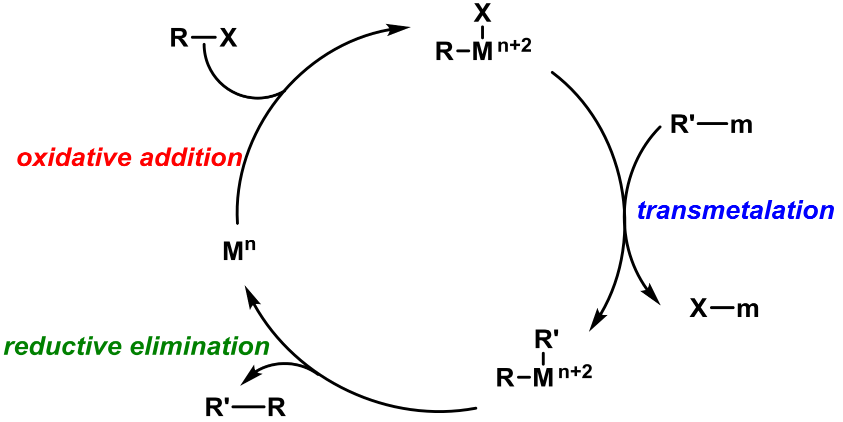
Reductive Cross-Couplings of Two Electrophiles

Yuanhong Ma

Cornella Group Meeting
07.12. 2018

Background

Conventional Cross-Coupling chemistry



Limitations of organometallic reagents:

- Sensitive to air and moisture
- Requirement of basic reagent to facilitate transmetalation
- Low functional group tolerance
- Inherent reactivity

$$\begin{tikzcd}
R^1{-}X \arrow[r, "\text{pre-activation}", "\textit{cross-coupling}"'] \arrow[rr, bend right=40, "\text{catalyst \& reductant}", "R^2{-}X"'] & R^1{-}[M] \arrow[r, "\text{catalyst}", "R^2{-}X"'] & R^1{-}R^2
\end{tikzcd}$$

reductive cross-coupling

Wide commercially availability. Air and moisture stable

Development of Reductive Cross-Couplings

Reductive dimerizations of electrophiles

Wurtz coupling 1855

$$2\ \text{Alkyl—X} \xrightarrow{\textit{Na}} \text{Alkyl—Alkyl}$$

Ullman coupling 1901

$$2\ \text{Ar—X} \xrightarrow{\textit{Cu}} \text{Ar—Ar}$$

General methods for the cross-coupling of electrophiles have lagged far behind cross-couplings of nucleophiles with electrophiles or even C-H functionalization.

Challenges: super difficult to control cross selectivity.

Equal reactivity of substrates

$$R^1{-}X + R^2{-}X \longrightarrow R^1{-}R^1 + R^1{-}R^2 + R^2{-}R^2$$

$R^1{-}X$ more reactive than $R^2{-}X$

$$R^1{-}X + R^2{-}X \longrightarrow R^1{-}R^1 + R^1{-}R^2 + R^2{-}R^2$$

$R^1{-}R^1$ *formed first*
$R^2{-}R^2$ *formed second*
incidental $R^2{-}R^2$ *formed*

Substantial breakthrough started from 2008.......

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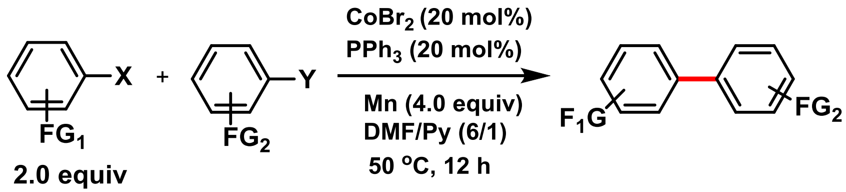
This presentation will mainly focus on cross electrophiles couplings including alkyl, aryl and vinyl electrophiles

Recent review: a) *Chem.-Eur. J.* **2014**, *20*, 6828. b) *J. Org. Chem.* **2014**, *79*, 4793. c) *Chem.-Eur. J.* **2014**, *20*, 8242. d) *Top. Curr. Chem.* (Z) **2016**, *374*, 43.

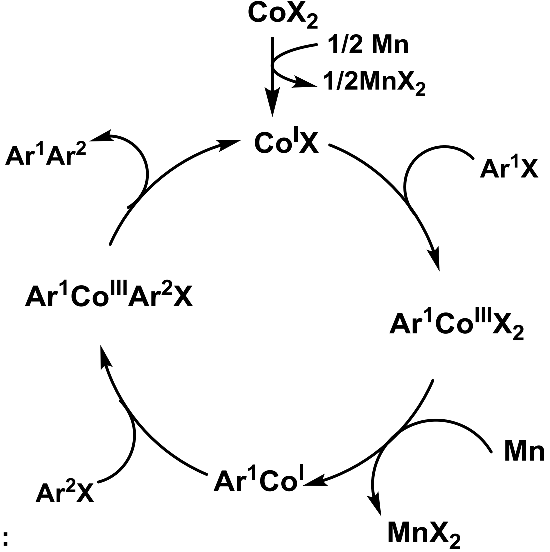
1. C(Sp^2)-C(Sp^2) cross-coupling

1.1 Formation of Biaryl Compounds

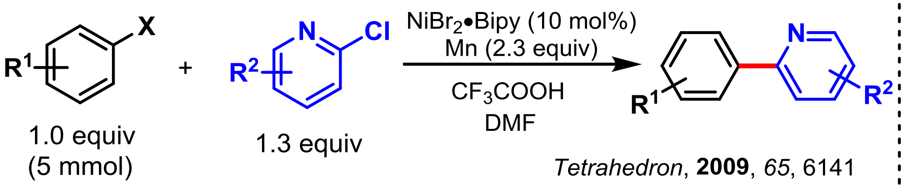


X = I, Br, Cl **Y = Br, Cl**

C. Gosmini, ACIE, **2008**, *47*, 2089

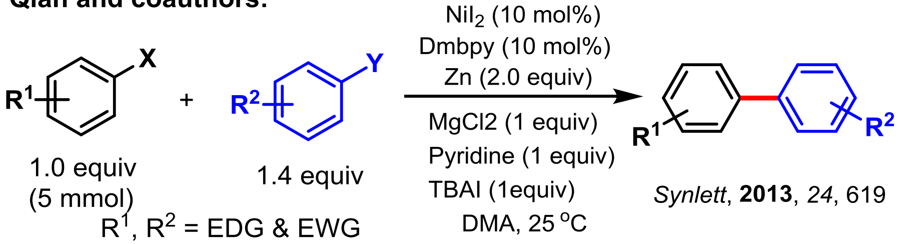


Gosmini:



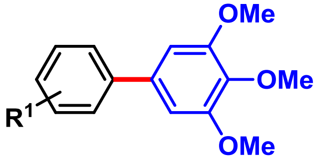
Tetrahedron, **2009**, *65*, 6141

Qian and coauthors:

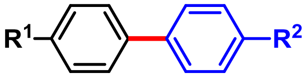


R^1, R^2 = EDG & EWG
X, Y = Br, Cl and I

Synlett, **2013**, *24*, 619

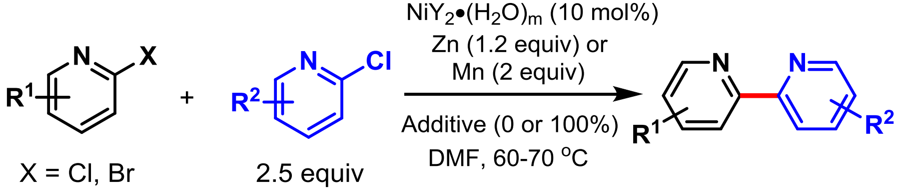


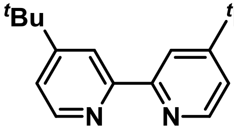
R^1 = H, 63% (X, Y = Br)
R^1 = 4-OMe, 60% (X, Y = Br)
R^1 = 4-CN, 43% (X, Y = Br)
R^1 = 3-OMe, 61% (X, Y = Br)



R^1 = CO_2Me, R^2 = H, 52% (X, Y = Br)
R^1 = CO_2Me, R^2 = CF_3, 48% (X = Br, Y = Cl)
R^1 = OMe, R^2 = CO_2Me, 32% (X = I, Y = Br)
R^1 = OMe, R^2 = C(O)Me, 52% (X, Y = Br)

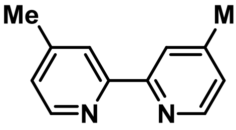
Weix (homocoupling)
Duan (homo- and cross-coupling)





90% (Weix: Mn, no additive)

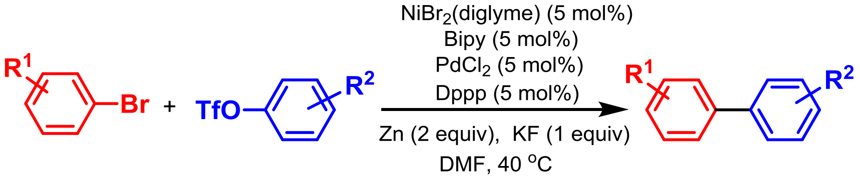
Synthesis, **2013**, *45*, 3099



81% (Duan: Zn, 1 equiv LiCl)

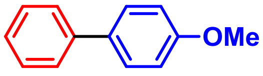
J. Org. Chem. **2014**, *79*, 777

Reductive Cross-Couplings of Two Electrophiles

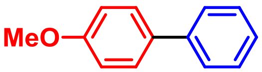


$NiBr_2$(diglyme) (5 mol%)
Bipy (5 mol%)
$PdCl_2$ (5 mol%)
Dppp (5 mol%)
Zn (2 equiv), KF (1 equiv)
DMF, 40 °C

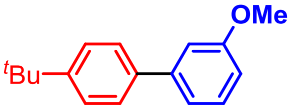
Selected examples



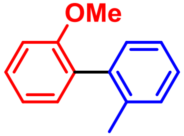
78% yield



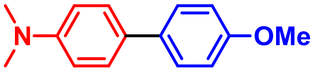
85% yield



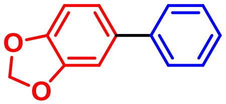
94% yield



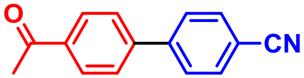
75% yield



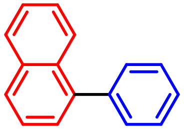
61% yield



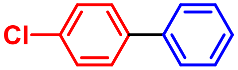
71% yield



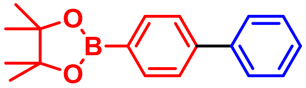
53% yield



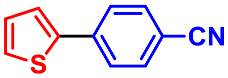
71% yield



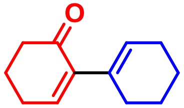
61% yield



59% yield

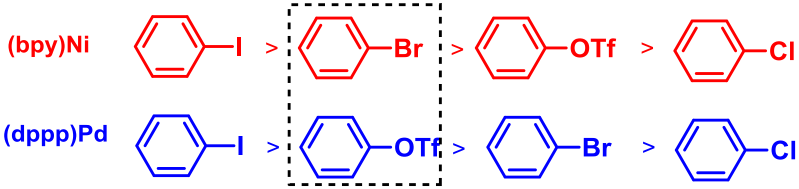


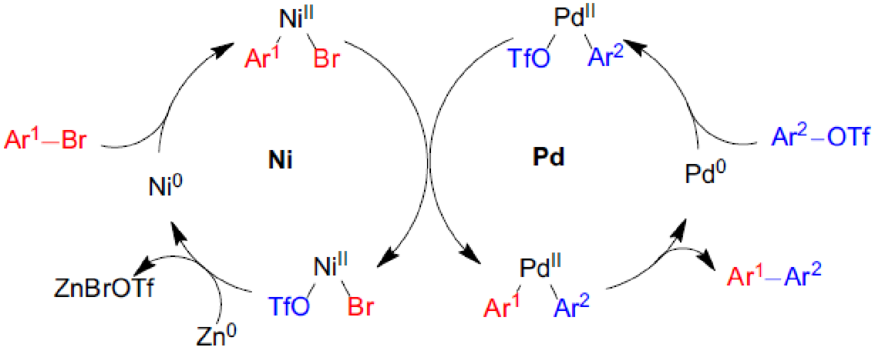
85% yield



75% yield

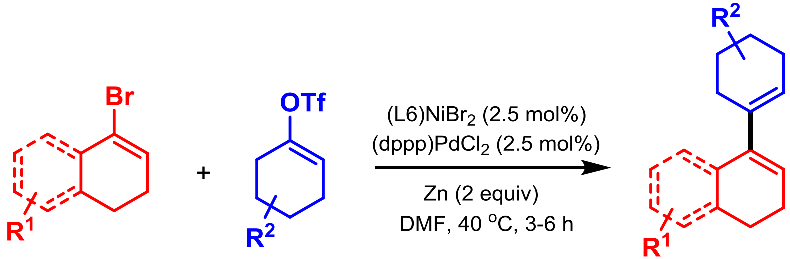
Relative reactivity of catalysts





Weix, *Nature*, **2015**, *524*, 455

1.2 Formation of 1,3-Dienes

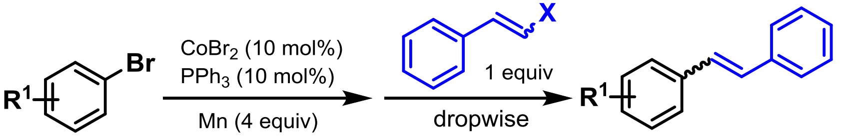


1 equiv 1 equiv

(L6)$NiBr_2$ (2.5 mol%)
(dppp)$PdCl_2$ (2.5 mol%)
Zn (2 equiv)
DMF, 40 °C, 3-6 h

Weix, *JACS*, **2018**, *140*, 2446

1.3 Reductive vinylation of aryl halides



$CoBr_2$ (10 mol%)
PPh_3 (10 mol%)
Mn (4 equiv)
CH_3CN, 50 °C

dropwise
10-40 min
X = Br or Cl

R^1 = COOMe, CF_3, H, MeO, etc

retention of E/Z configuration
yield: 55-84%, 13 examples

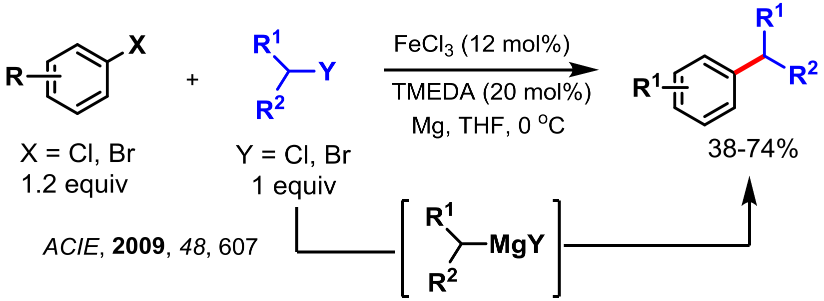
JOC, **2012**, *77*, 5056

Reductive Cross-Couplings of Two Electrophiles

2. C(Sp^2)-C(Sp^3) Cross-Coupling

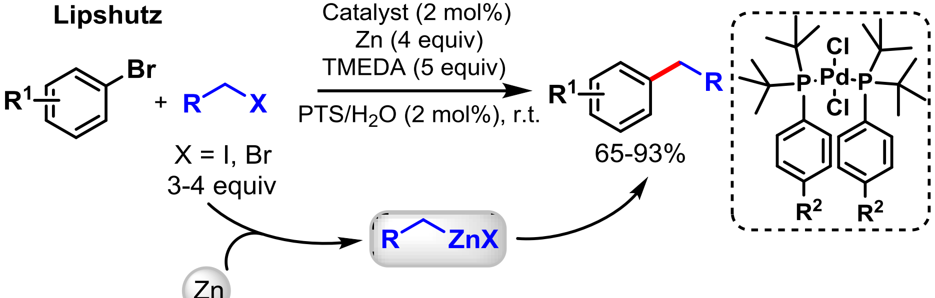
2.1 Reductive Arylation of Alkyl Halides

Jacobi von Wangelin



ACIE, **2009**, *48*, 607

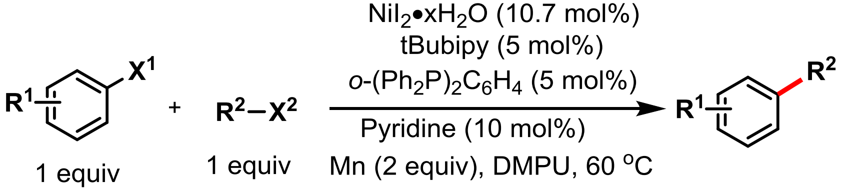
Lipshutz



JACS, **2009**, *131*, 15592

In situ formation of Gignard and Zinc reagents are proposed.

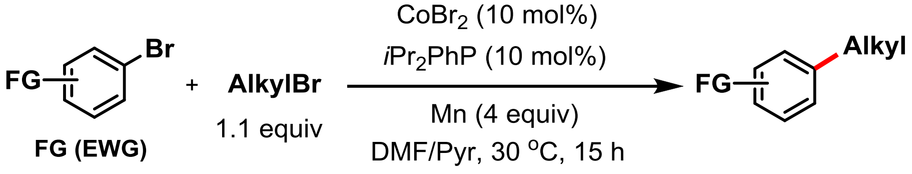
Weix



JACS, **2010**, *132*, 920

Primary alkyl halides, only one example for secondary alkyl halides

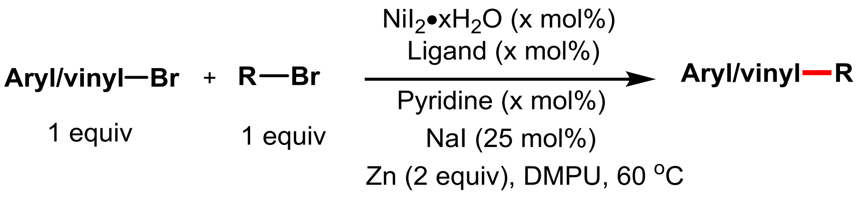
Gosmini

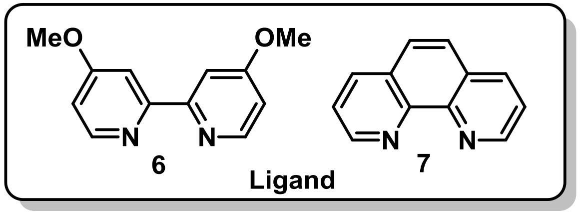


Primary alkyl halides

Chem. Eur. J. **2010**, *16*, 5848

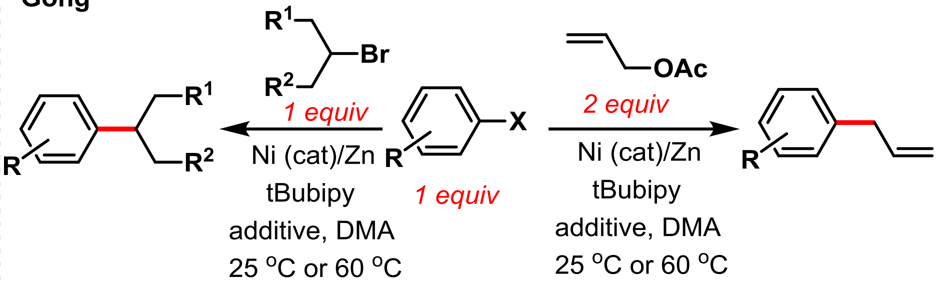
Weix





JACS, **2012**, *134*, 6146

Gong



MgCl$_2$ (1.0 equiv) as additive

OL, **2012**, *14*, 3352

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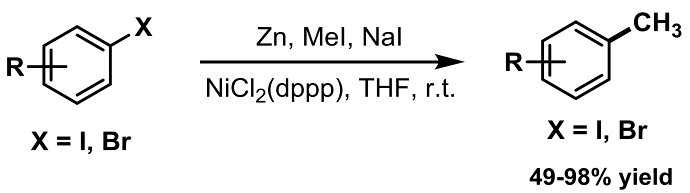
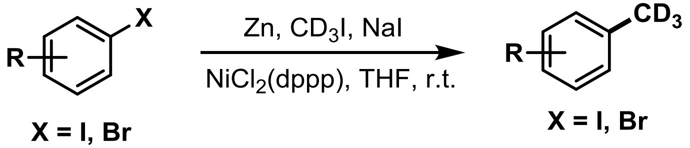
Aryl Halides with Deuterated Methyl Iodide



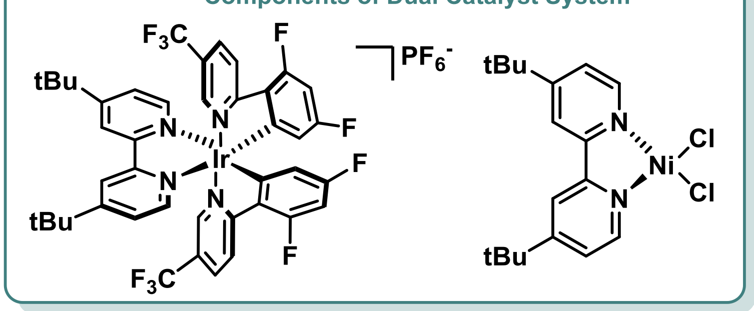


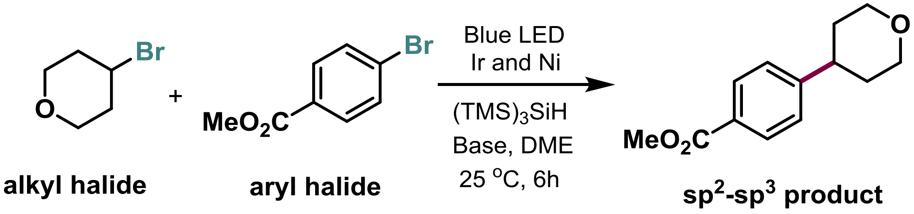
X. Liao, ACIE, **2016**, *55*, 9743

Formation of Zinc reagent in situ is proposed.

MacMillan

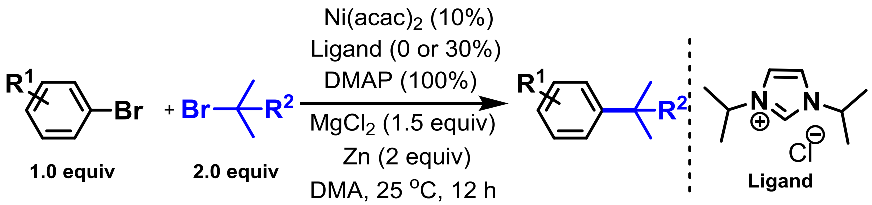
Components of Dual Catalyst System



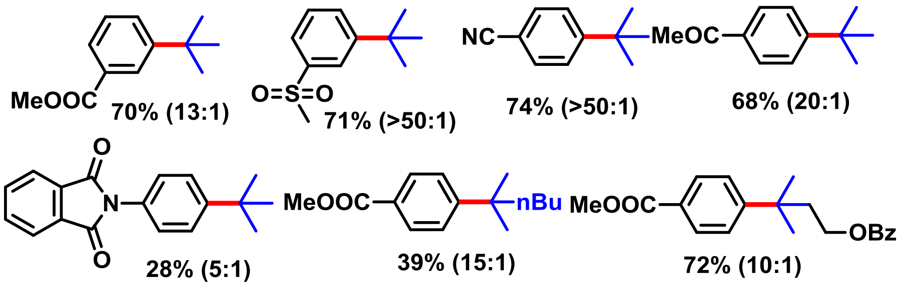


JACS, **2016**, *138*, 8084

Gong Coupling of Aryl Bromides with Tertiary Alkyl Halides



Selected examples

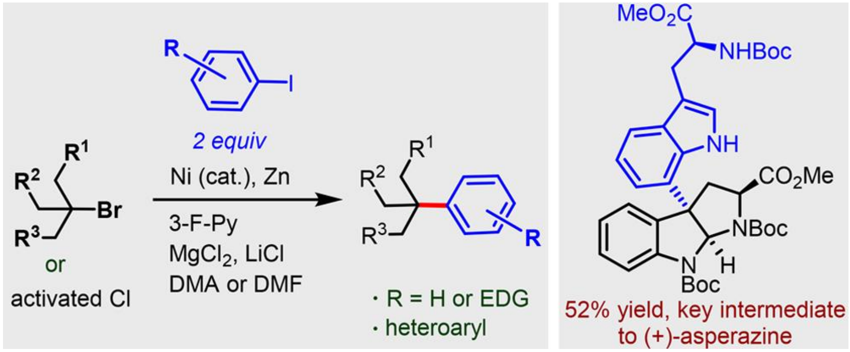


JACS, **2015**, *137*, 11562

Electron-rich aryl halides are less effective

Gong

Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides



1.0 equiv 3-fluropyridine is crucial for success.

JACS, **2018**, *140*, 14490

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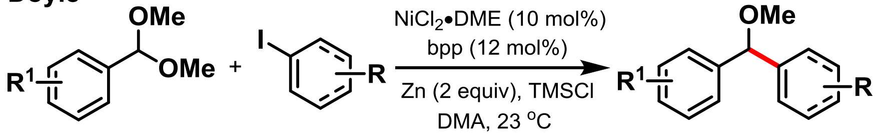
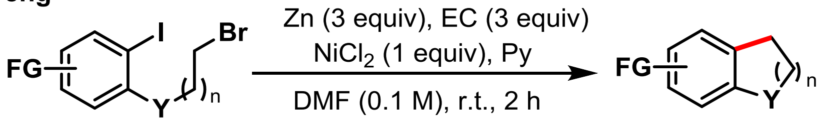
Doyle



ACIE, **2015**, *54*, 9876

2.2 Intramolecular Arylation of Alkyl Electrophile

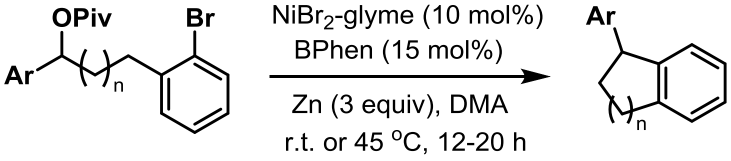
Peng



Y = O, N-PG
n = 1, 2, 3

Chem. Eur. J. **2012**, *18*, 6039

Jarvo



ACIE, **2016**, *55*, 6730

2.3 Mechanism studies in detail (Weix)

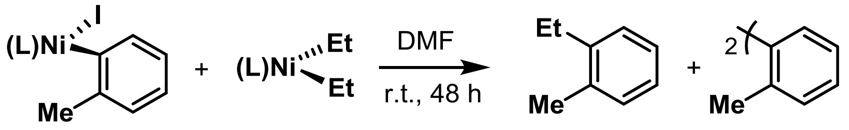
A. $R^1{-}I \xrightarrow{Mn^0} R^1{-}Mn{-}I \xrightarrow[R^2{-}I]{[Ni]} R^1{-}R^2$

B. $R^1{-}I \xrightarrow{[Ni]} R^1{-}[Ni]{-}I \xrightarrow{R^2{-}[Ni]{-}I} R^1{-}R^2$

C. $R^1{-}I \xrightarrow{[Ni]} R^1{-}[Ni]{-}I \xrightarrow{R^2{-}I} R^1{-}R^2$

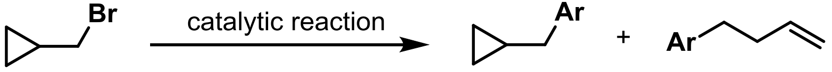
D. $R^1{-}I \xrightarrow{[Ni]} R^1{-}[Ni]{-}I \xrightarrow{R^2\cdot} R^1{-}R^2$

Tetrakis(dimethylamino)ethylene (TDAE) can replace Mn or Zn, providing about six turnovers. This result appears to rule out mechanism A.



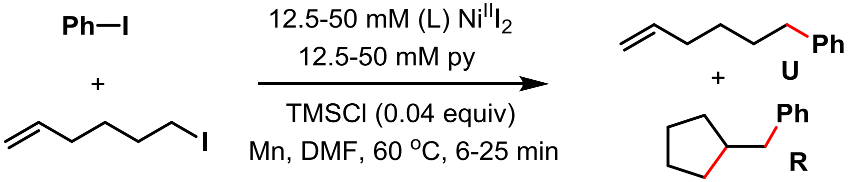
generated in situ as a
1 : 1 mixture with $(L)NiI_2$

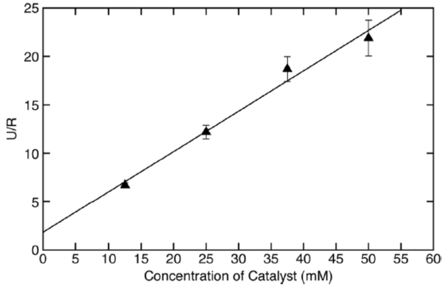
1 : 36
This result appear to rule out mechanism B

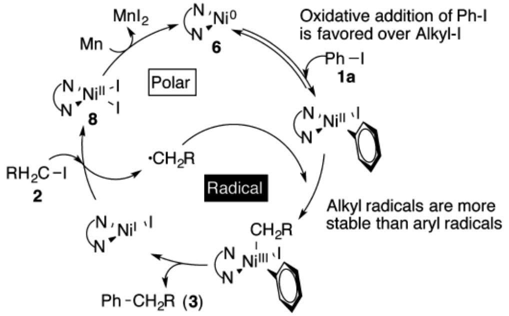


Reaction with $(L)Ni^{II}$(2-tol)I

	unrearranged	rearranged
Reaction with $(L)Ni^{II}$(2-tol)I	N.D.	56% yield (Ar = tol)







Oxidative addition of Ph-I is favored over Alkyl-I

Alkyl radicals are more stable than aryl radicals

(1) selective oxidative addition of iodoarene over iodoalkane
(2) selective formation of alkyl radical over an aryl radical

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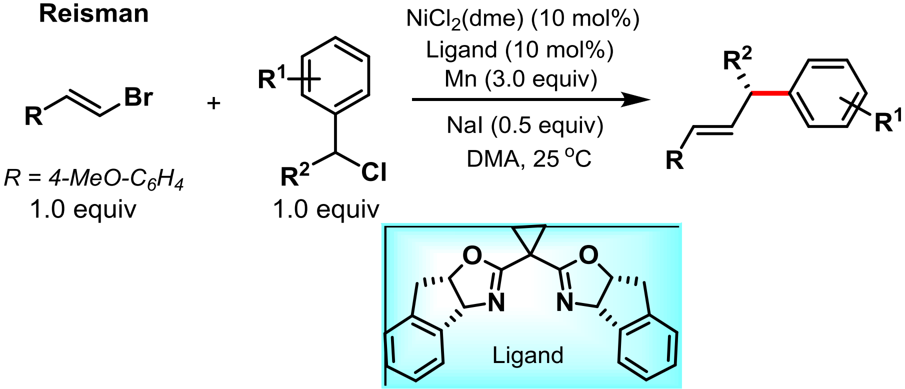
2. C(Sp^2)-C(Sp^3) Cross-Coupling

2.4 Enantioselective C(Sp^3)–C(Sp^2) Bond Formation

Control of enantioselectivity in reductive coupling chemistry is exceedingly sophisticated due to the radical nature of alkyl groups.

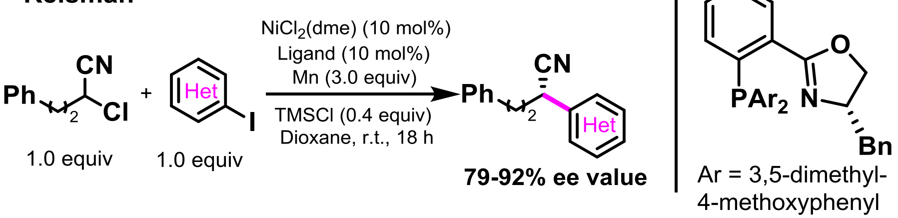
Reisman



entry	R^1	R^2	pdt	Yield (%)	ee (%)
1	H	Me	3a	91	93
2	4-Me	Me	3b	82	94
3	3-Me	Me	3c	88	93
4	2-Me	Me	3d	44	85
5	4-OMe	Me	3e	64	93
6	4-F	Me	3f	81	89
7	4-Cl	Me	3g	75	88
8	4-Br	Me	3h	59	90
9	4-OCF$_3$	Me	3i	84	88
10	H	Et	3j	80	97
11	H	Bn	3k	82	93
12	H	4-pentenyl	3l	68	94

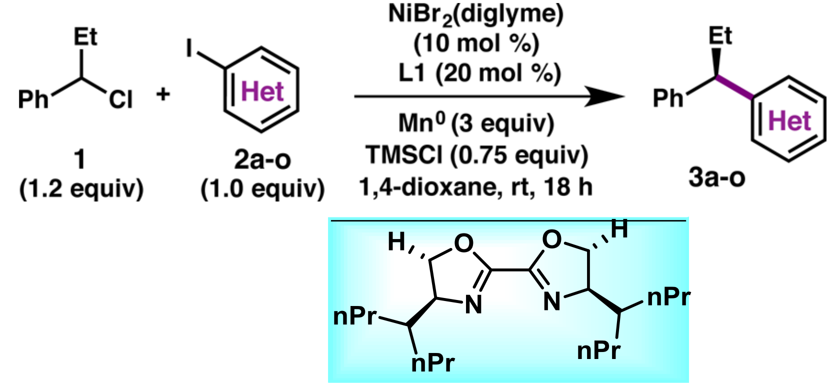
J. Am. Chem. Soc. **2014**, *136*, 14365

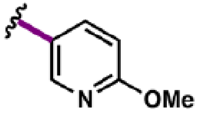
Reisman



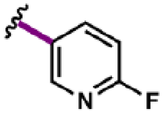
J. Am. Chem. Soc. **2015**, *137*, 10480

Reisman

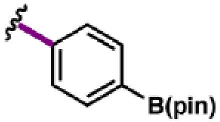




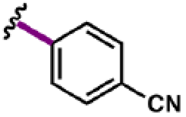
3a
84% yield
91% ee



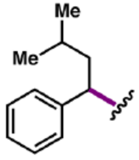
3b
63% yield
90% ee



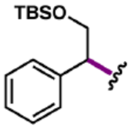
3l
72% yield
83% ee



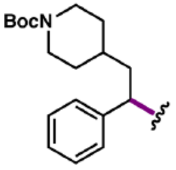
3m
62% yield
89% ee



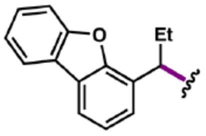
8j
74% yield
94% ee



8k
36% yield
94% ee



8l
60% yield
94% ee



8m
48% yield
93% ee

J. Am. Chem. Soc. **2017**, *139*, 5684

Reductive Cross-Couplings of Two Electrophiles

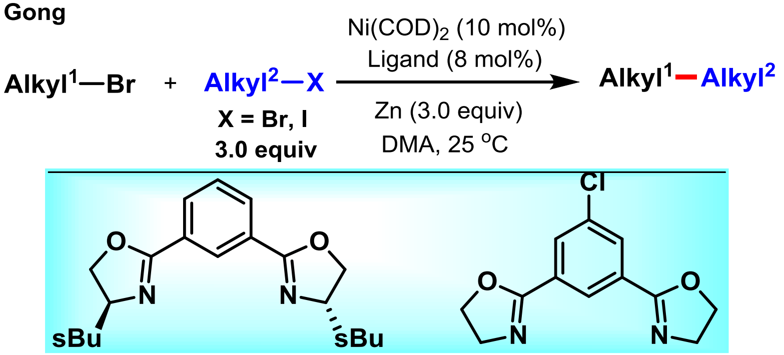
Yuanhong Ma

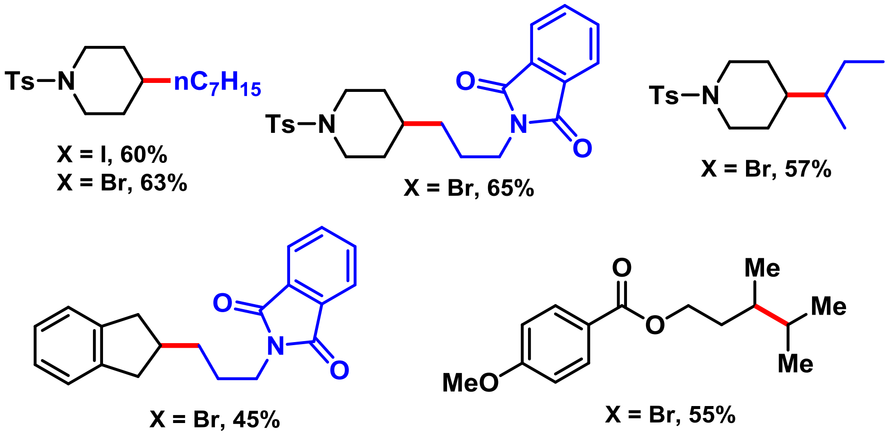
Cornella Group Meeting
07.12.2018

3. C(Sp^3)-C(Sp^3) Cross-Coupling

3.1 C(Sp^3)–C(Sp^3) coupling (Primary and secondary)

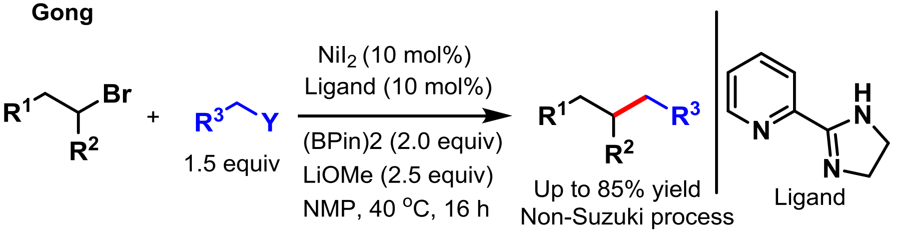
Gong





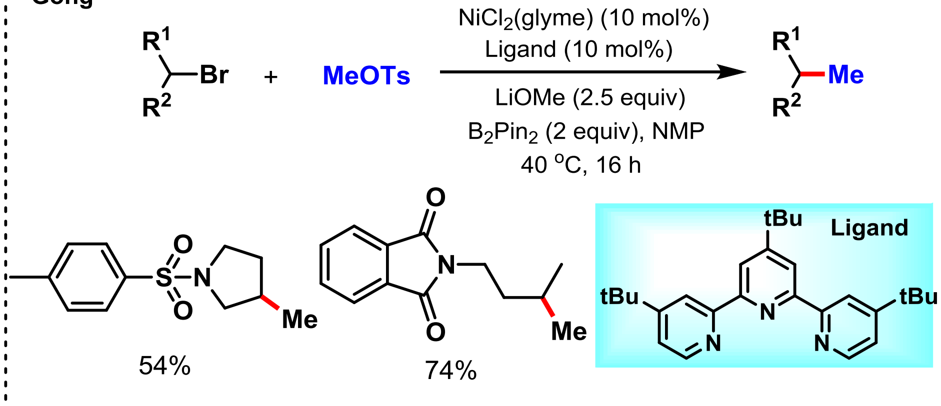
OL **2011**, *13*, 2138

Gong



Chem. Sci., **2013**, *4*, 4022

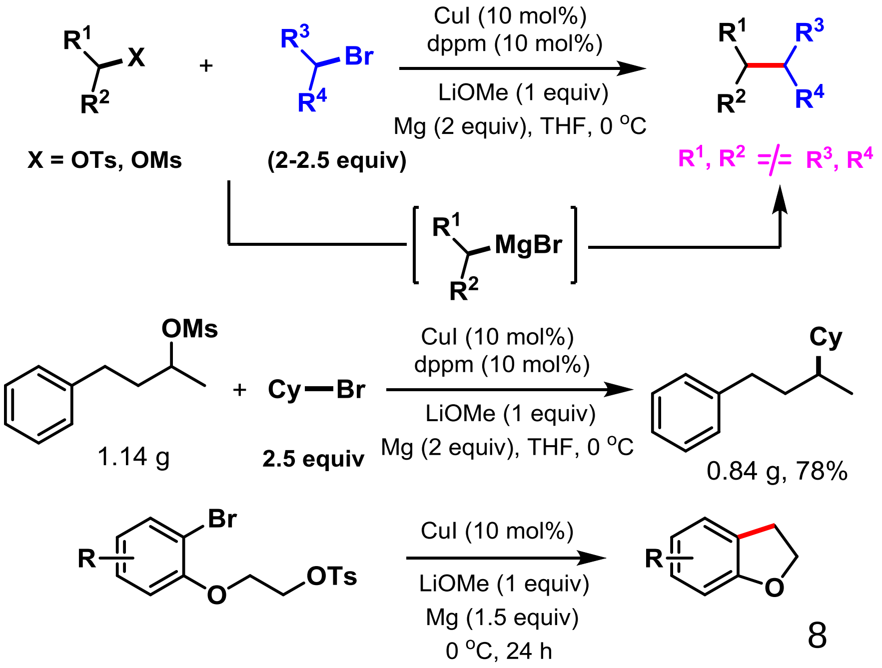
Gong



OL **2014**, *16*, 5620

Liu and Fu (Copper catalysis)

Nonactivated Tosylates and Mesylates with Alkyl and Aryl Bromides



Chem. Eur. J. **2014**, *20*, 15334

Reductive Cross-Couplings of Two Electrophiles

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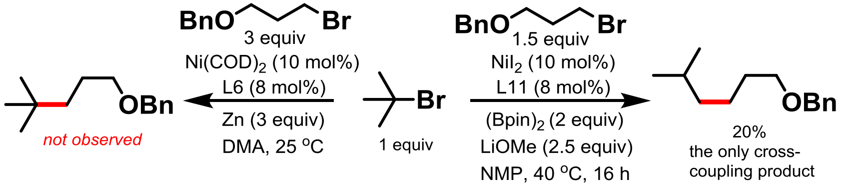
07.12. 2018

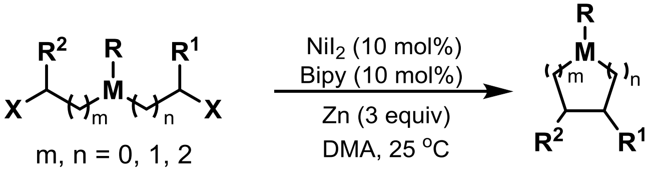
Gong



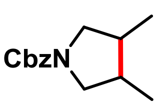
Chem.Sci., **2013**, *4*, 4022

3.2 C(Sp^3)–C(Sp^3) coupling (Intramolecular)

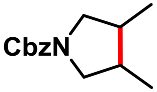
Gong



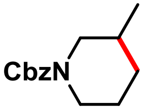
M = N, C
R^1, **R^2** = H, alkyl, aryl
X = I, Br, Cl



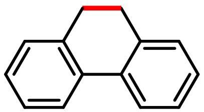
(X = Br) 71%



(X = Cl) 40%



(X = Br) 61%

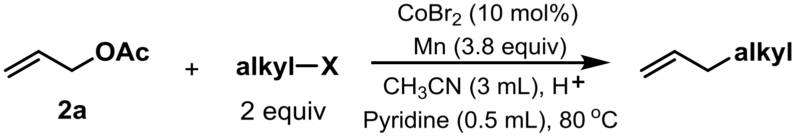


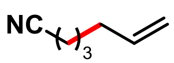
(X = Br) 66%

OL, **2014**, *16*, 4984

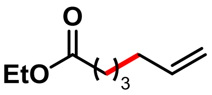
3.3 Reductive Allylation of Alkyl Halides

Gosmini

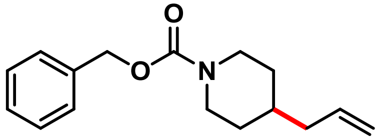




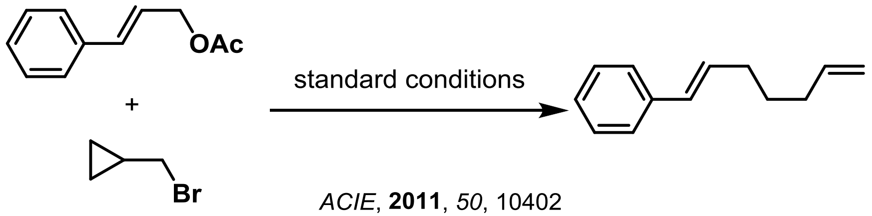
90%



88%

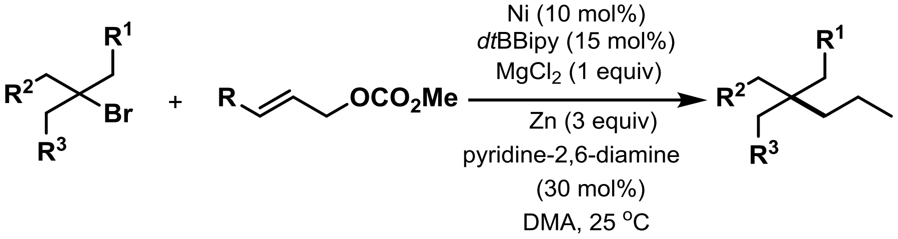


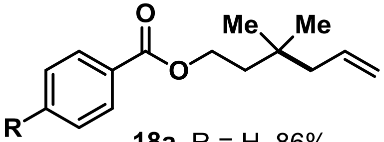
70%



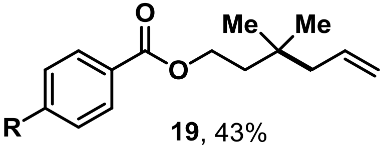
ACIE, **2011**, *50*, 10402

Gong **Allylation of Tertiary Alkyl Halides**





18a, R = H, 86%
18b, R = OMe, 87%
18c, R = CF_3, 83%
18d, R = Ac, 63%



19, 43%

ACIE, **2017**, *56*, 13103

4. Outlook

- Deverlopment of novel electrophiles
- Different transition metals
- Broaden the substrate scope
- More detailed mechanistic studies