Literature Report 4

Multimetallic Catalysed Cross-Coupling of Aryl Halide with Aryl Triflates

Reporter: Han Wang
Checker: Bo Wu
Date: 2019.11.25

Weix, D. J.* *et al*. *Nature* **2015**, *524*, 454-457.
Weix, D. J.* *et al*. *J. Am. Chem. Soc.* **2019**, *141*, 10978-10983.

CV of Dr. Daniel J. Weix

Background:

- **1996-2000** B.S., Columbia University
- **2000-2005** Ph.D., University of California, Berkeley
- **2005-2006** Postdoctor, Yale University (Prof John Hartwig)
- **2006-2008** Postdoctor, University of Illinois at Urbana-Champaign
- **2008-2014** Assistant Professor, University of Rochester
- **2014-now** Associate Professor, University of Wisconsin-Madison

Research:

Development of conceptually new catalytic methods for organic synthesis.

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2 Cross-Coupling of Aryl Bromides with Aryl Triflates

3 Cross-Coupling of Aryl Chlorides with Aryl Triflates

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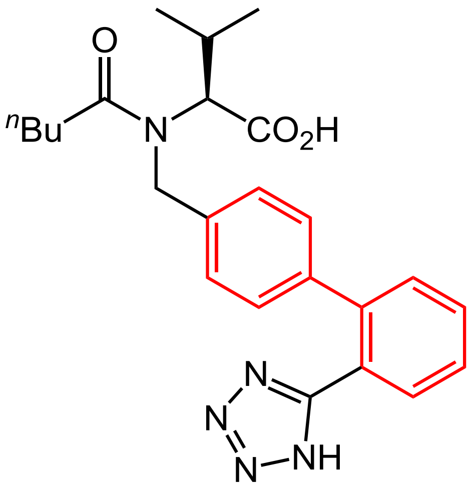
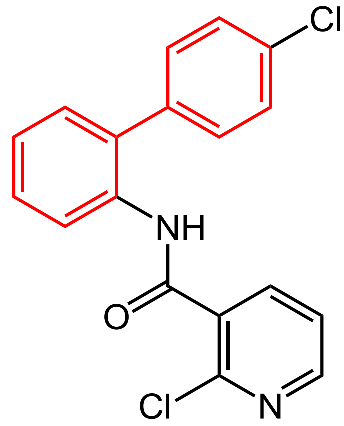
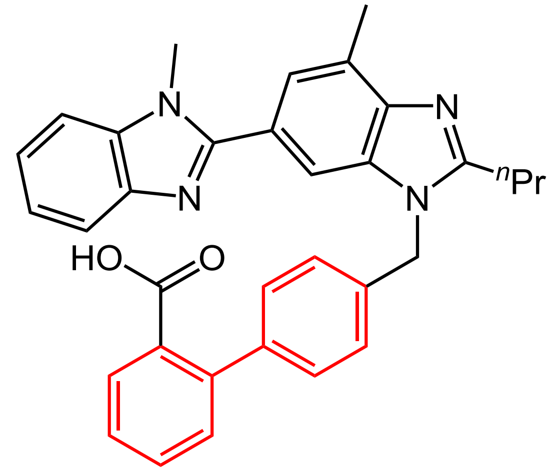
Introduction



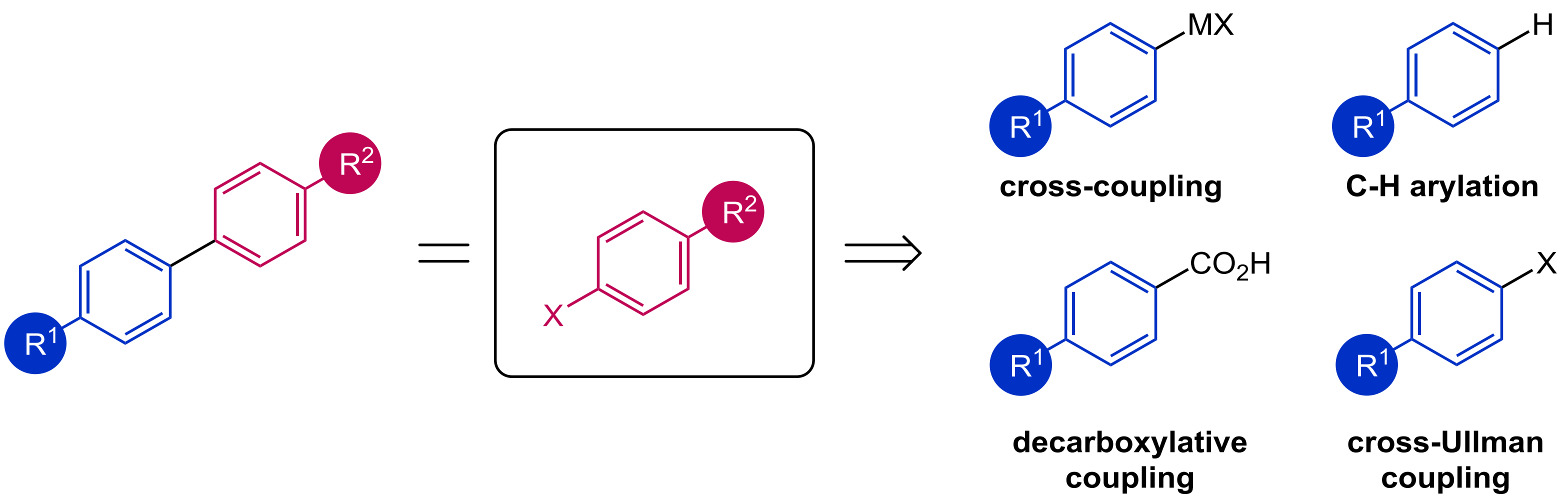
Diovan (Valsartan, Novartis)



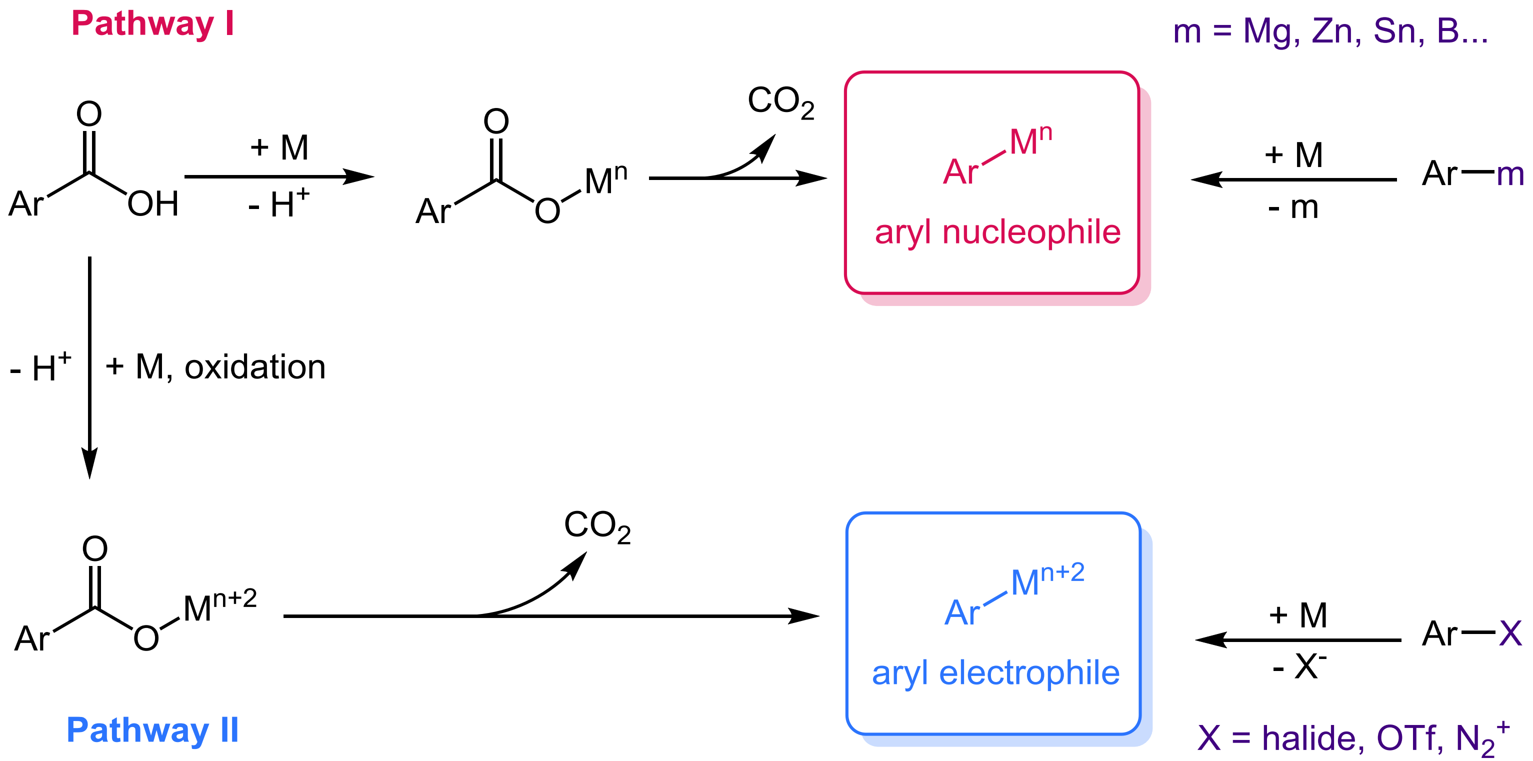
Boscalid (BASF)



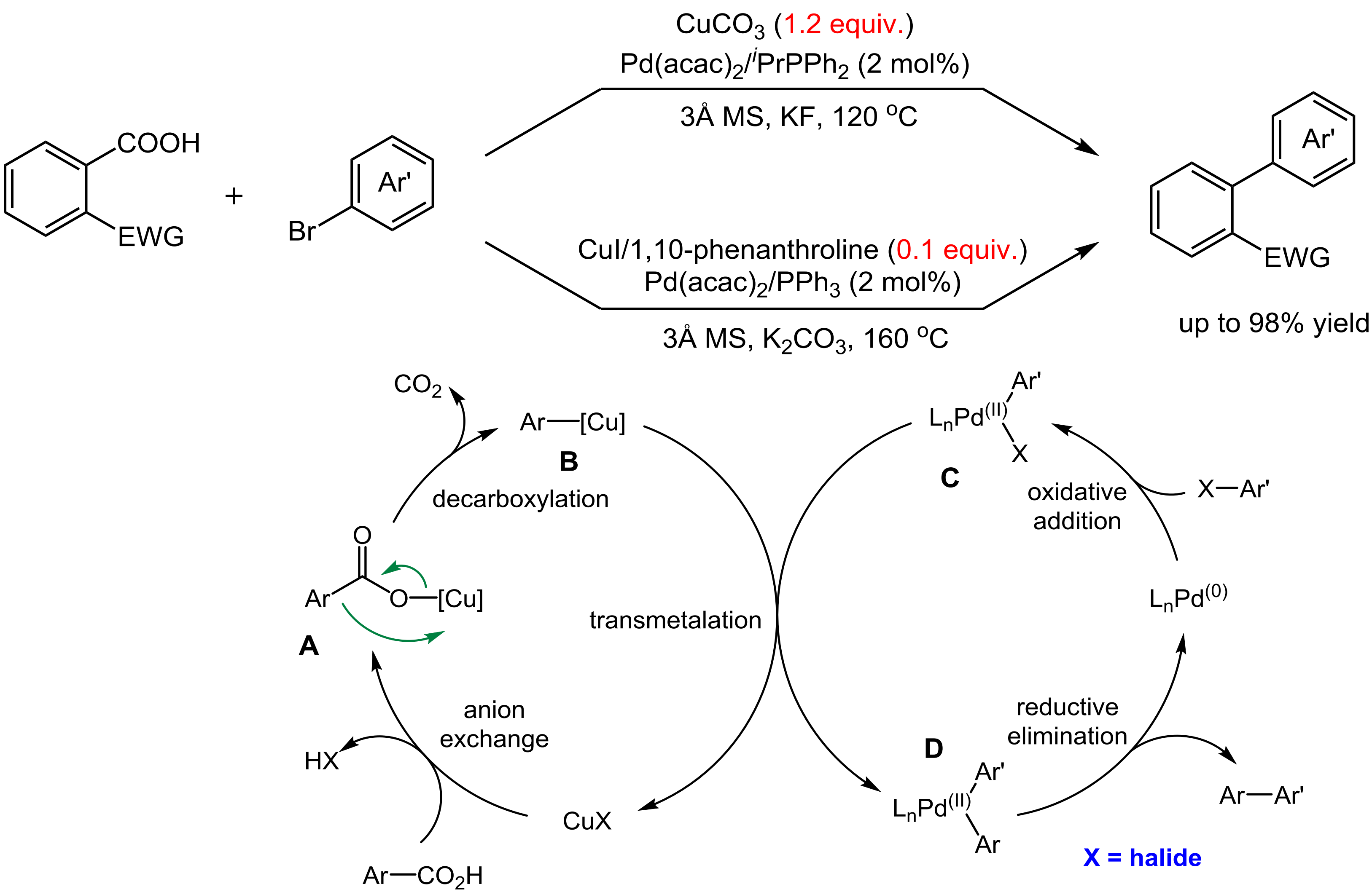
Micardis (Telmisartan, Boehringer)



Introduction

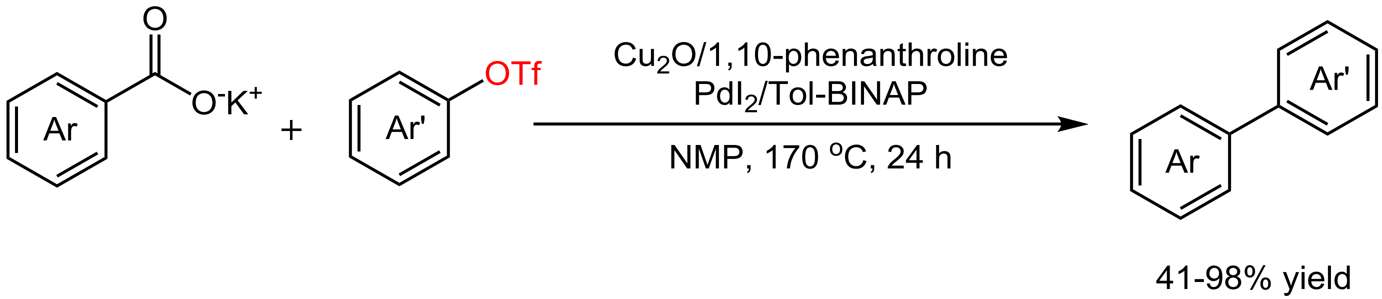


Decarboxylative Cross-Coupling

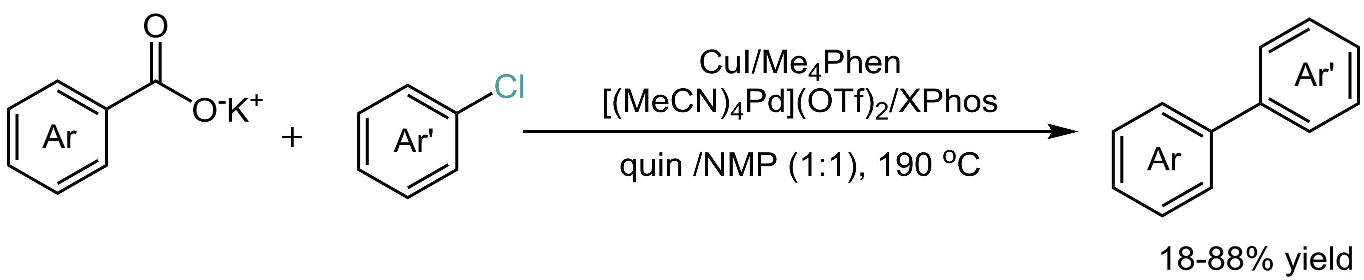


Goossen, L. J. *et al*. *Science* **2006**, *313*, 662.

Decarboxylative Cross-Coupling



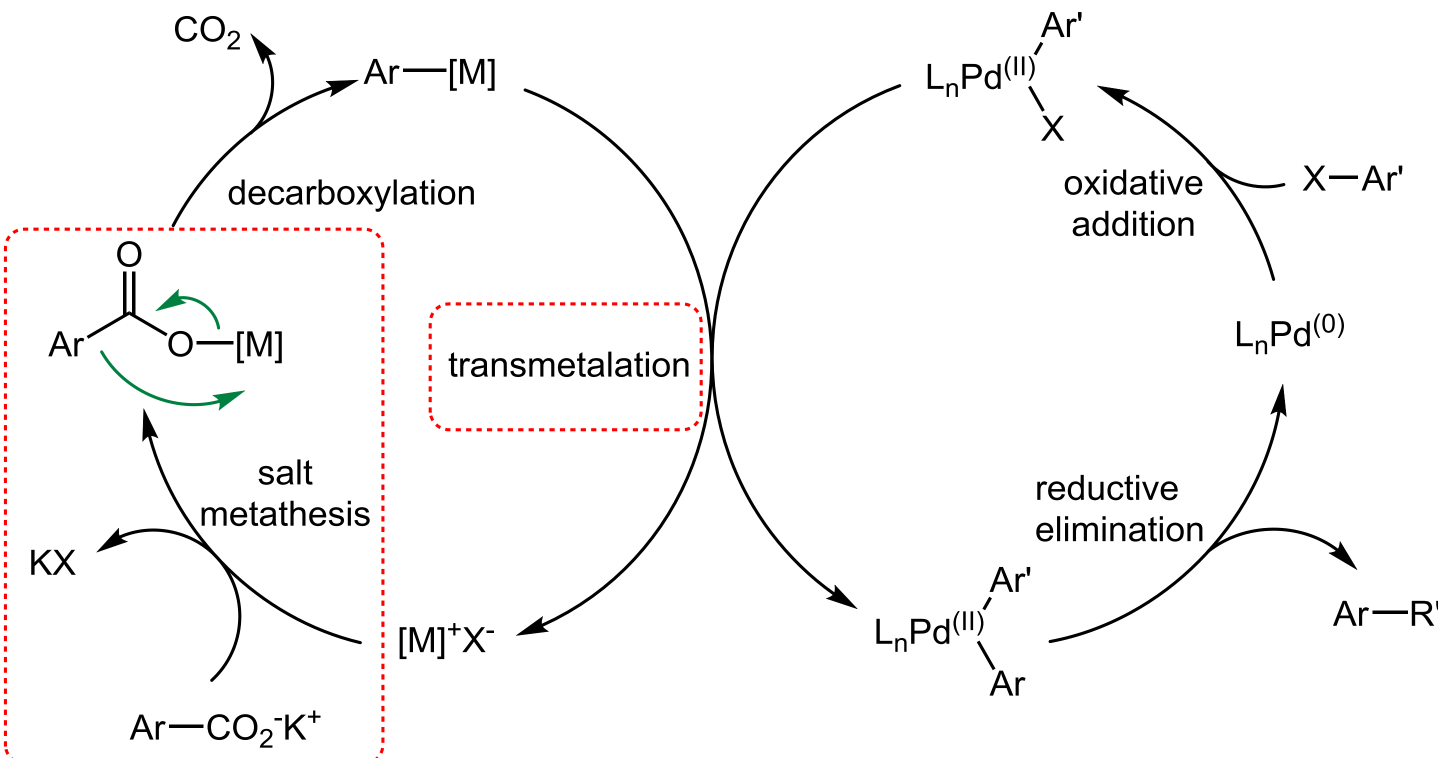
Goossen, L. J. *et al*. *J. Am. Chem. Soc.* **2008**, *130*, 15248.



Goossen, L. J. *et al*. *Angew. Chem. Int. Ed.* **2015**, *54*, 13130.

Decarboxylative Cross-Coupling

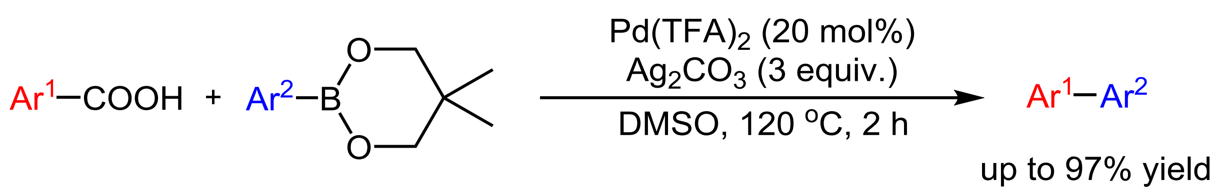
$$Ar{-}CO_2K + Ar'{-}X \xrightarrow[\text{solvent}]{\text{Pd/M-cat}} Ar{-}Ar' + CO_2 + KX$$

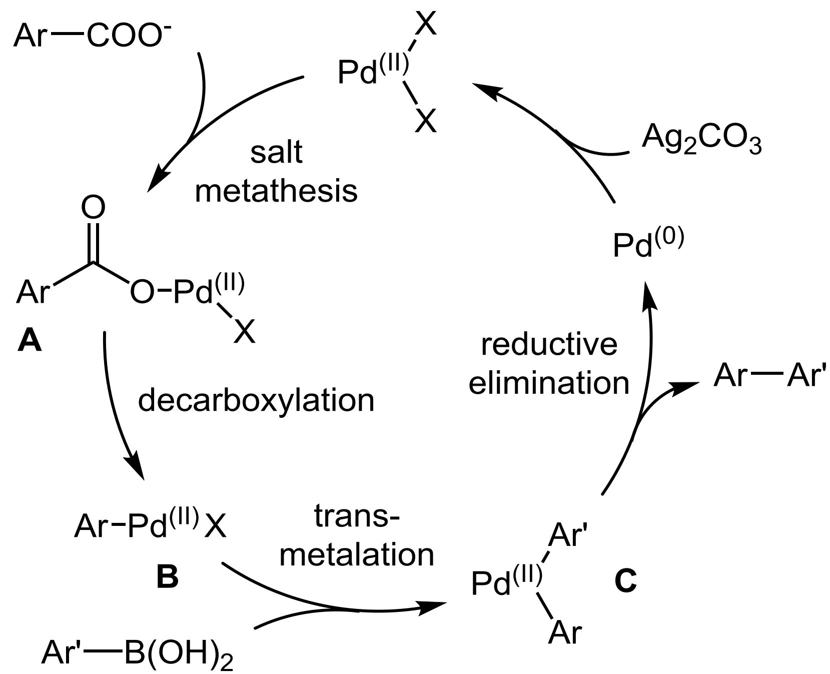


[M] = Cu, Ag

X = halide, OTf, OTs

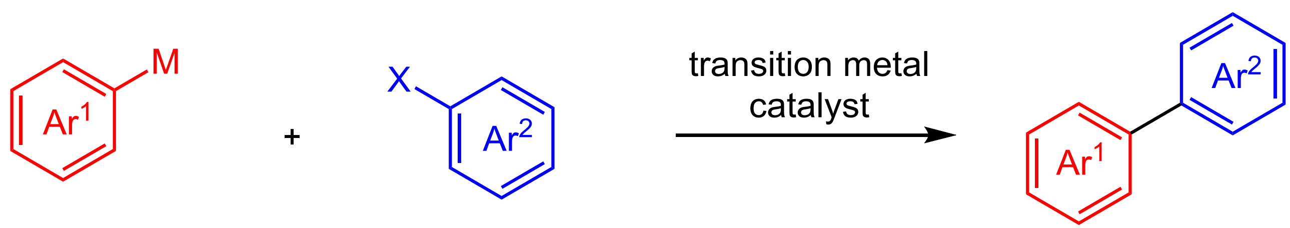
Oxidative Decarboxylative Cross-Coupling





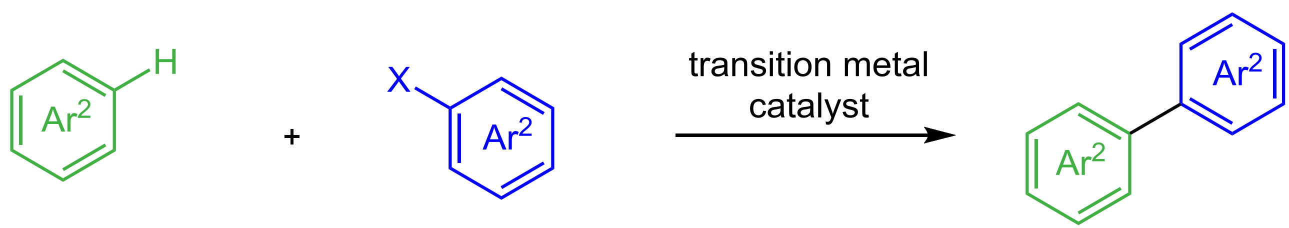
Liu, L. *et al. Chem. Commun.* **2011**, *47,* 677.

Introduction



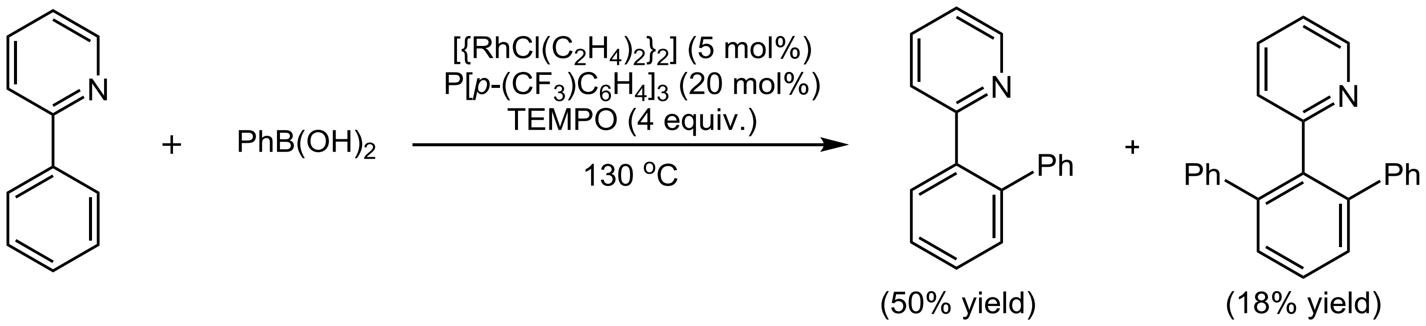
M = B, Sn, Si, Mg, Zn

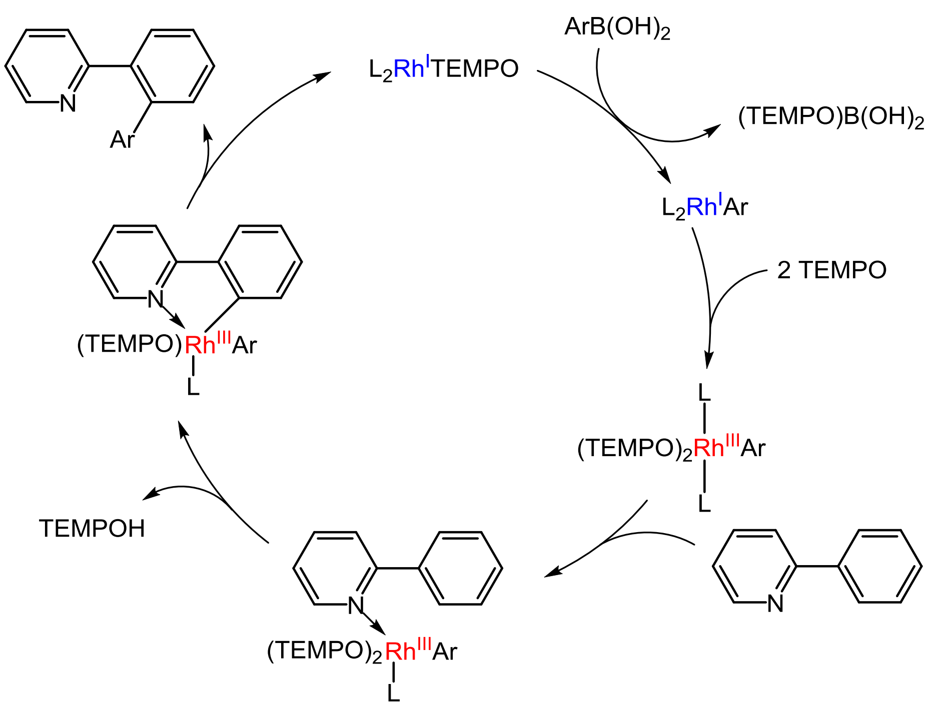
X = I, Br, Cl, OTf



X = I, Br, Cl, OTf
B, Sn, Si, Mg, Zn

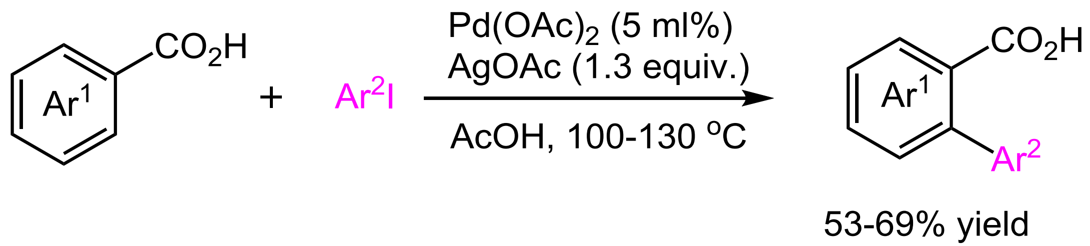
Direct C-H Arylation

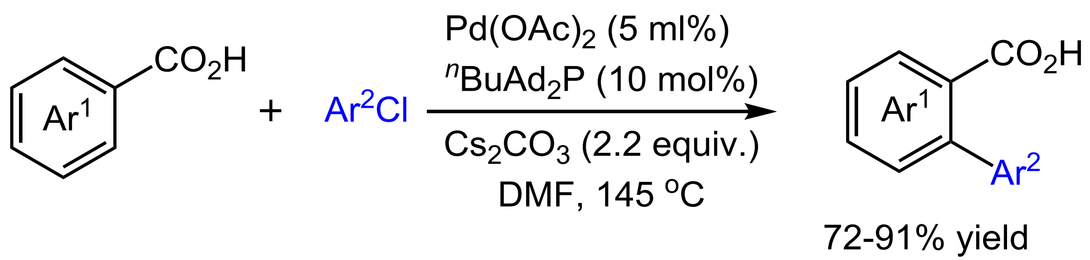




Studer, A. *et al*. *Org. Lett*. **2008**, *10*, 129.

Direct C-H Arylation

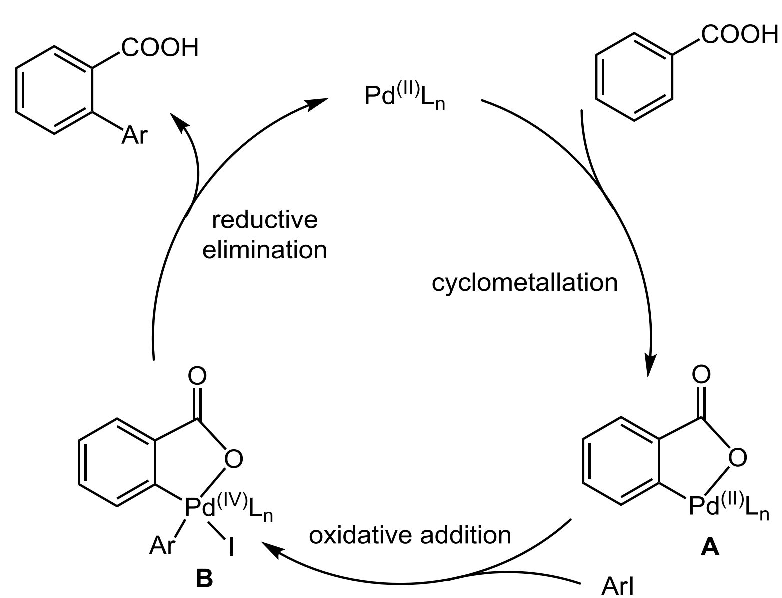




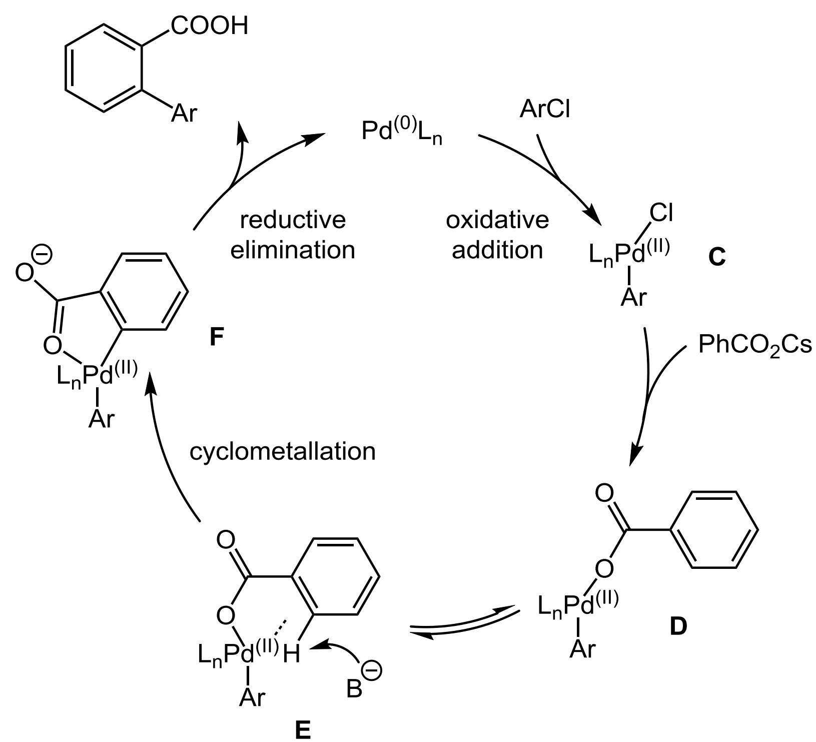
Daugulis , O. *et al*. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

Direct C-H Arylation

Pd(II)-Pd(IV) Mechanism

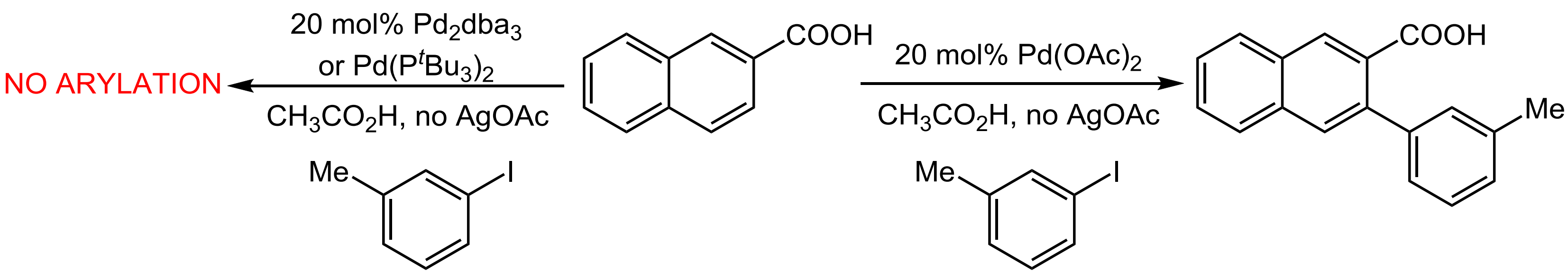


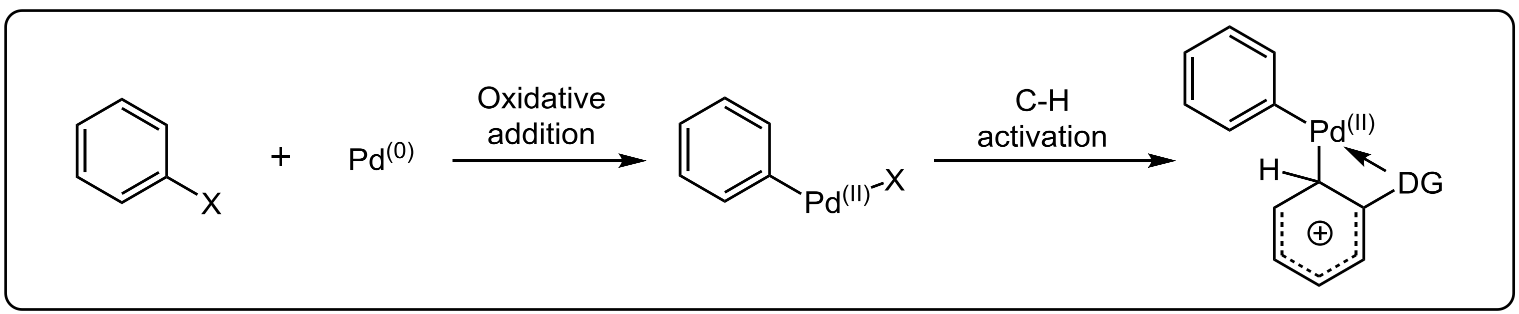
Pd(0)-Pd(II) Mechanism



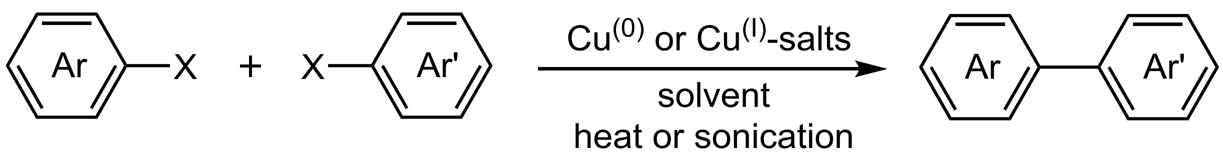
Daugulis , O. *et al*. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

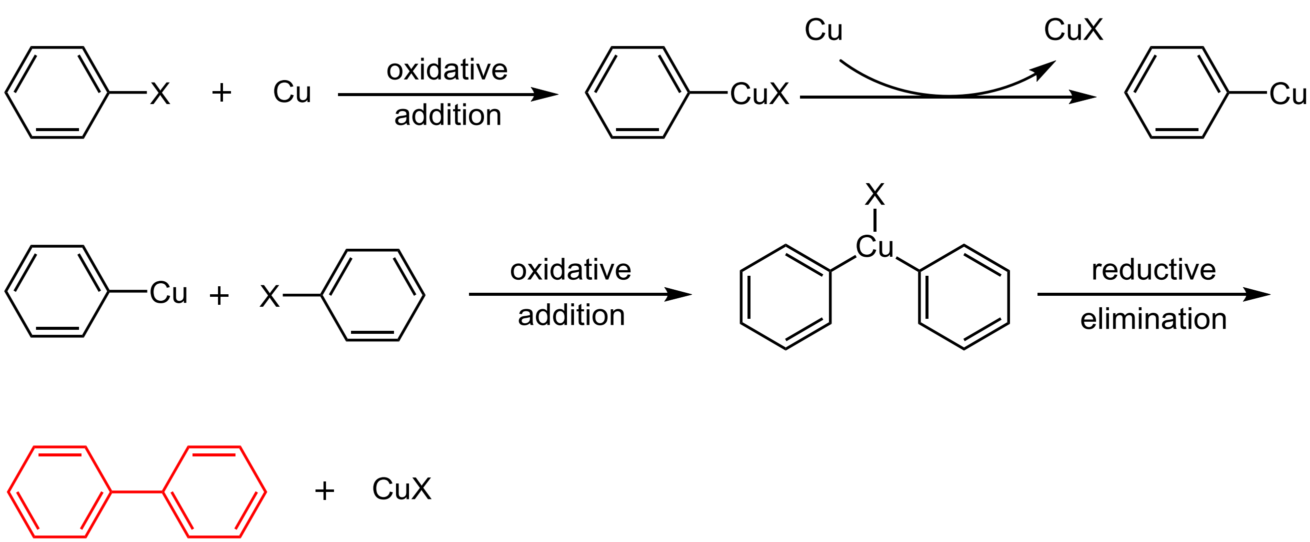
Direct C-H Arylation



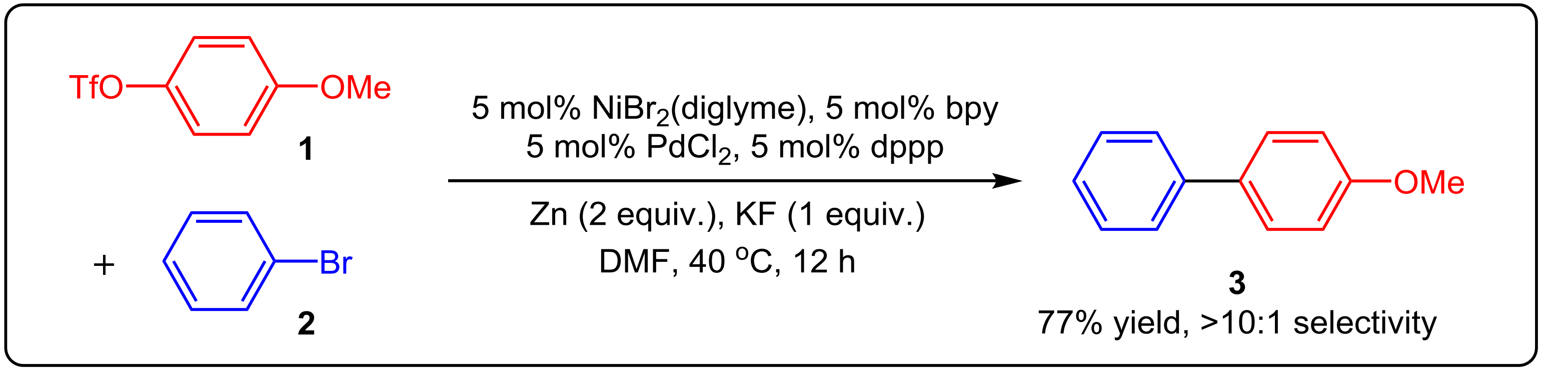


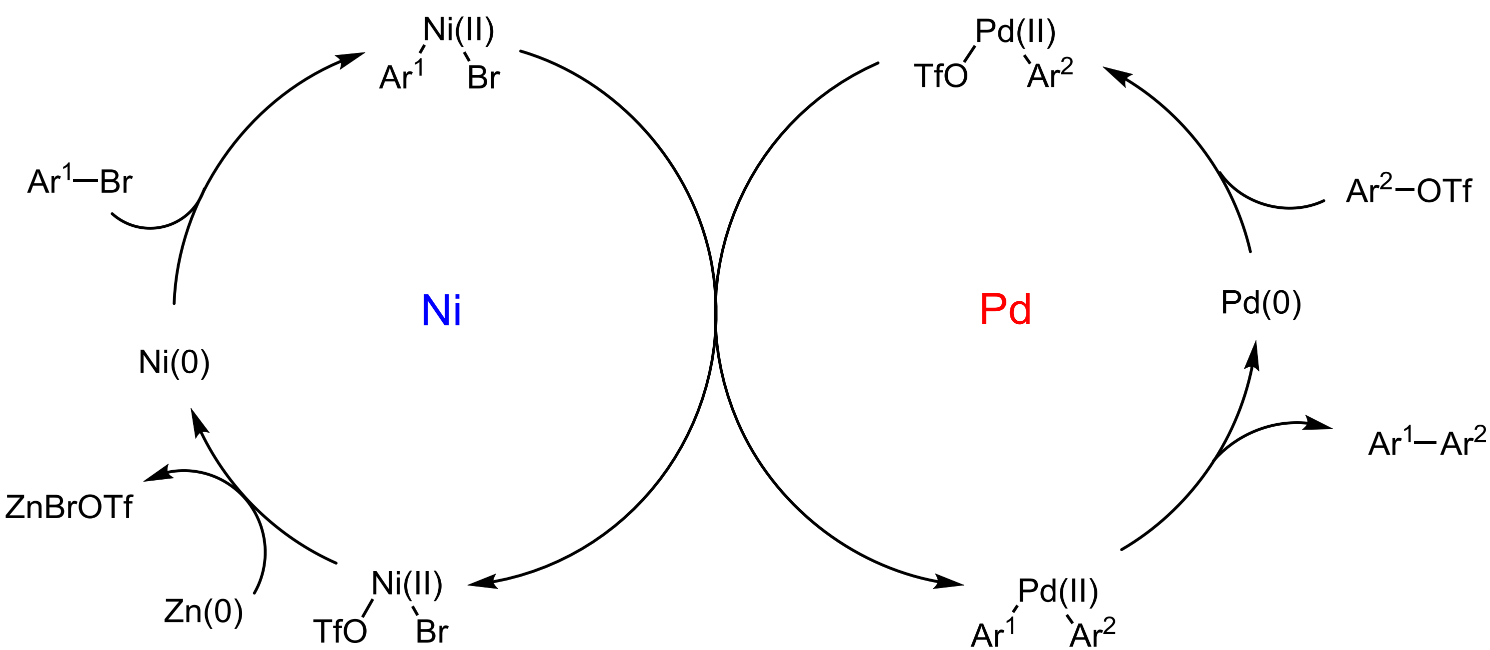
Ullmann Coupling





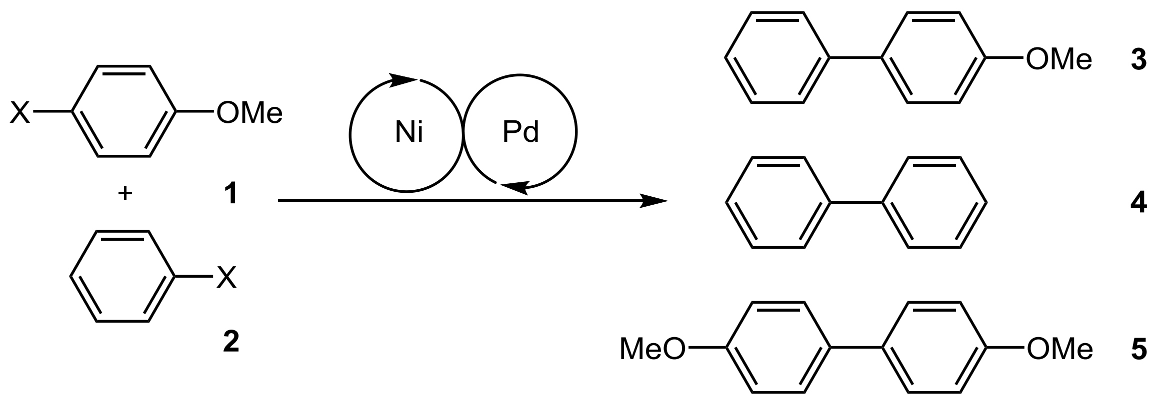
Cross-Coupling of Ar-Br with Ar-OTf



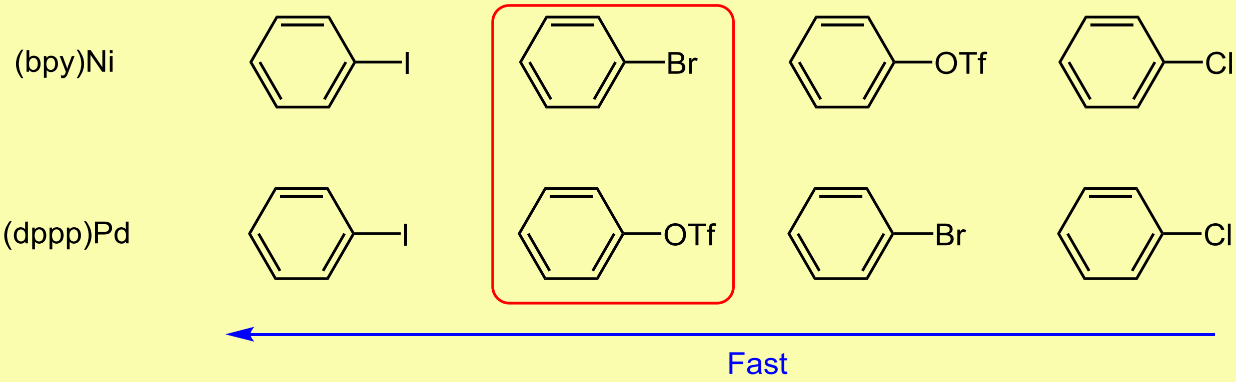


Weix, D. J. *et al*. *Nature* **2015**, *524*, 454.

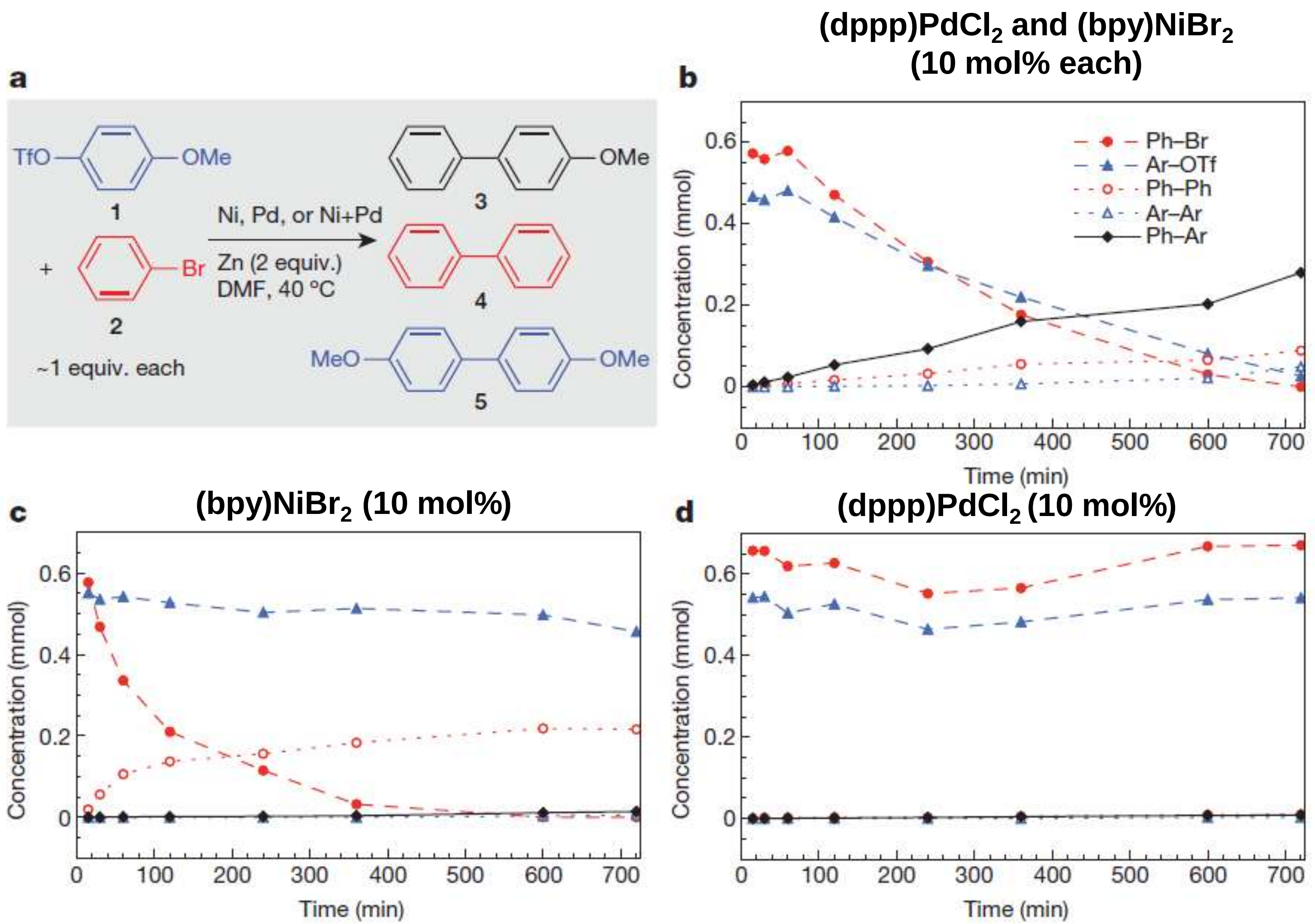
Conditions for Cross-Coupling



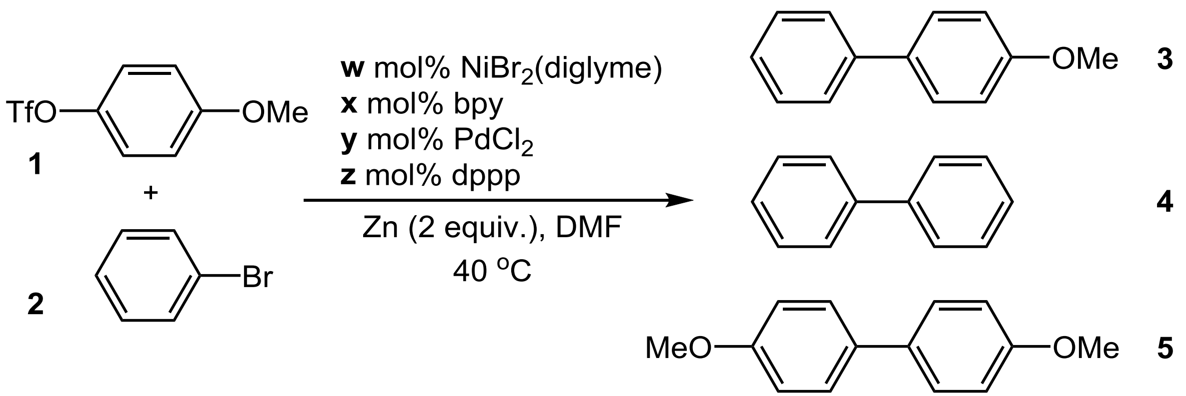
Reactivity of Catalysts



Selectivites of Ni and Pd Catalysts



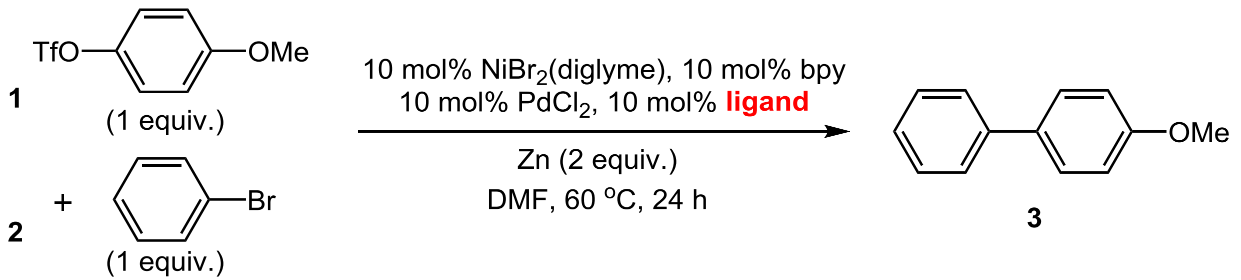
Conditions for Cross-Coupling



Entry[a]	w	x	y	z	3 (%)	4 (%)	5 (%)
1	5	5	5	5	62	21	14
2[b]	**5**	**5**	**5**	**5**	**77**	**7**	**4**
3	10	10	10	10	70	17	10
4	5	5	10	10	61	20	14
5	10	10	5	5	66	18	13
6	0	0	0	0	0	0	0

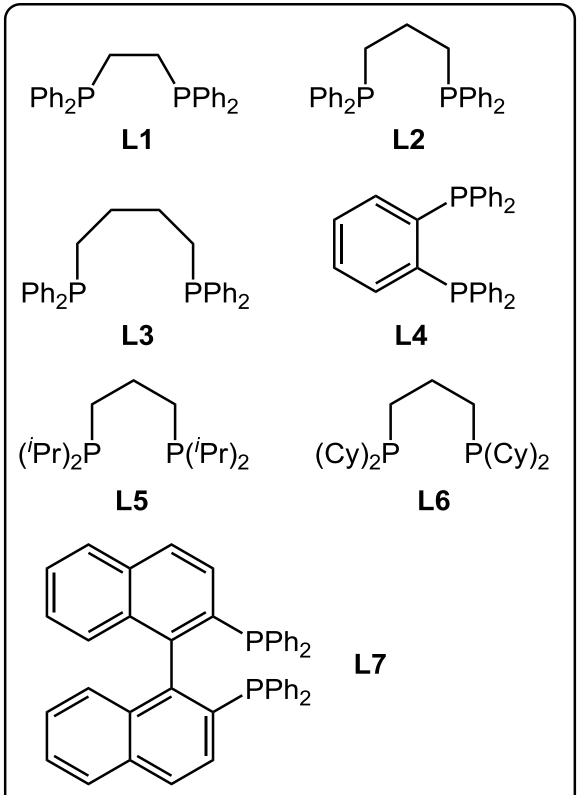
[a] Conditions:**1** (0.5 mmol), **2** (0.5 mmol), DMF (2 mL), 24 h.
[b] One equivalent of KF was added.

Optimization of Reaction Parameters

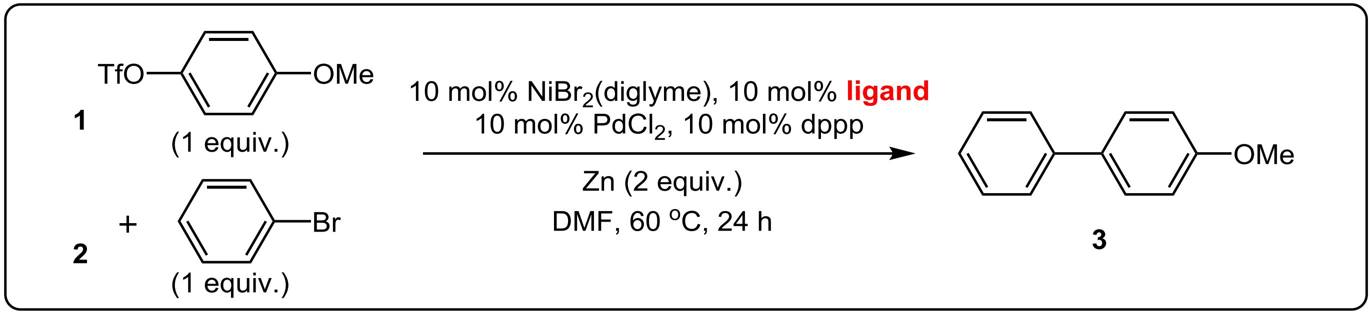


Entry[a]	Ligand	3 (%)
1	**L1**	28
2	**L2**	61
3	**L3**	26
4	**L4**	56
5	**L5**	2
6	**L6**	2
7	**L7**	11

[a] Conditions: **1** (0.5 mmol), **2** (0.5 mmol), DMF (2 mL), 24 h.

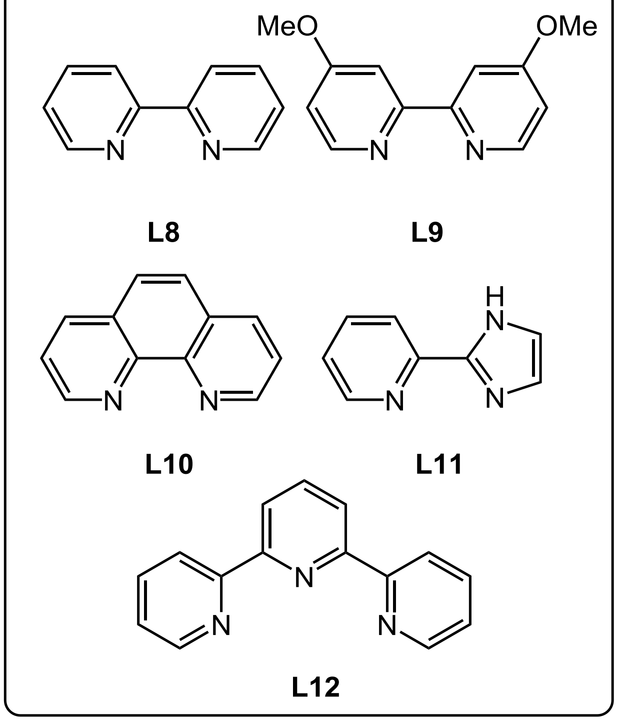


Optimization of Reaction Parameters

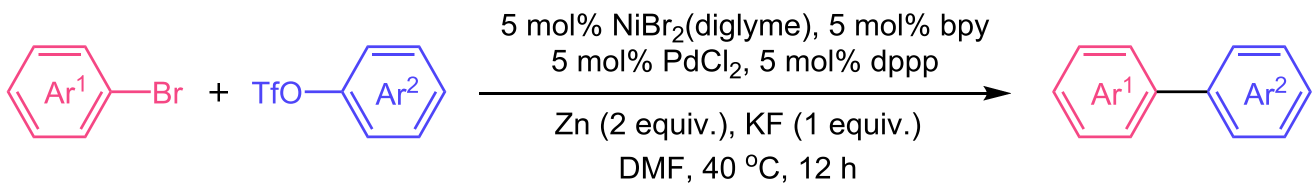


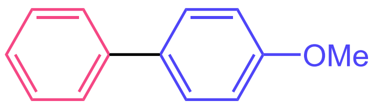
Entry[a]	Ligand	3 (%)
1	**L8**	61
2[b]	**L9**	47
3	**L10**	59
4[b]	**L11**	53
5	**L12**	54

[a] Conditions: **1** (0.5 mmol), **2** (0.5 mmol), DMF (2 mL), 24 h.
[b] Reactions were monitored for 64 h.

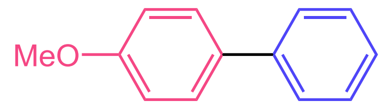


Substrate Scope

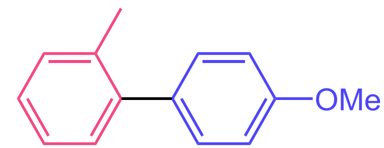




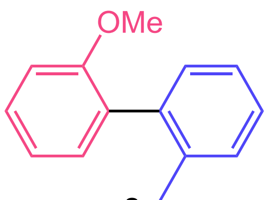
3
78% yield



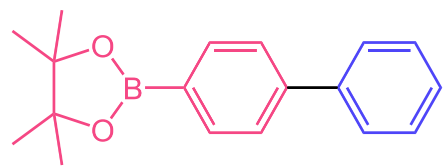
6
85% yield



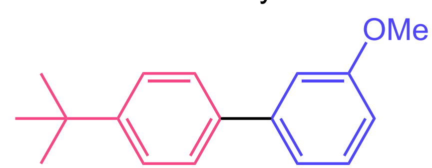
7
87% yield



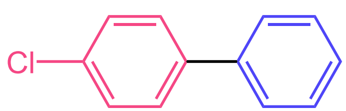
8
75% yield



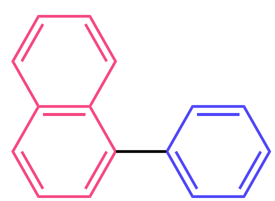
9
59% yield



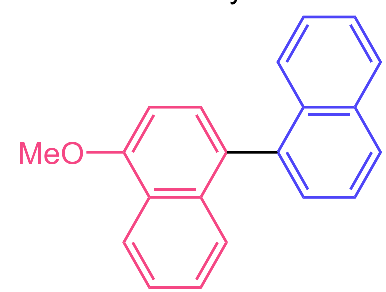
10
94% yield



11
61% yield

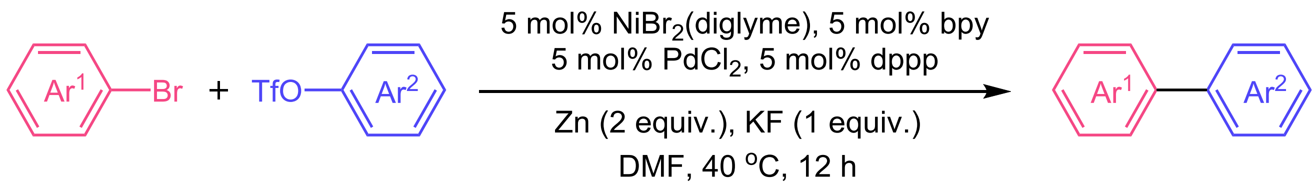


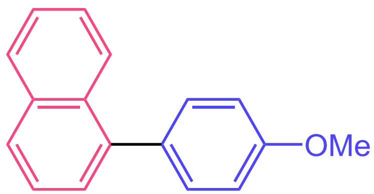
12
71% yield



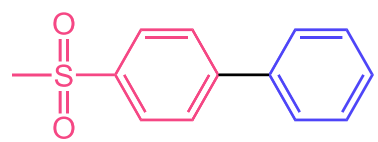
13
71% yield

Substrate Scope

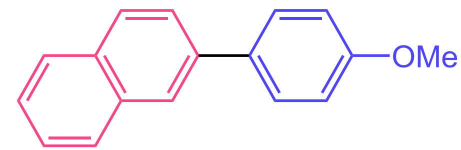




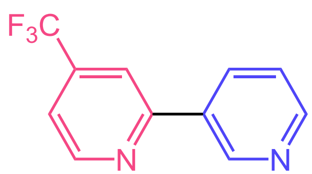
14
X = I
78% yield



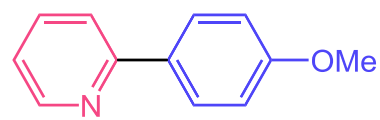
15
X = Cl
78% yield



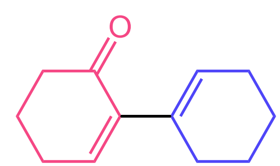
16
X = Cl
75% yield



17
X = Cl
61% yield

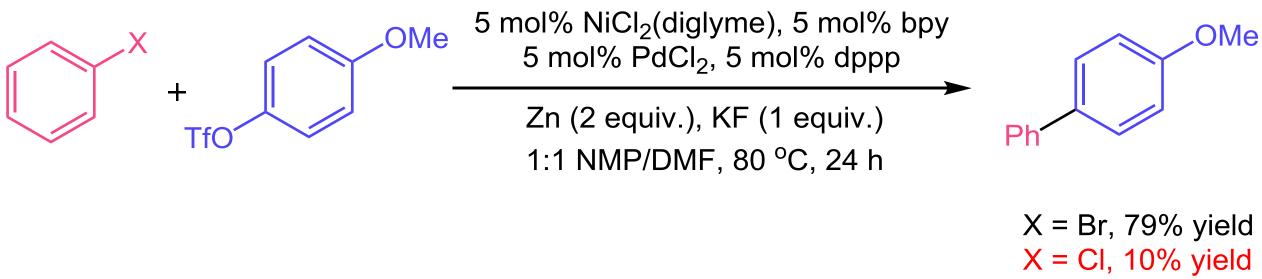


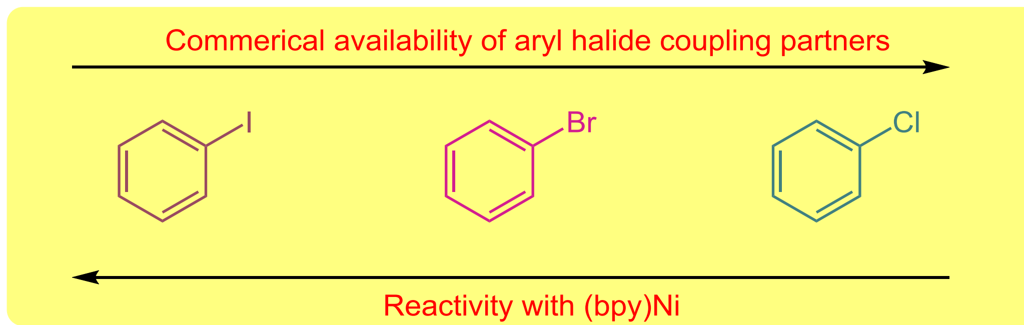
18
X = Cl
59% yield

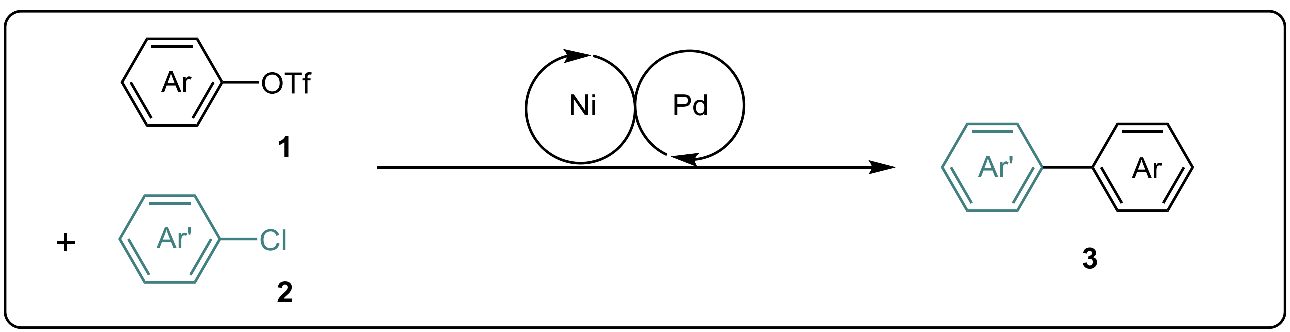


19
X = Br
60% yield

LiCl-Accelerated Ullmann Cross-Coupling







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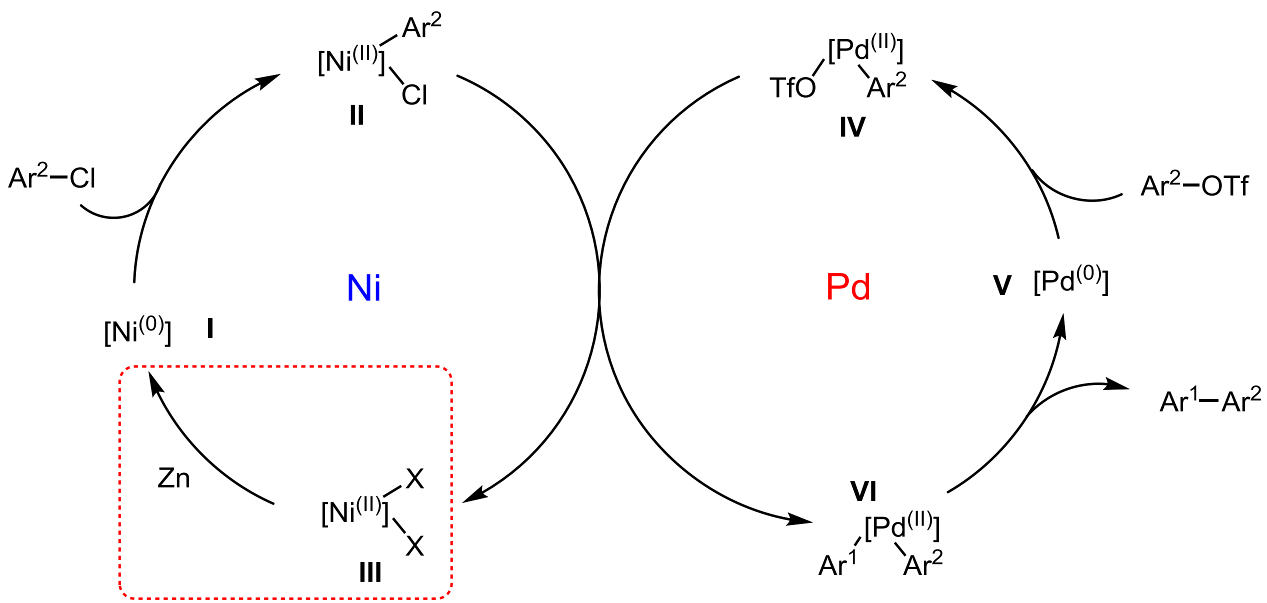
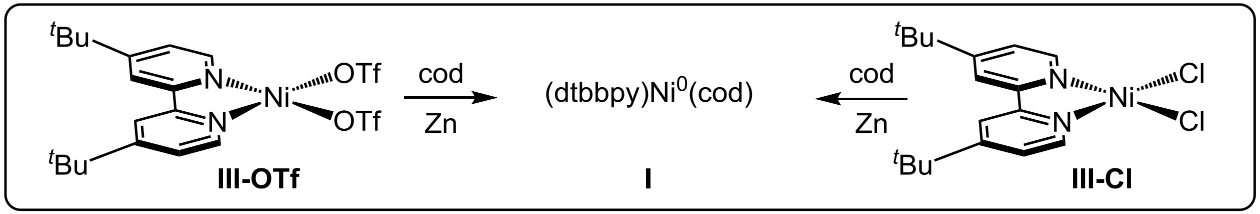
Mechanistic Study

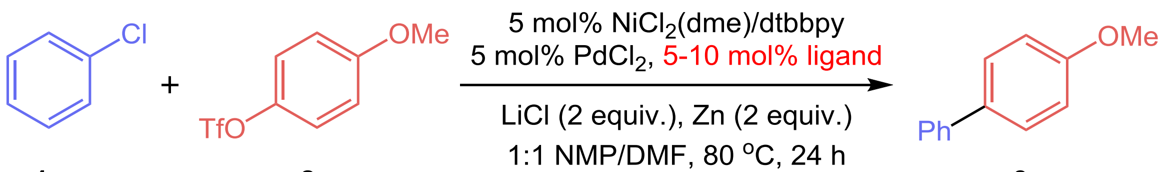




[a]Additive	Yield from III-OTf	Yield from III-Cl
none	0%	37%
$ZnCl_2$	2%	5%
LiCl (40 equiv.)	**44%**	**86%**

[a]Reduction of **III** was conducted in DMF at a concentration of 0.025 M with Zn powder (40 equiv).

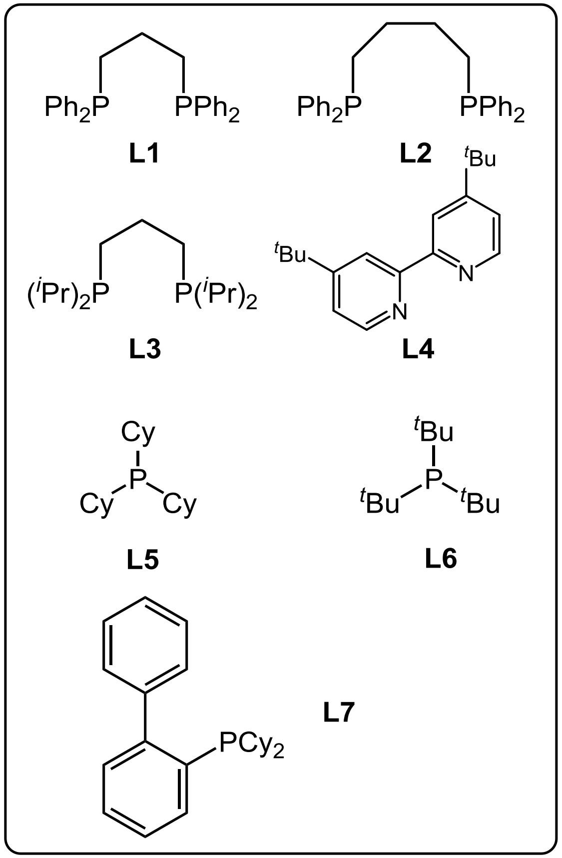
Optimization of Reaction Parameters



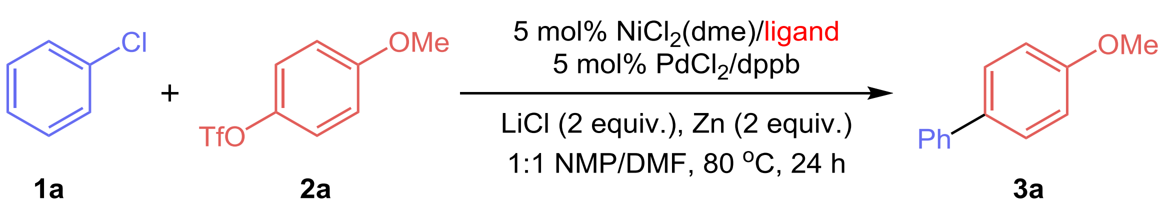
1a 2a 3a

Entry[a]	Ligand	3a (%)
1	**L1**	62
2	**L2**	85
3	**L3**	30
4	**L4**	46
5	**L5**	81
6	**L6**	36
7	**L7**	67

[a] Reactions were run on a 0.5 mmol scale in 2 mL of solvent. Yields are expressed as corrected GC yields vs. dodecane as an internal standard.

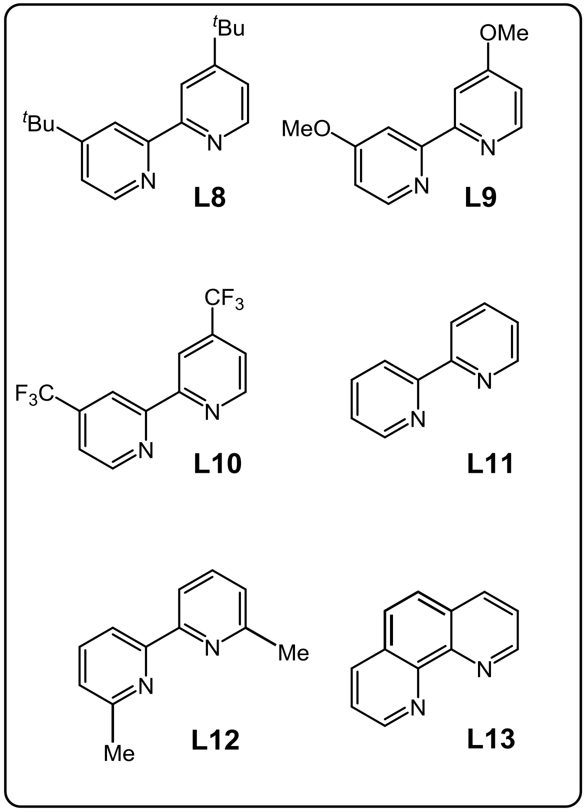


Optimization of Reaction Parameters

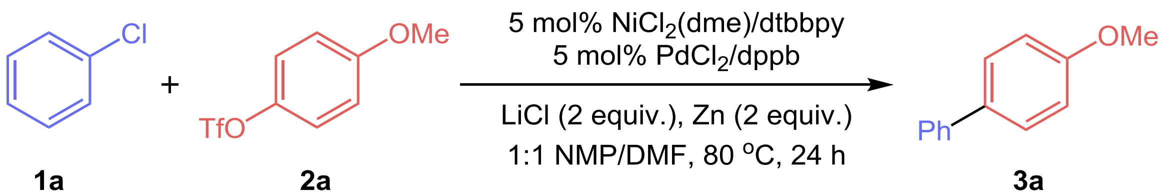


Entry[a]	Ligand	3a (%)
1	L8	85
2	L9	73
3	L10	13
4	L11	71
5	L12	38
6	L13	35

[a] Reactions were run on a 0.5 mmol scale in 2 mL of solvent. Yields are expressed as corrected GC yields vs. dodecane as an internal standard.



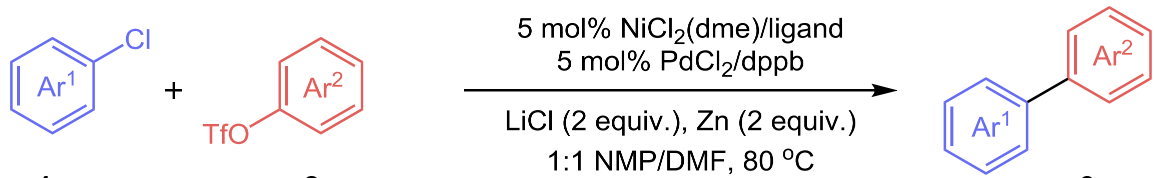
Optimization of Reaction Parameters



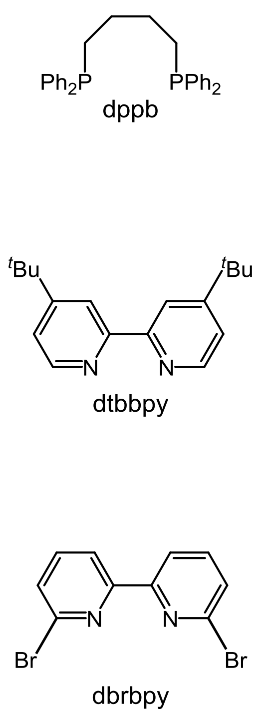
Entry	Change from the optimized conditions[a]	3a (%)[b]
1	**none**	84
2	NaCl instead of LiCl	62
3	LiBr instead of LiCl	59
4	TMSCl instead of LiCl	16
5	no LiCl	<10
6	Mn instead of Zn	62
7	Mn instead of Zn, LiBr instead of LiCl	77
8	Reaction set up on the benchtop[c]	80
9	**1.2 equiv of 2a**	**90 (89)[d]**

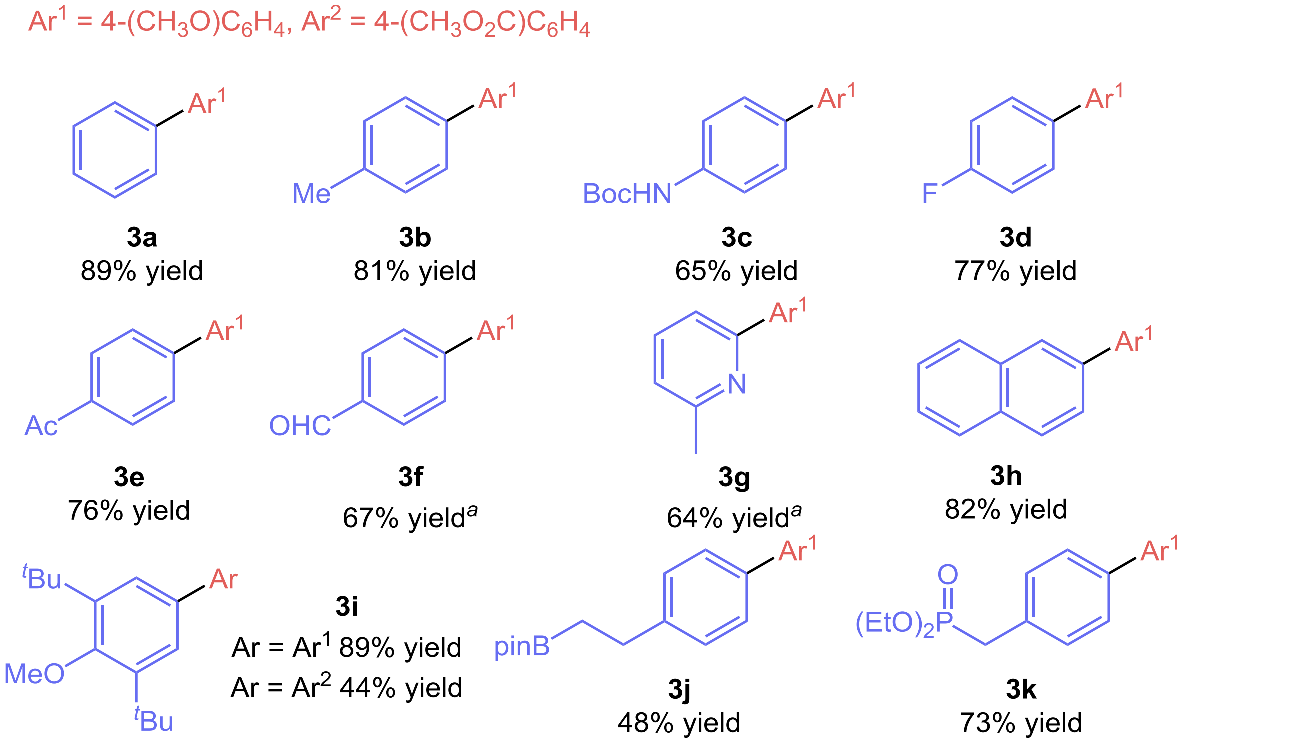
[a] Reactions were run on a 0.5 mmol scale in 2 mL of solvent. [b]GC yield vs dodecane as an internal standard. [c]The reaction was set up under air with dry solvent. [d]Isolated yield.

Substrate Scope



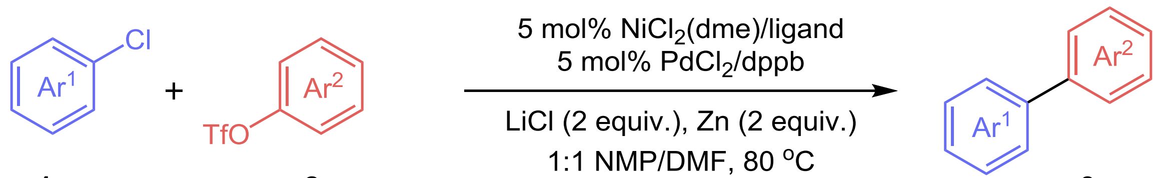
1 **2** *1.2 equiv.* **3**





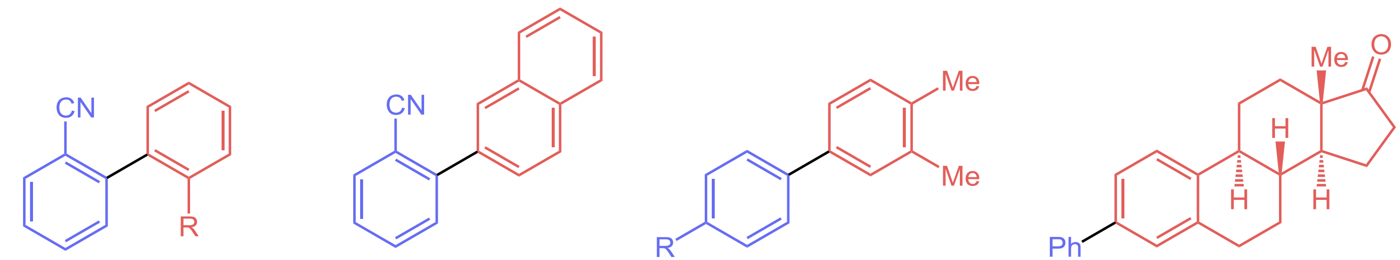
[a]Using 5 mol% 6,6'-dibromo-2,2'-bipyridine instead of dtbbpy.

Substrate Scope



1 **2** **3**

1.2 equiv.



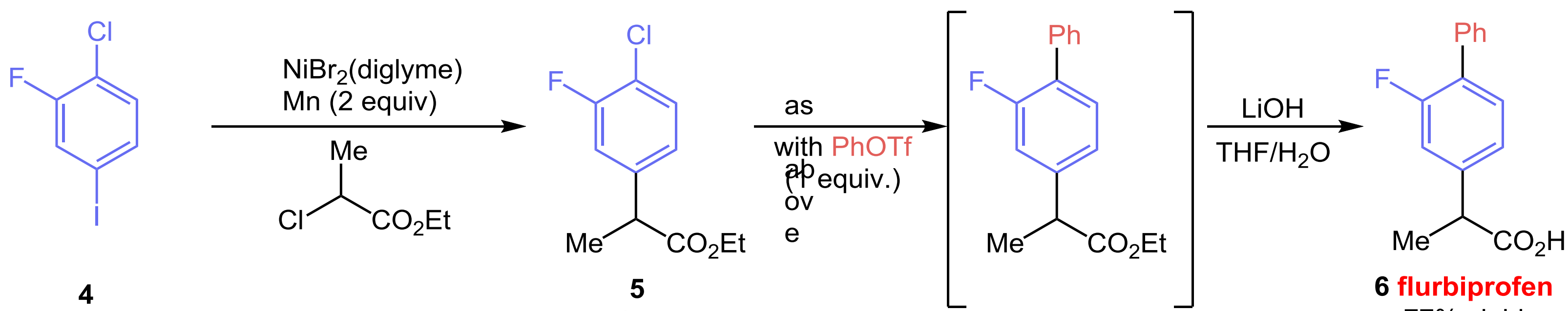
R = H, **3l** 74% yield
R = ^{t}Bu, **3m** 62% yield
R = Ph, **3n** 52% yield

3o
56% yield

R = OMe, **3p** 88% yield
R = CO_2Me, **3q** 75% yield

3r
60% yield

Utility in Synthesis



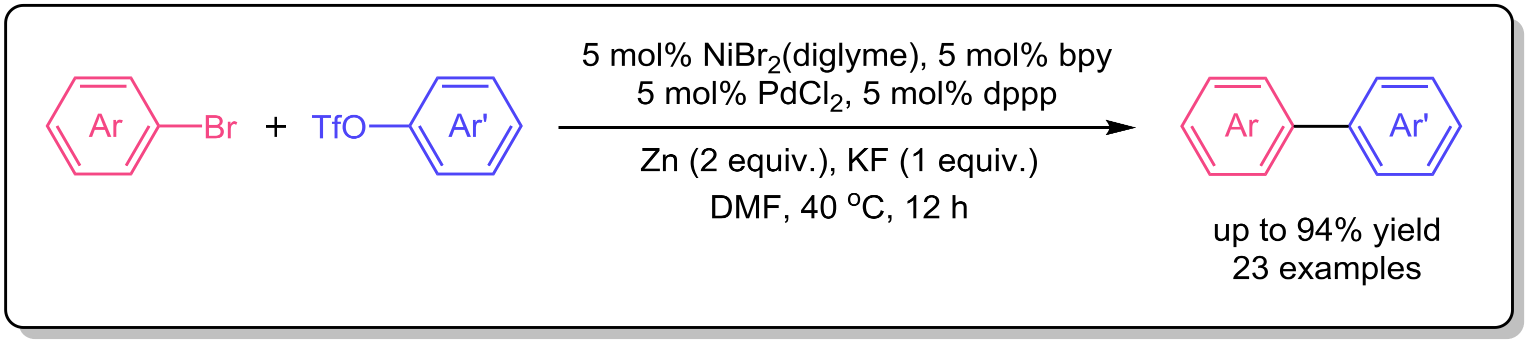
4

5
71% yield

6 flurbiprofen
77% yield

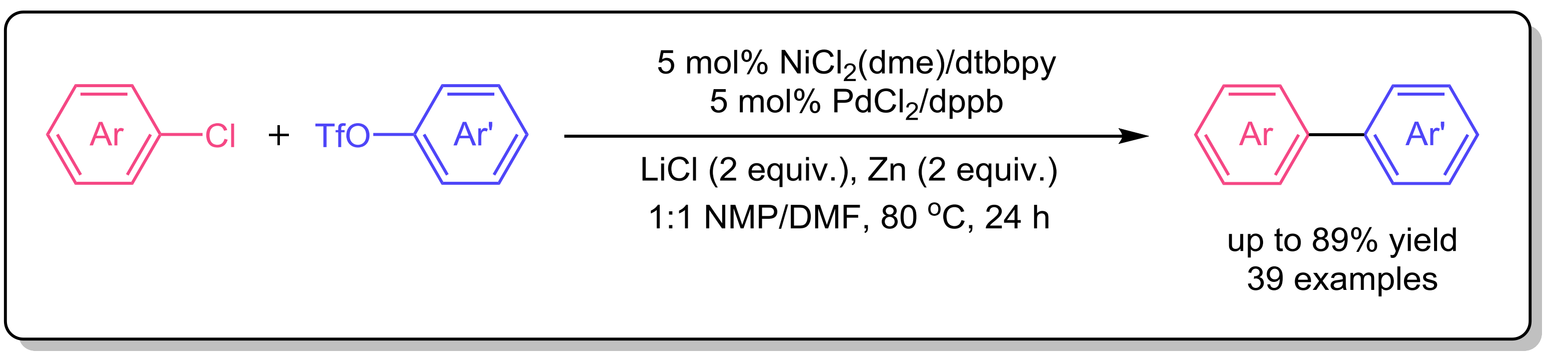
Summary

Ullman Cross-Coupling of Ar-Br with Ar-OTf



Weix, D. J. *et al*. *Nature* **2015**, *524*, 454.

Ullman Cross-Coupling of Ar-Cl with Ar-OTf



Weix, D. J. *et al*. *J. Am. Chem. Soc.* **2019**, *141*, 10978.

The First Paragraph

写作思路

联苯结构重要性

↓

联苯合成方法

↓

现有合成方法的局限

↓

前期工作，新的挑战，引出课题设想

The First Paragraph

The synthesis of biaryls has become one of the most commonly used reactions in pharmaceutical, agrochemical, and materials science industries, yet access to arylmetal reagents remains limiting. The low commercial availability of arylmetal reagents has inspired a number of active areas of research, including improved methods for arylmetal synthesis, C−H arylation, and decarboxylative cross-coupling. The relative abundance of aryl electrophile would make the cross-Ullman reaction an attractive approach, but our recently reported catalytic nickel and palladium method was not broadly effective with the most abundant and versatile aryl electrophiles, aryl chlorides.

The First Paragraph

In addition to opening up more chemical space, aryl chlorides are often lower in cost, and their lower reactivity would allow for sequential coupling in fragment-based drug discovery or late-stage coupling on complex molecules

The Last Paragraph

写作思路

工作特点：LiCl加速偶联

⇩

工作意义：LiCl加速作用可以应用于新反应的开发

The Last Paragraph

This report shows how the nickel and palladium system can be rationally modulated to couple less reactive substrates: an unselective multimetallic reaction was made selective with the use of an additive, LiCl, that facilitates the reduction of the nickel catalyst at the zinc surface. Combined with our previous reports, these results suggest that the Ni/Pd system is general and that multimetallic catalysis may have broad generality. Finally, this work demonstrates how reactivity in cross-electrophile coupling reactions can be influenced by the reductant choice as much as the ligand choice: salts formed in the reaction may be autoinhibitory, and new reductant combinations can unlock new reactivity.

Representative Examples

In addition to opening up more chemical space, aryl chlorides are often lower in cost, and their lower reactivity ...

This report shows how the nickel and palladium system can **be rationally modulated to** couple less reactive substrates: an unselective multimetallic reaction was made selective with the use of an additive, LiCl, that facilitates the reduction of the nickel catalyst.

Combined with our previous reports, these results suggest that the Ni/Pd system is general and that multimetallic catalysis may have **broad generality.**

Electron-poor fluorine-containing substrates as well as electron-neutral and electron-rich substrates were well-tolerated, including **sensitive functionalities** such as...

Acknowledgement

Thanks

for your attention