAT), involving the redox couple Cu(I)/Cu(II) and radical intermediates.

$$\text{Initiator} + \text{ArX} \xrightarrow{\text{SET}} (\text{ArX})^{\bullet -} \longrightarrow \text{Ar}^{\bullet} + \text{X}^{-}$$

$$\text{Ar}^{\bullet} + \text{NH}_2^{-} \longrightarrow (\text{ArNH}_2)^{\bullet -}$$

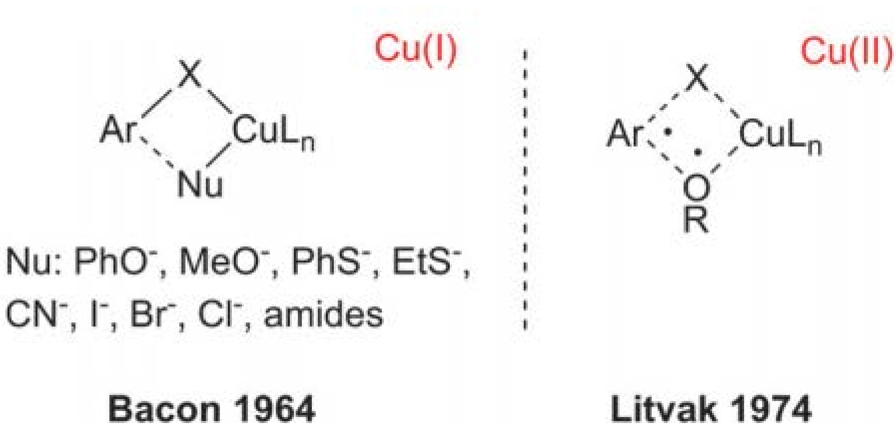
$$(\text{ArNH}_2)^{\bullet -} + \text{ArX} \longrightarrow \text{ArNH}_2 + (\text{ArX})^{\bullet -}$$

$$\text{ArX} + \text{Cu(I)X} \longrightarrow \text{Ar}^{\bullet} + \text{Cu(II)X}_2$$

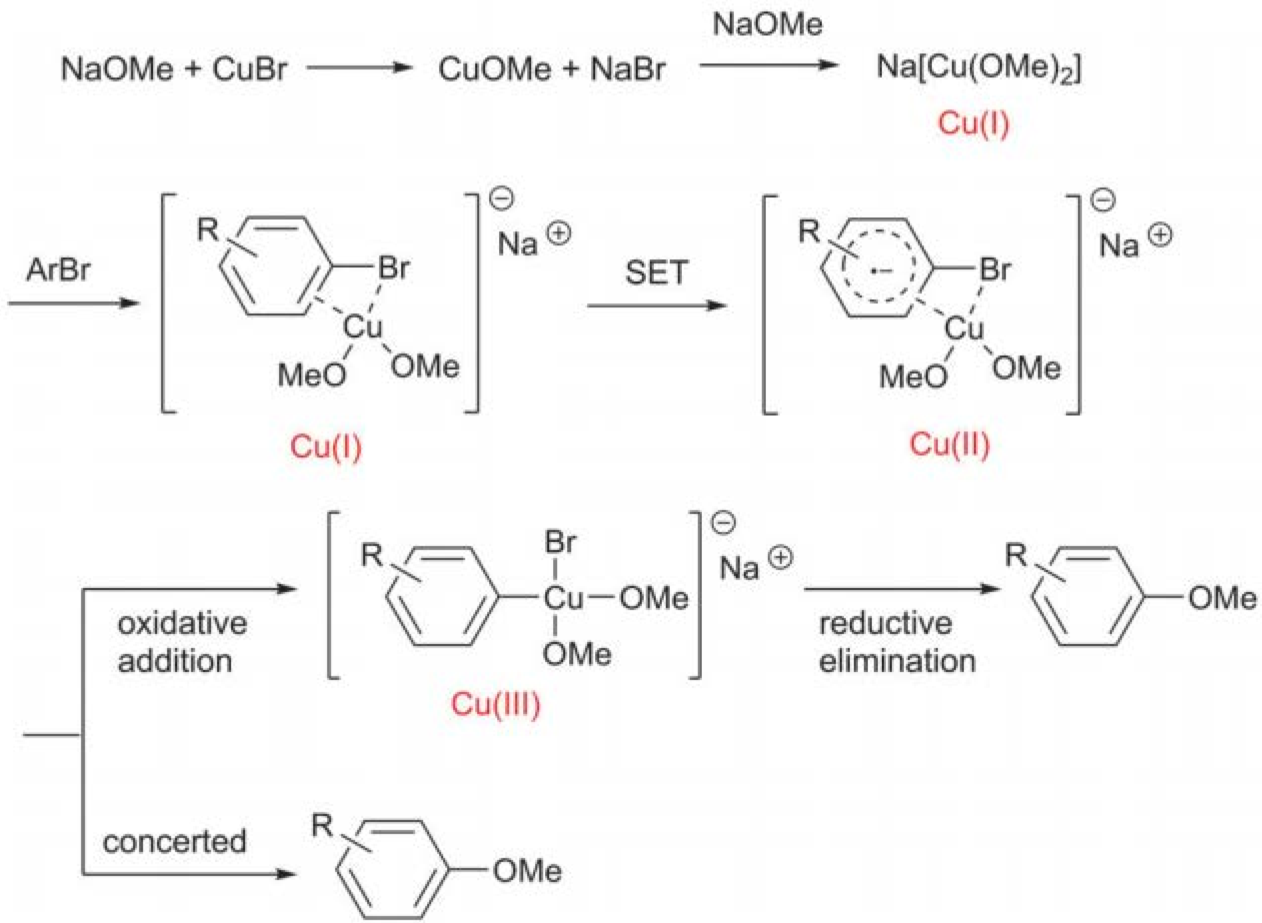
$$\text{Ar}^{\bullet} + \text{Nu}^{-} \longrightarrow (\text{ArNu})^{\bullet -}$$

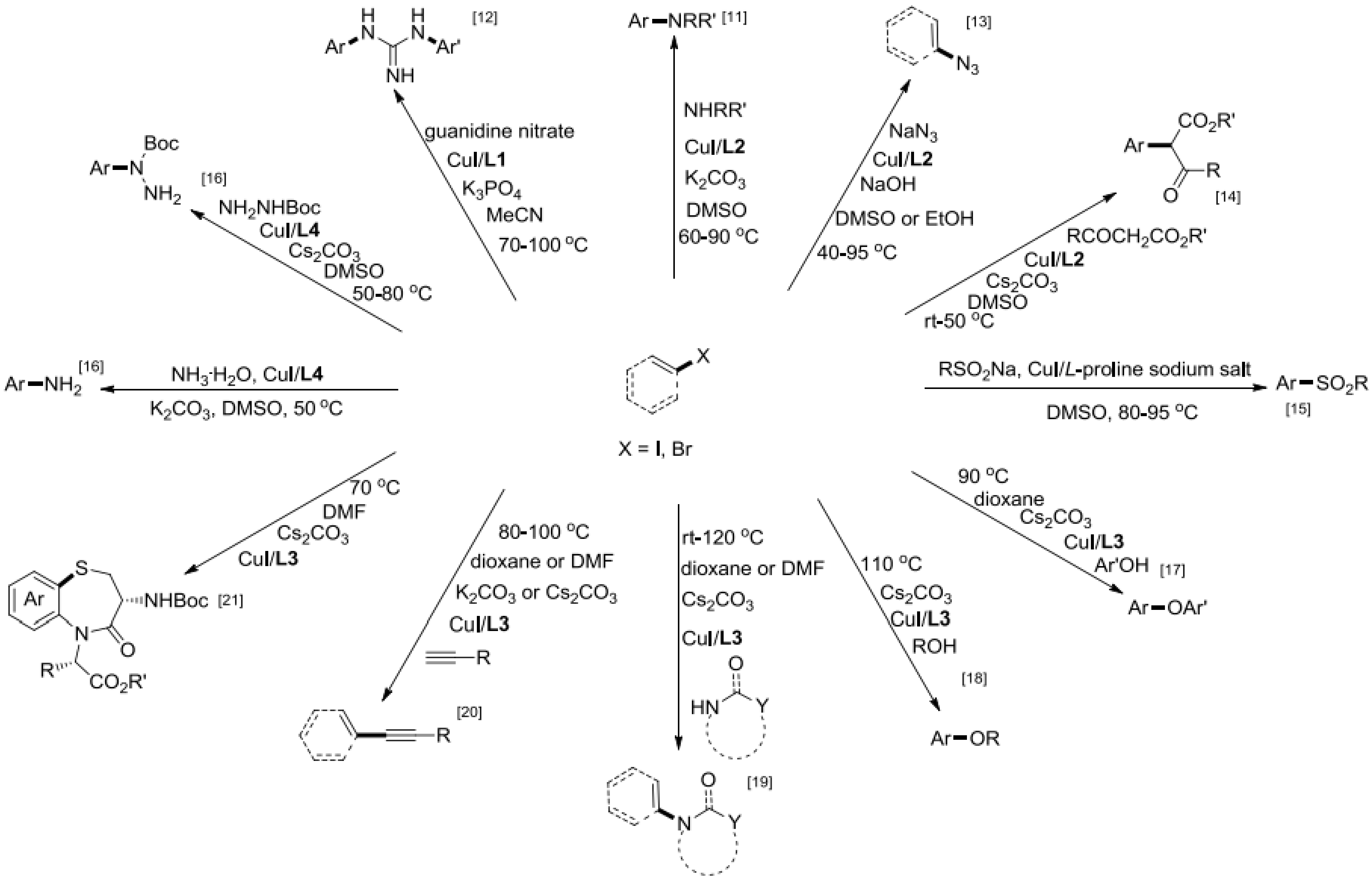
$$(\text{ArNu})^{\bullet -} + \text{Cu(II)X}_2 \longrightarrow \text{ArNu} + \text{Cu(I)X} + \text{X}^{-}$$

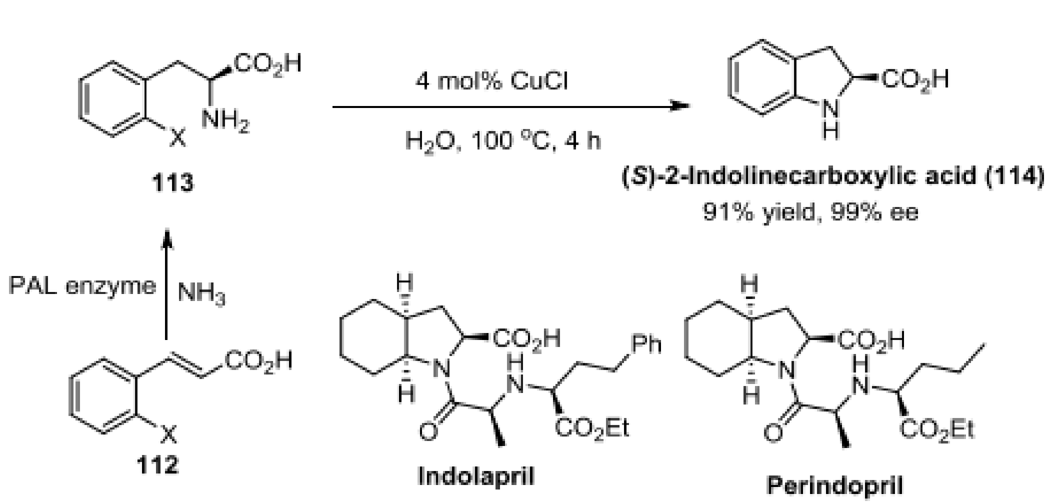
Metathesis mechanisms, leading to the formation of fourmembered cyclic transition states, through coordination of Cu to the halogen atom of the aryl halide, making it a better leaving group.

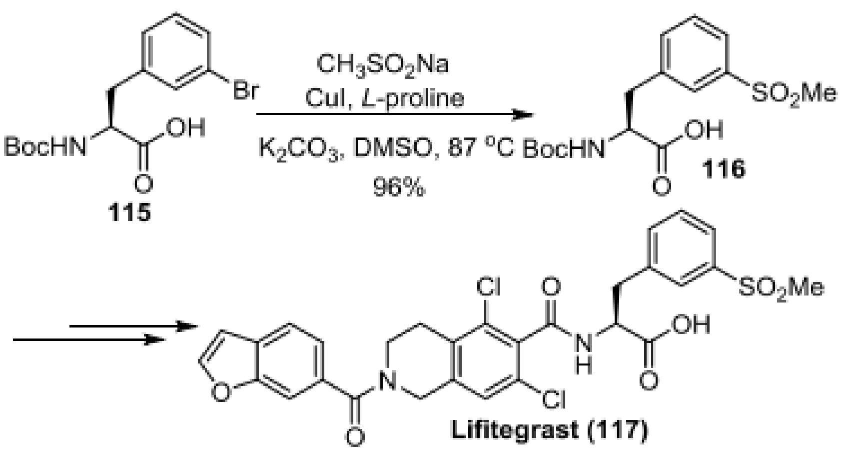


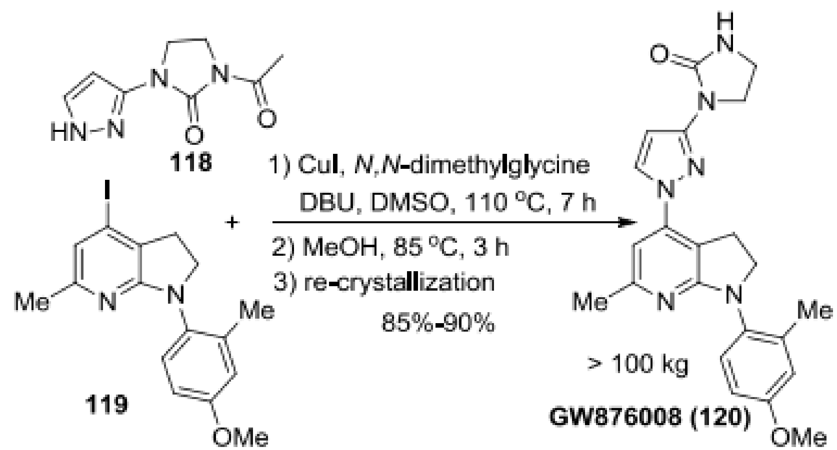
Mechanisms involving an oxidative addition–reductive elimination cycle with Cu(III) intermediates, either via direct oxidation Cu(I)/Cu(III) or stepwise oxidation Cu(I)/Cu(II)/Cu(III).



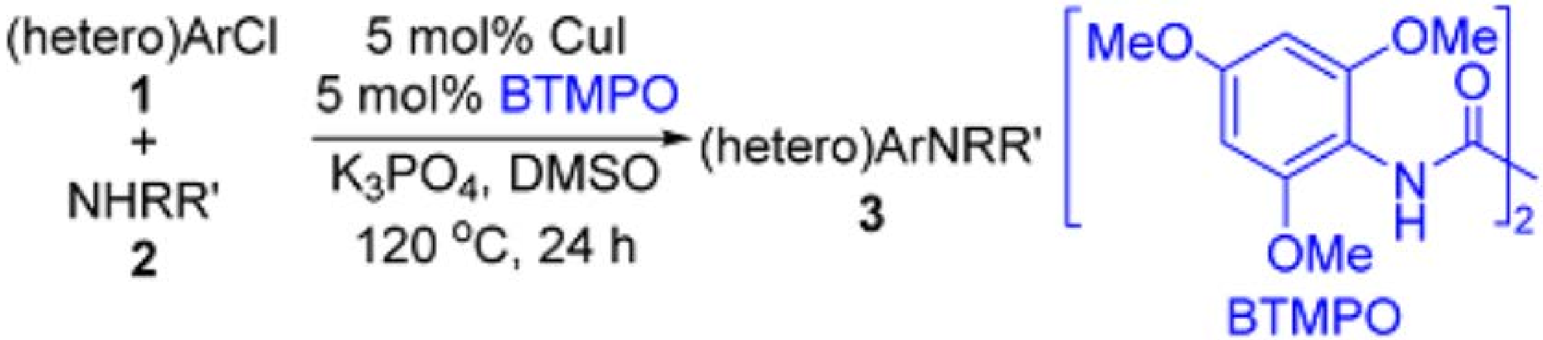

X = I, Br
NHRR'
CuI/L2
K2CO3
DMSO
60-90 °C
Ar–NRR' [11]
guanidine nitrate
CuI/L1
K3PO4
MeCN
70-100 °C
[12]
NaN3
CuI/L2
NaOH
DMSO or EtOH
40-95 °C
[13]
RCOCH2CO2R'
CuI/L2
Cs2CO3
DMSO
rt-50 °C
[14]
RSO2Na, CuI/L-proline sodium salt
DMSO, 80-95 °C
Ar–SO2R
[15]
NH2NHBoc
CuI/L4
Cs2CO3
DMSO
50-80 °C
[16]
NH3·H2O, CuI/L4
K2CO3, DMSO, 50 °C
Ar–NH2 [16]
90 °C
dioxane
Cs2CO3
CuI/L3
Ar'OH
[17]
Ar–OAr'
110 °C
Cs2CO3
CuI/L3
ROH
[18]
Ar–OR
rt-120 °C
dioxane or DMF
Cs2CO3
CuI/L3
[19]
80-100 °C
dioxane or DMF
K2CO3 or Cs2CO3
CuI/L3
[20]
70 °C
DMF
Cs2CO3
CuI/L3
NHBoc [21]


CO2H
NH2
X
113
4 mol% CuCl
H2O, 100 °C, 4 h
CO2H
H
(S)-2-Indolinecarboxylic acid (114)
91% yield, 99% ee
PAL enzyme
NH3
CO2H
X
112
Indolapril
Perindopril
Ph
CO2Et

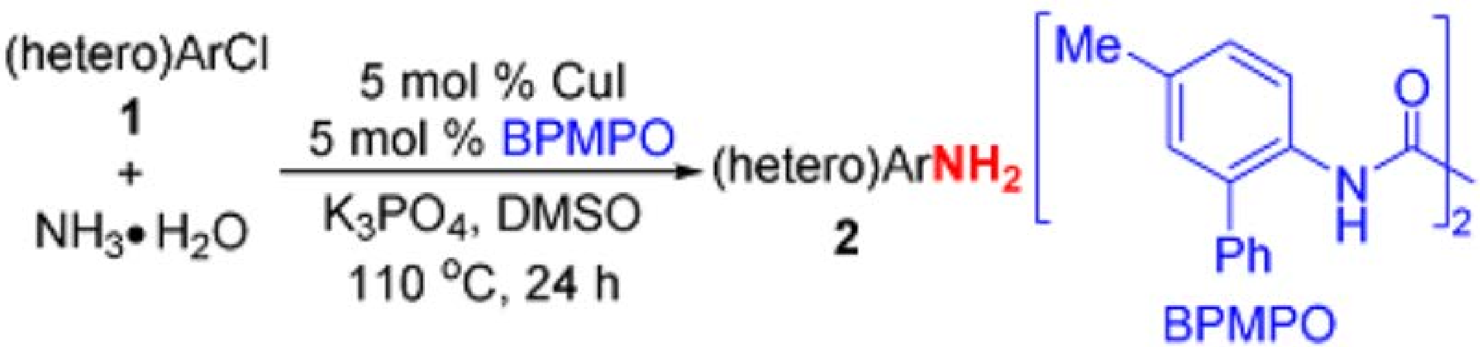

Br
BocHN
OH
115
CH3SO2Na
CuI, L-proline
K2CO3, DMSO, 87 °C
96%
SO2Me
116
Cl
Lifitegrast (117)


118
119
1) CuI, N,N-dimethylglycine
DBU, DMSO, 110 °C, 7 h
2) MeOH, 85 °C, 3 h
3) re-crystallization
85%-90%
> 100 kg
GW876008 (120)
Me
OMe

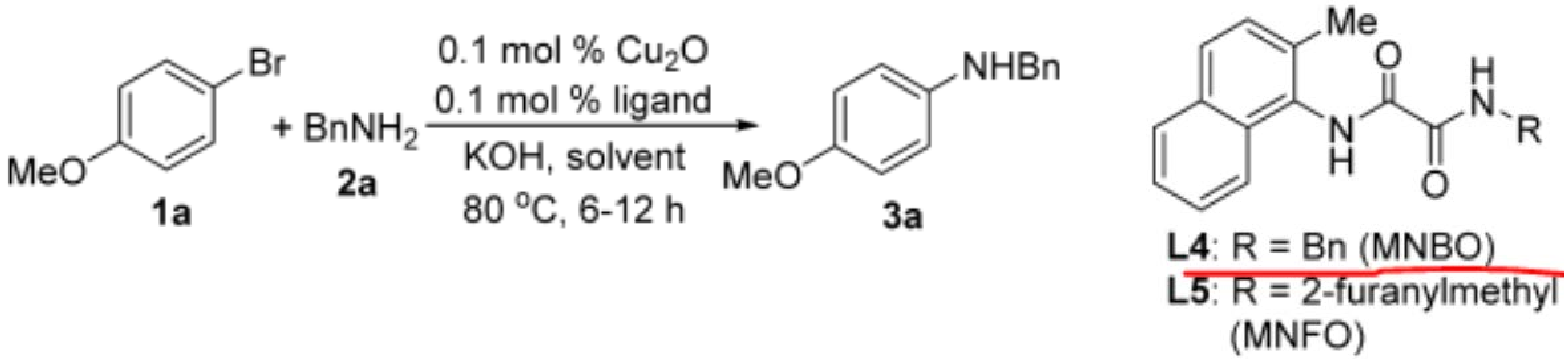
（1）氯带芳烃与胺的偶联，JACS, 2015, 137, 11942



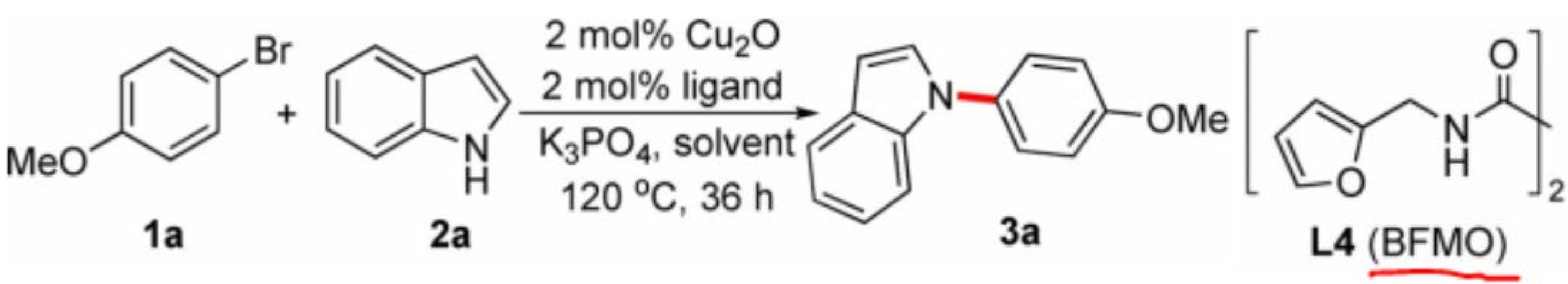
（2）一级芳胺的合成，Org. Lett. 2015, 17, 5934



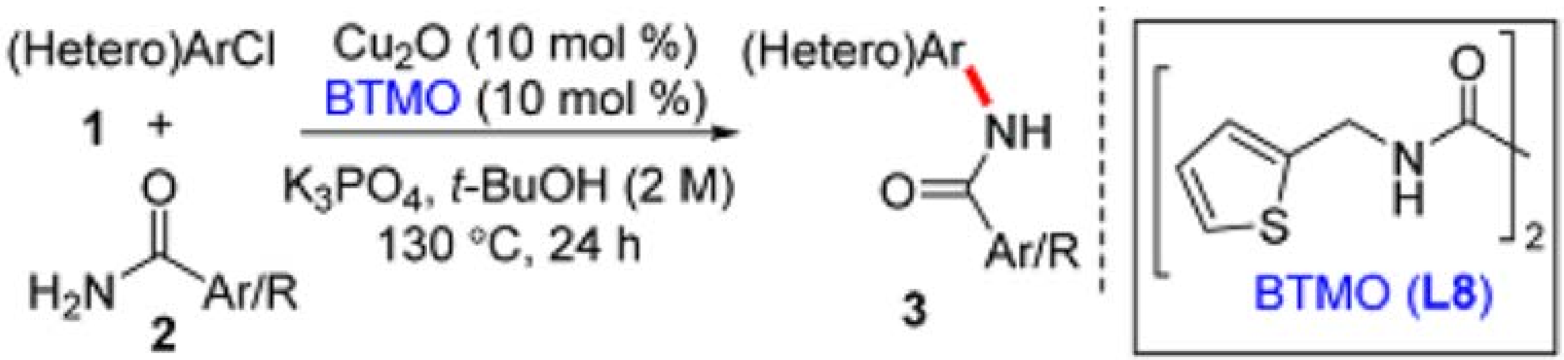
(3）更高效配体的发现，Org. Lett.2017, 19, 2809

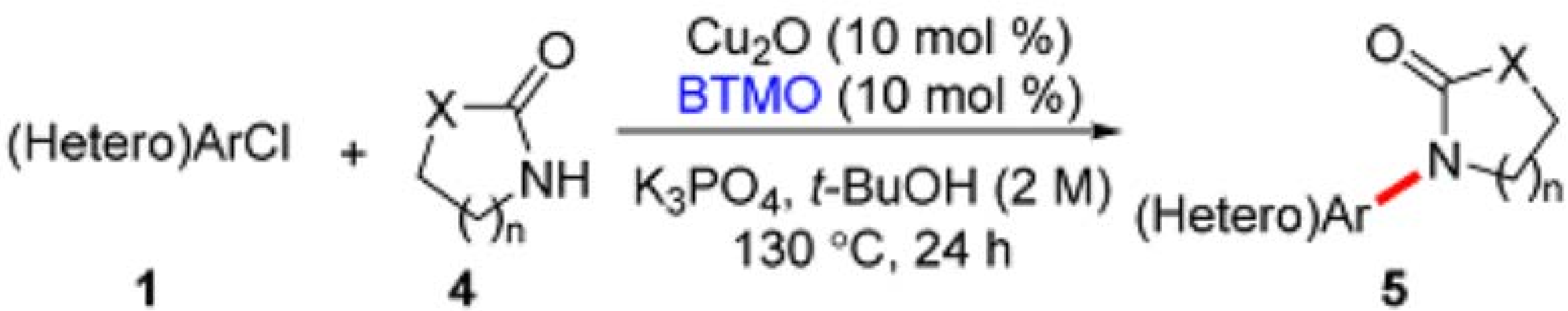


(4）氮杂环与卤代芳烃偶联，Adv.Synth. Catal. 2017, 359,1631

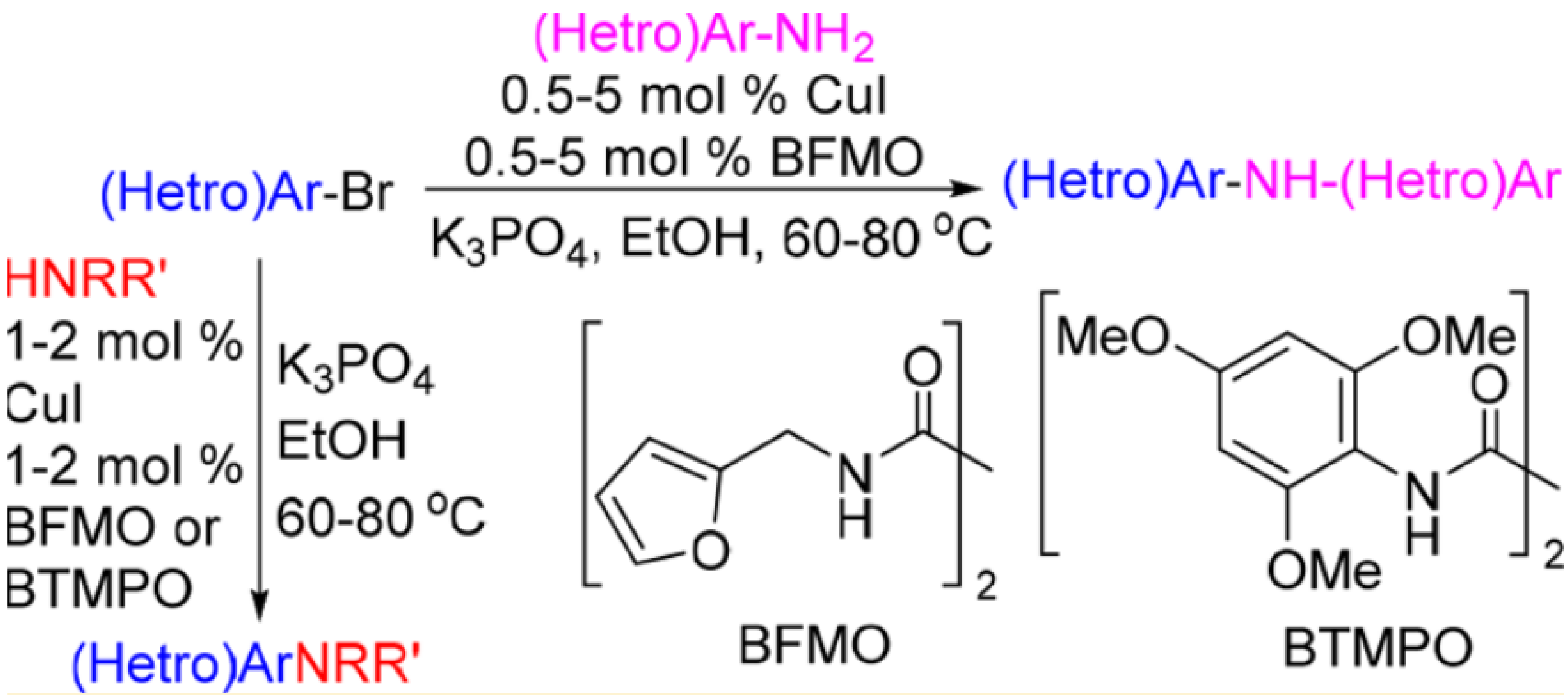


(5）氯带芳烃与酰胺偶联，Org. Lett. 2017, 19, 4864

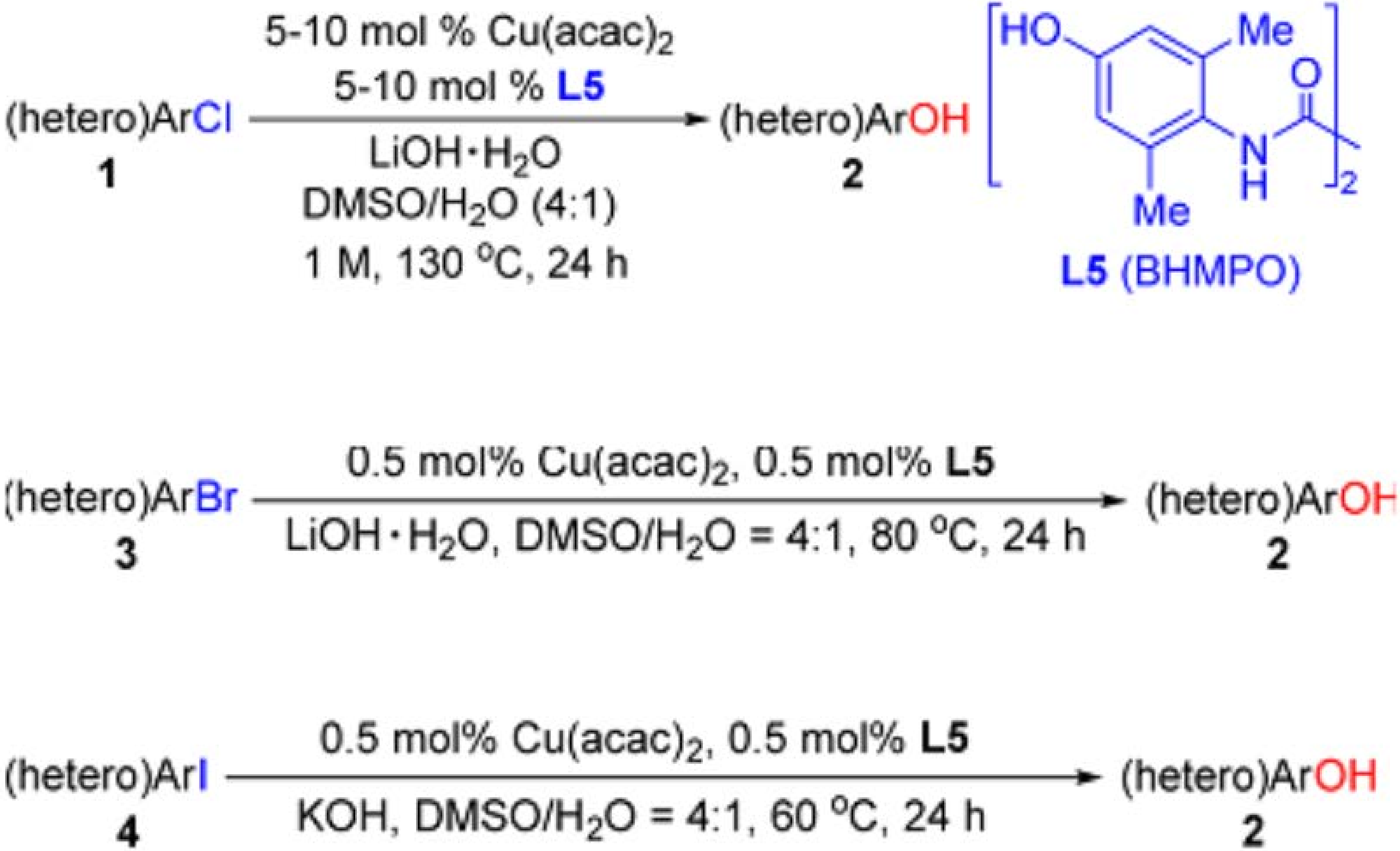




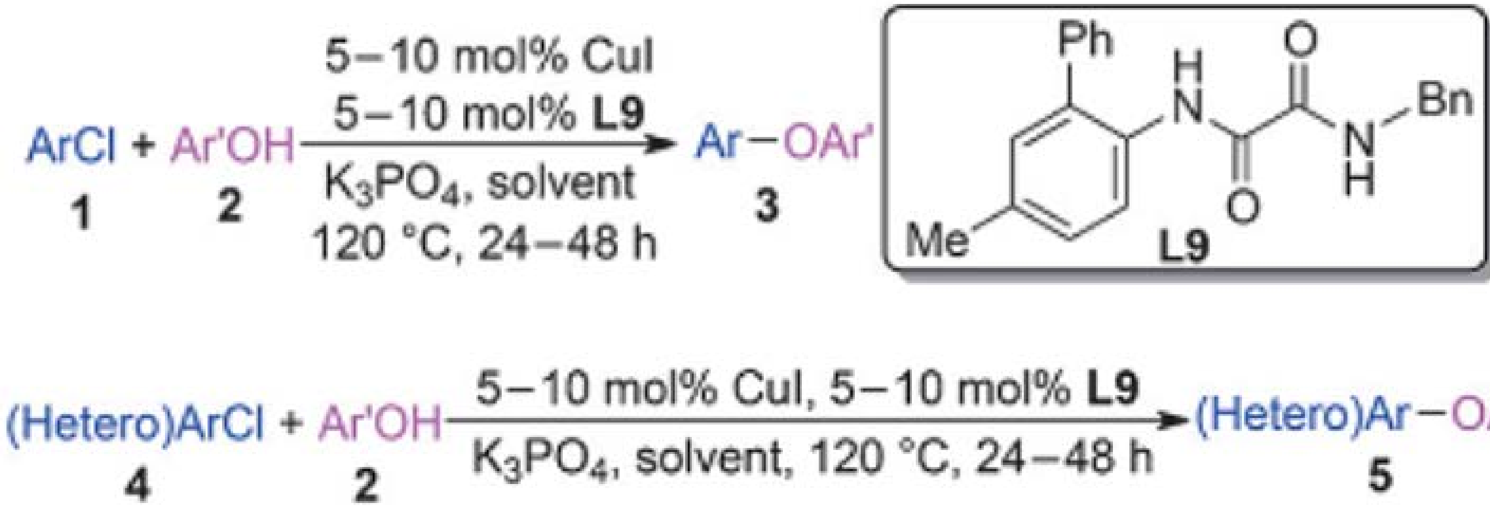
(6）芳胺或二级胺与溴代芳烃偶联，JOC, 2017, 82, 12603



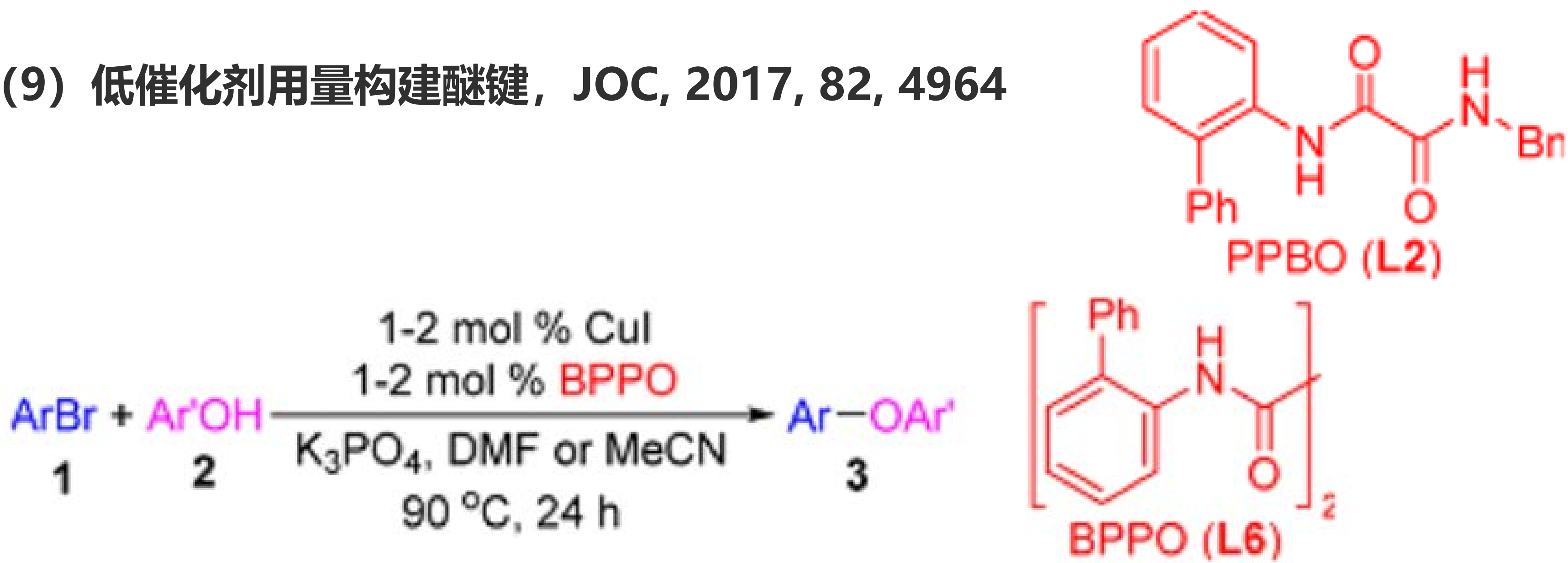
（7）卤代芳烃的羟基化反应，JACS, 2016, 138, 13493



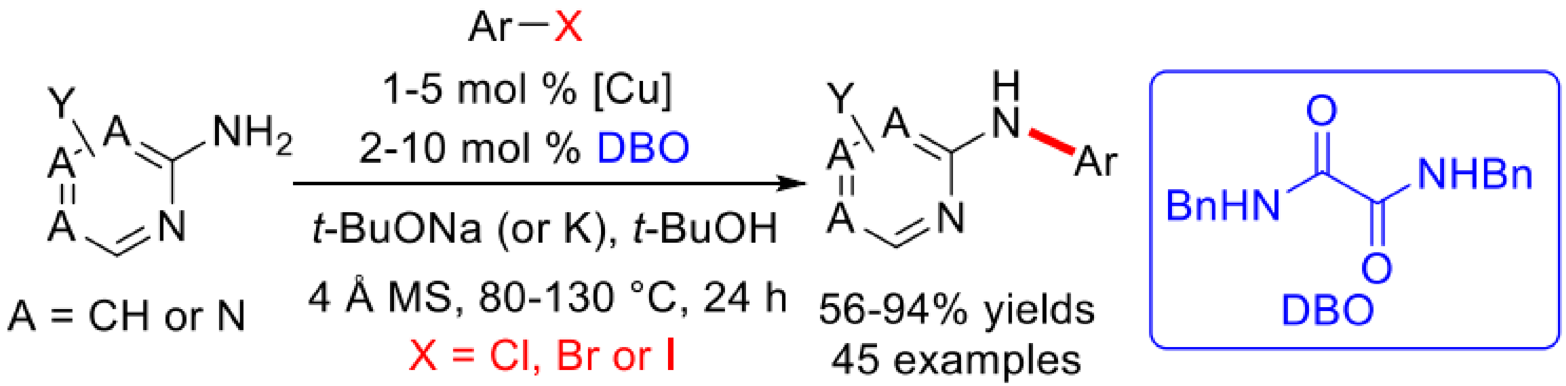
(8）氯带芳烃构建醚键，Angew.Chem. Int.Ed. 2016, 55,6211

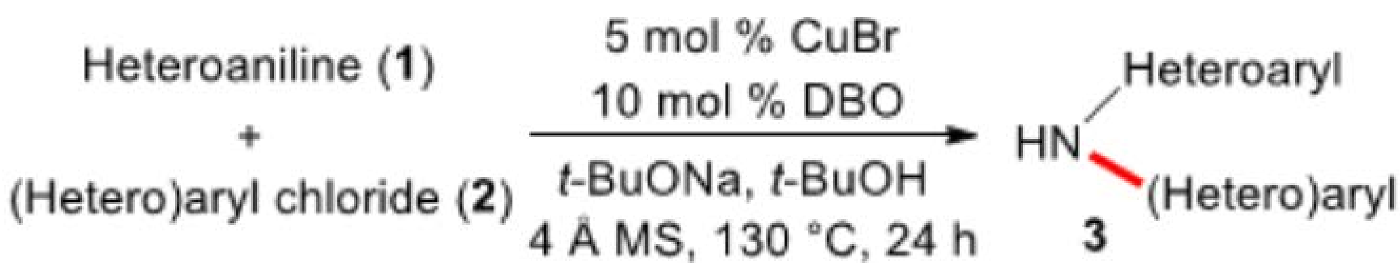


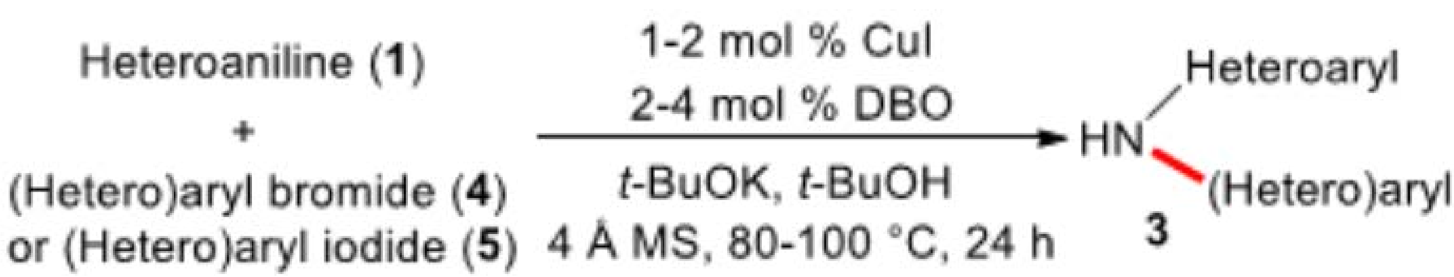
(9）低催化剂用量构建醚键，JOC, 2017, 82, 4964



（10）杂芳胺参与的偶联，Org. Lett.2019, 21, 6874







（11）烷基芳基醚构建，JACS, 2019, 141, 3541