# *Recent Developments in C-H Activation of Simple Arenes*

**Keywords:**
non-chelate-assisted
C–H activation · reactivity ·
selectivity · simple arenes

*Dedicated to Professor Shinji Murai*

Angewandte
Chemie

***Ying Chen***

***Jan 13 , 2014***

# *Two Fundamental Challenges in C-H Activation*

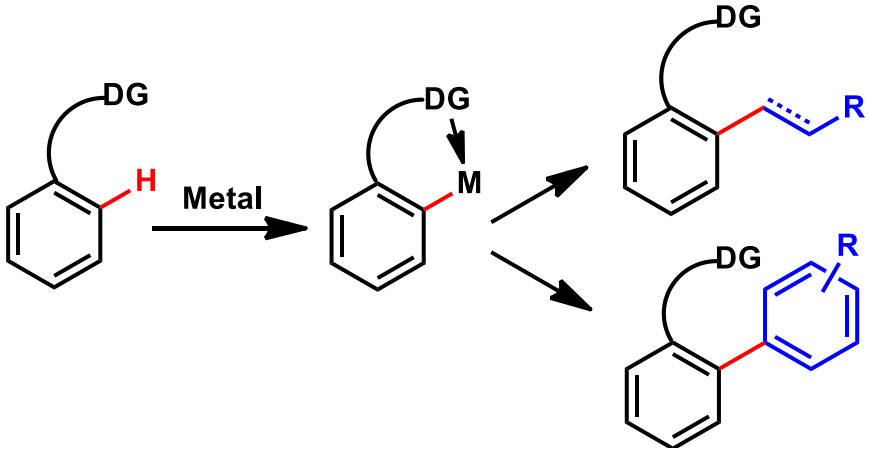
## *Reactivity and Selectivity*

- Use of Transition metals

Transition metals can react with C-H bonds to produce C-M bonds

"Transition Metal Catalyst"

- Use of Directing Groups

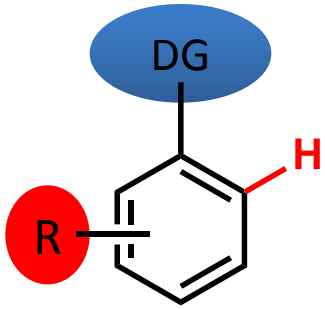



DG bind to the metal center
And selectively deliver the catalyst to a proximal C-H bond

*T. W. Lyons, M. S. Sanford, Chem. Rev.* ***2010****, 110, 1147*
*C. S. Yeung, V. M. Dong, Chem. Rev.* ***2011****, 111, 1215*
*P. B. Arockiam, C. Bruneau, P. H. Dixneuf, Chem. Rev.* ***2012,*** *ASAP*

# *Limitations of Directing Groups*

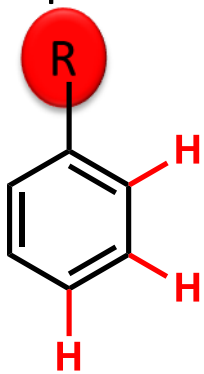
DG-assisted
C-H ACTIVATION




+ Increased reactivity because of metal pre-coordination
+ High regio-selectivity

- DG must be pre-installed and remains in the product
- Generally limited to ortho selectiv

C-H ACTIVATION
of simple arenes




+ No extra steps required to install and/or remove DG

- Possibility of meta or para selectivity

## CHALLENGES

Increase of **REACTIVITY**
Toward transition metals

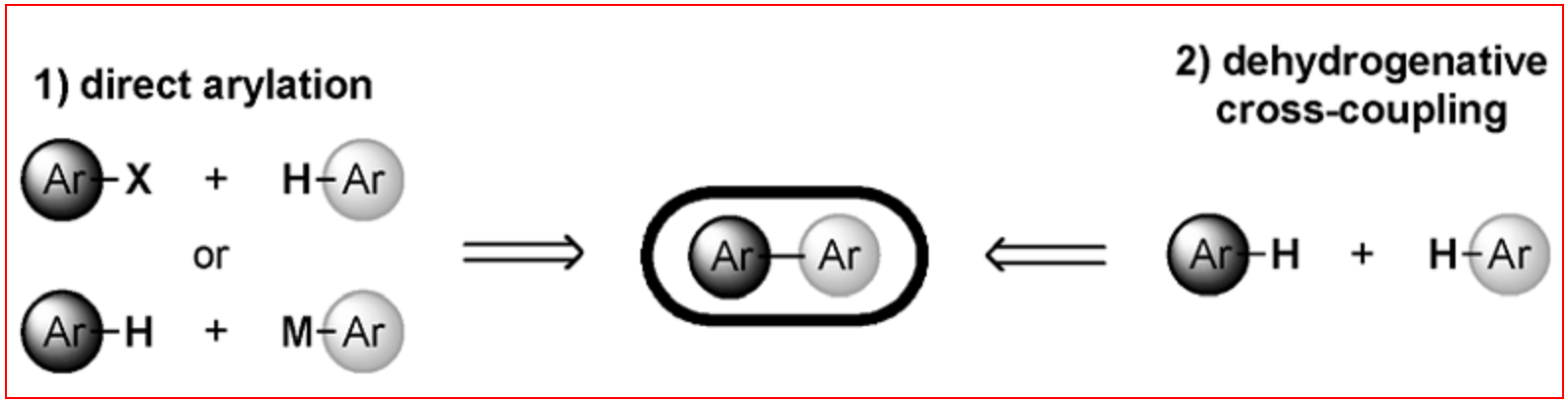
Devise new strategies to control
**REGIOSELECTIVITY**

*N.Matthew , F. Glorius. Angew. Chem. Int. Ed.* ***2012****, 51, 10236 – 10254*

# *C-C Bond Formation*

## *Biaryl Formation*

- Two classes of C-H arylation reactions



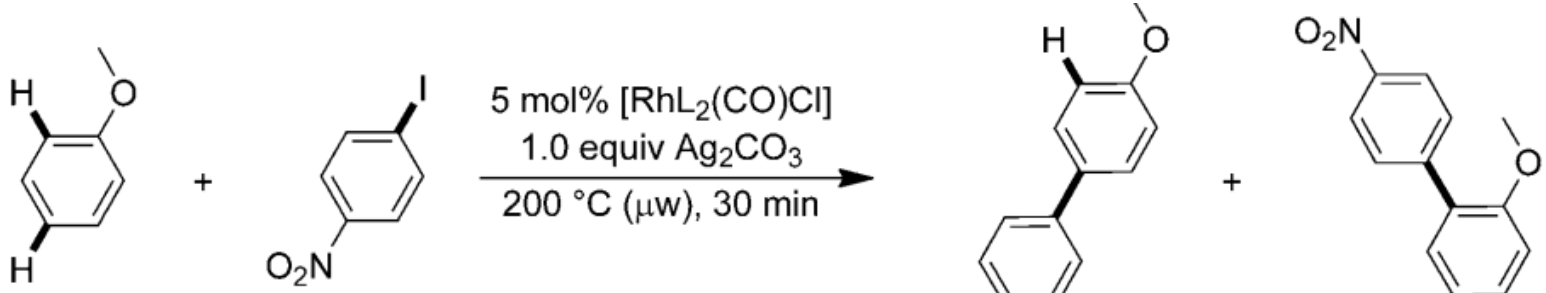

- Non-Oxidative Direct Arylation
- Oxidative Direct Arylation Using Iodonium Salts
- Oxidative Direct Arylation (Ar-H + Ar-M)

- Cross-Dehydrogenative Couplings (CDC)
- Chelate-Assisted Cross-Dehydrogenative Couplings

*N.Matthew , F. Glorius. Angew. Chem. Int. Ed.* ***2012****, 51, 10236 – 10254*

# *Biaryl Formation*

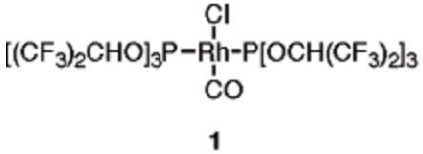
## *Non-Oxidative Direct Arylation (Ar-X + Ar-H)*

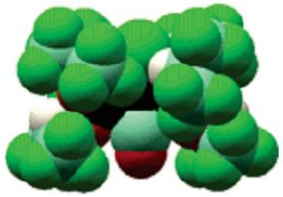



27 equiv
**comparatively unreactive arene**

1.0 equiv
**more reactive aryl halide**

L = $P[OCH(CF_3)_2]_3$



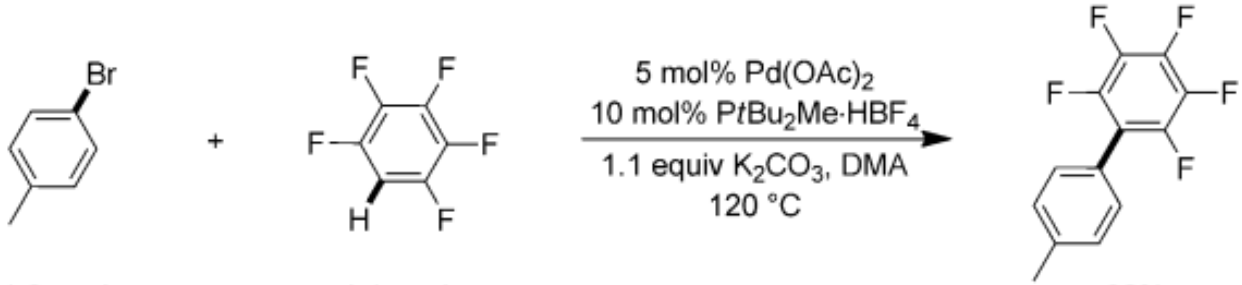



X-ray structure of 1

Rhodium(I) complex that bears two bulky, p-accepting phosphite ligands and that was proposed to promote C-H activation through an electrophilic metalation pathway

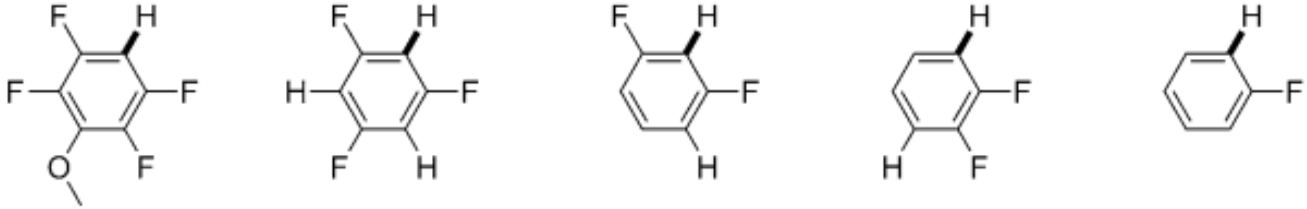

*S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, Tetrahedron,* ***2008****, 64, 6073 – 6081;*
*S. Yanagisawa, T. Sudo, R. Noyori, K.Itami, J. Am. Chem. Soc.* ***2006,*** *128, 11748 – 11749.*

# Concerted metalation–deprotonation (CMD) mechanism

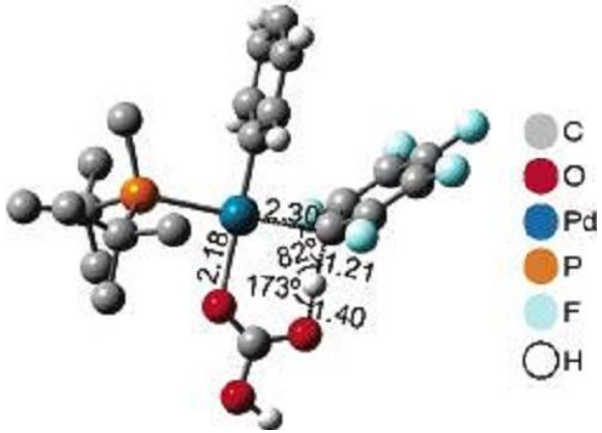



1.0 equiv 1.1 equiv 98%

*Selected examples:*




92% 69%[a] 85%[a] 29%[a] 8%




Calculated transition state structure

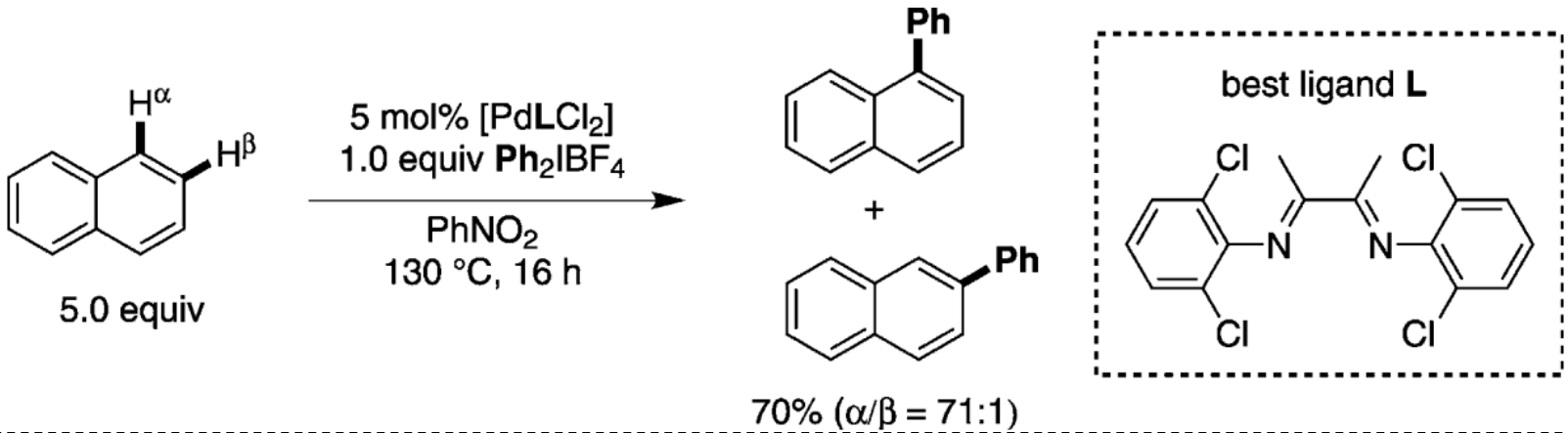
In CMD mechanism in the carbonate base, coordinated to the palladium-aryl intermediate, promotes the C-H activation step on the polyfluorinated arene via a six-membered transition state.

Thus, reactivity and regioselectivity were found to correlate well with the acidity of the functionalized fluoroarene.



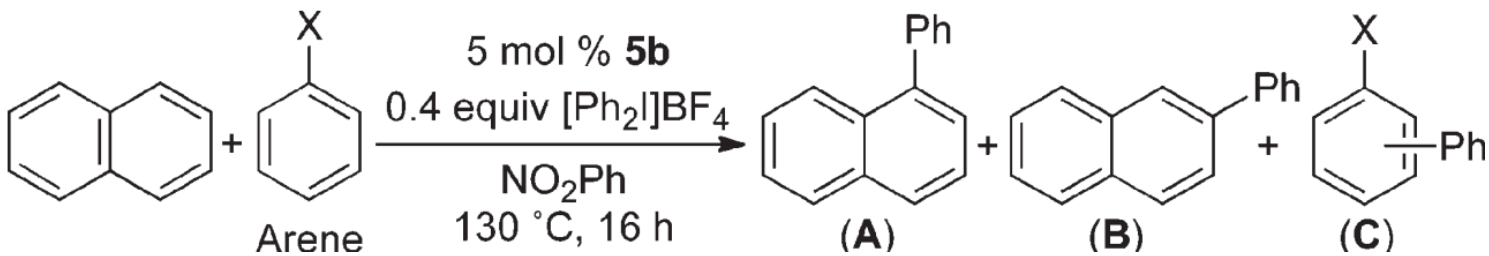
*M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, J. Am.Chem. Soc.2006, 128, 8754 – 8756.*

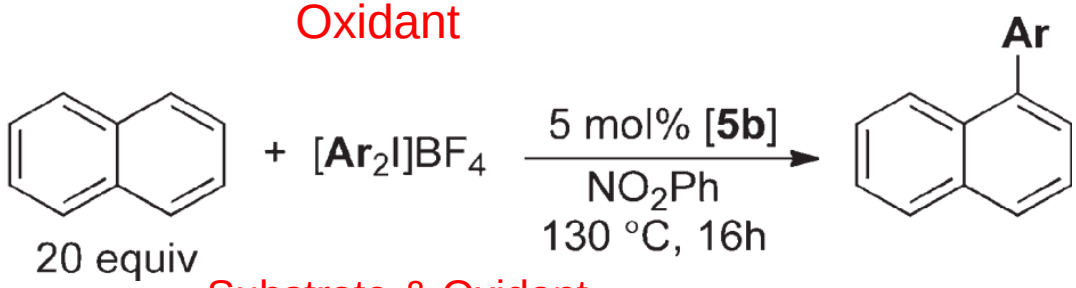
# Oxidative Direct Arylation Using Iodonium Salts




The choice of ligand for the palladium catalyst was shown to be crucial for the selective arylation process.

The iodonium salt played a dual role as both substrate and oxidant.

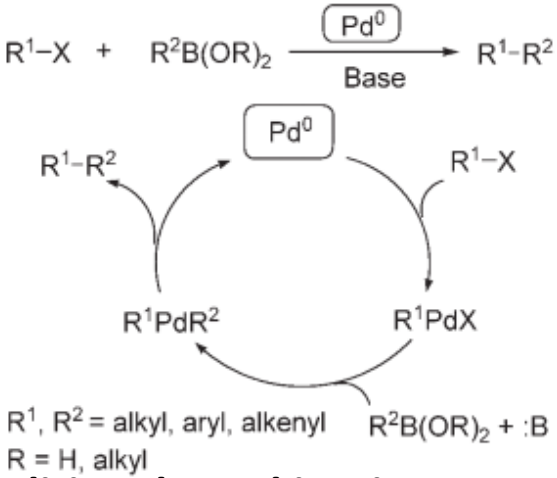


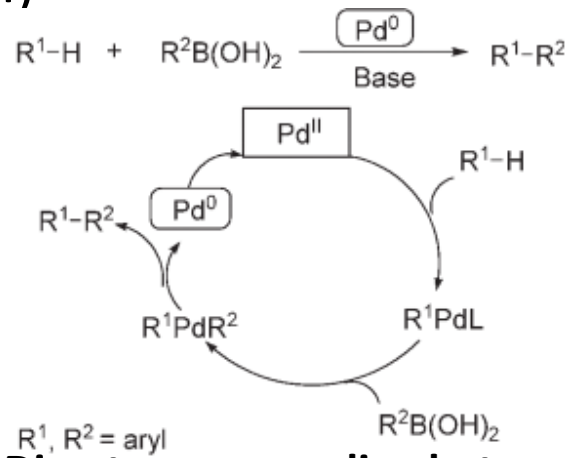



*A. J. Hickman, M. S. Sanford,ACS Catal.2011, 1, 170 – 174.*

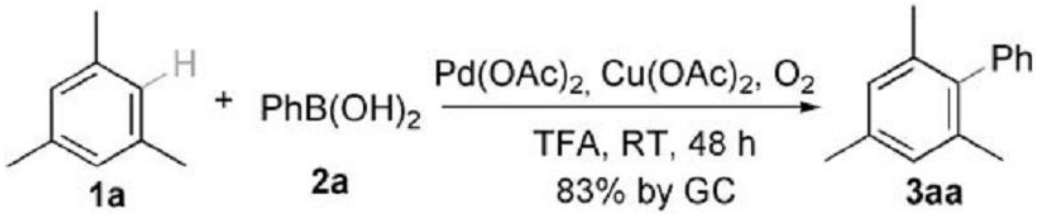
# Oxidative Direct Arylation (Ar-H+Ar-M)

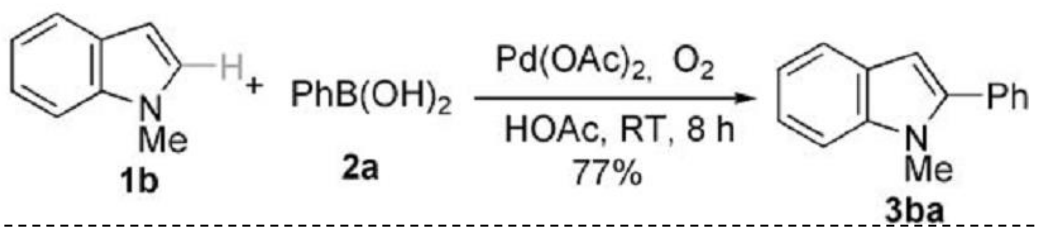



**Traditional Suzuki–Miyaura coupling**




**Direct cross-coupling between C-H bonds and C-B bonds**




As oxidative addition of a latetransition metal into an aryl C-H bond does not generally occur, stoichiometric amounts of an additional oxidant are required for these reactions . To avoid undesired homocoupling of the boronic acid, acidic conditions, which retard transmetalation of the boronic acid onto the catalyst, were applied.



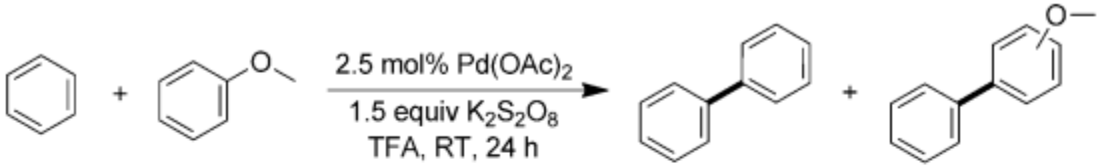
*S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, Angew. Chem.2008, 120, 1495 – 1498*

# Cross-Dehydrogenative Couplings (CDC)

- The most elegant and environmentally attractive method for the construction of the biaryl motif.
- Employing readily available arene starting materials and does not generate stoichiometric amounts of halogenated or organometallic by-products.

- How reactivity of an unreactive arene
- How the catalyst differentiates between the two C-H bond-containing components to achieve a chemoselective reaction.
- The regioselectivity issues of the reactants themselves.

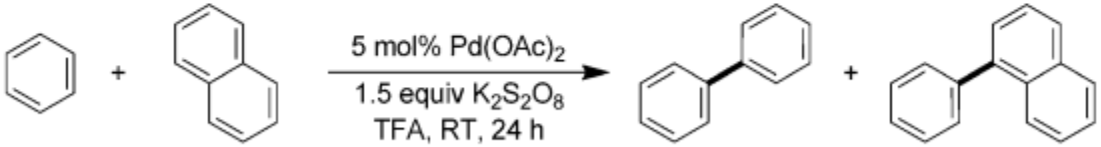
*1) Selected example showing the effect of the TFA amount:*




| | | | | |
|---|---|---|---|---|
| 11 equiv | 1 equiv | 6.3 equiv TFA | 56:44[a] | TON = 5.8 |
| 11 equiv | 1 equiv | 0.63 equiv TFA | 21:79[a] | TON = 2.8 |

There are two distinct chemoselectivity-determining factors:
1) the amount of trifluoroacetic acid
2) the ratio of the coupling partners.

*2) Selected example showing the effect of the arene ratio:*




| | | | | | |
|---|---|---|---|---|---|
| 25 equiv | 1 equiv | 0.5 equiv TFA | not observed | 15% (93%[b]) | TON = 3.1 |
| 100 equiv | 1 equiv | 1.3 equiv TFA | not observed | 32% (>99%[b]) | TON = 3.2 |

However, under the optimized conditions, the formation of significant amounts of homo-coupled biaryl compounds could not be avoided.



*R. Li, L. Jiang, W. Lu,Organometallics2006,25, 5973 – 5975*

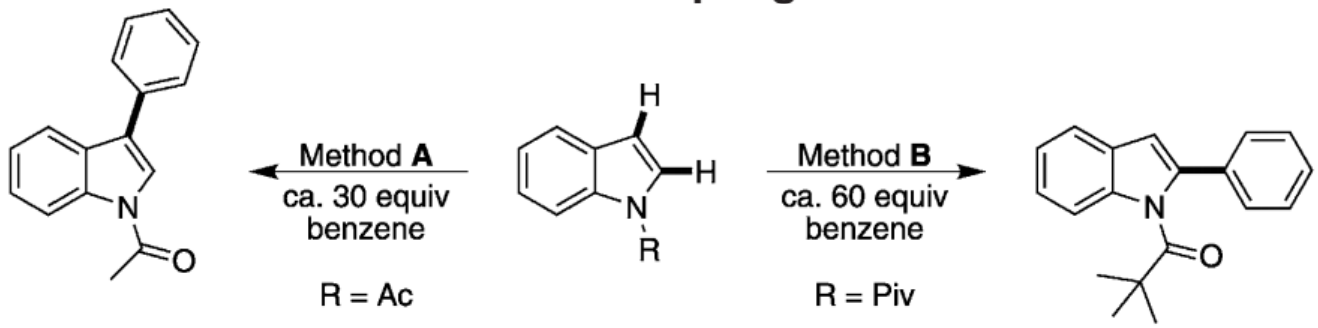
Science
AAAS

**The Catalytic Cross-Coupling of Unactivated Arenes**
David R. Stuart and Keith Fagnou
*Science* **316**, 1172 (2007);
DOI: 10.1126/science.1141956

J|A|C|S
COMMUNICATIONS

Published on Web 09/19/2007

## Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling




87%
8.9:1:0.26[a] *[a] Ratio of C3/C2/double arylation.*

84%
1:25:0.7[a]

Method **A**:
10 mol% $Pd(TFA)_2$, 10 mol% 3-nitropyridine
40 mol% CsOPiv, PivOH, 3.0 equiv $Cu(OAc)_2$
140 °C (µw), 5 h

Method **B**:
5 mol% $Pd(TFA)_2$, 6.0 equiv PivOH
3.0 equiv AgOAc
110 °C, 3 h

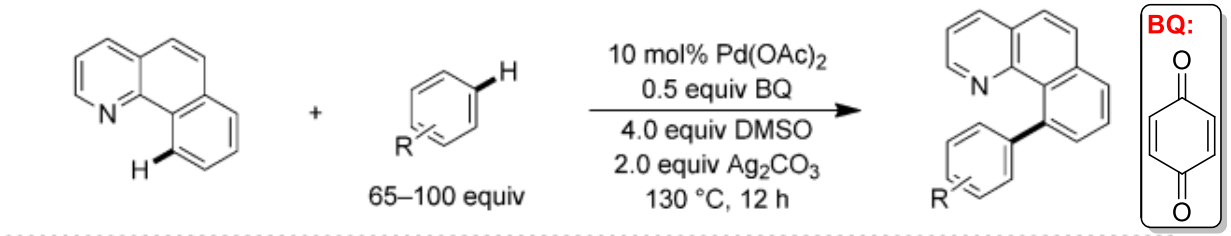
Fagnou and others demonstrated that a CMD-type mechanism is surprisingly operative for the C-H activation of both reaction partners, but not the initial hypothesis that chemoselectivity might be controlled by a difference in C-H activation mechanism.



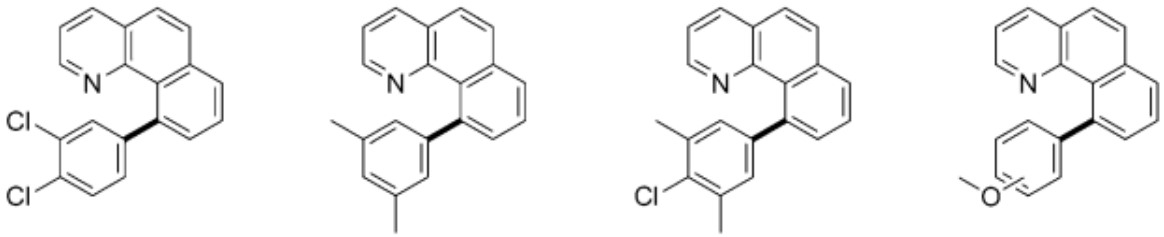
*S. I. Gorelsky, D. Lapointe, K. Fagnou, J. Am. Chem. Soc. 2008, 130, 10848–10849.*

# Chelate-Assisted Cross-Dehydrogenative Couplings

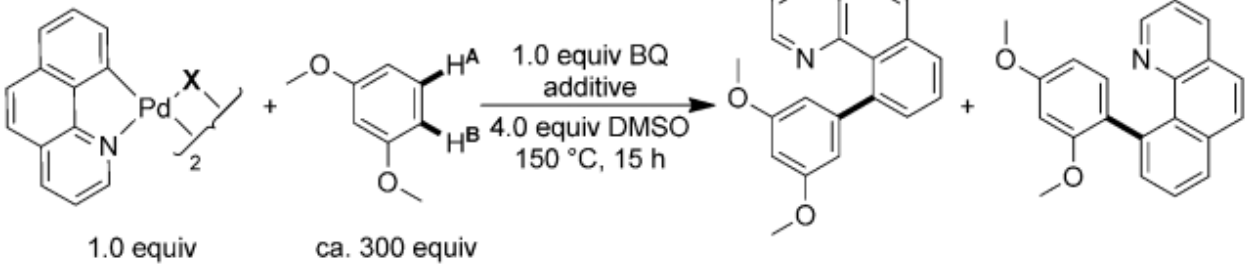
The cross-coupling of two different simple arenes can be achieved when a chelating group is installed onto one coupling partner.




*Selected examples:*



93% 69% 74% 80%
*o/m/p* = 1:2.6:3.3




1.0 equiv ca. 300 equiv

| | | |
|---|---|---|
| **X** = OAc | 3.0 equiv AcOH | 15 : 1 |
| **X** = $CO_3^{2-}$ | no additive | 1 : 11 |

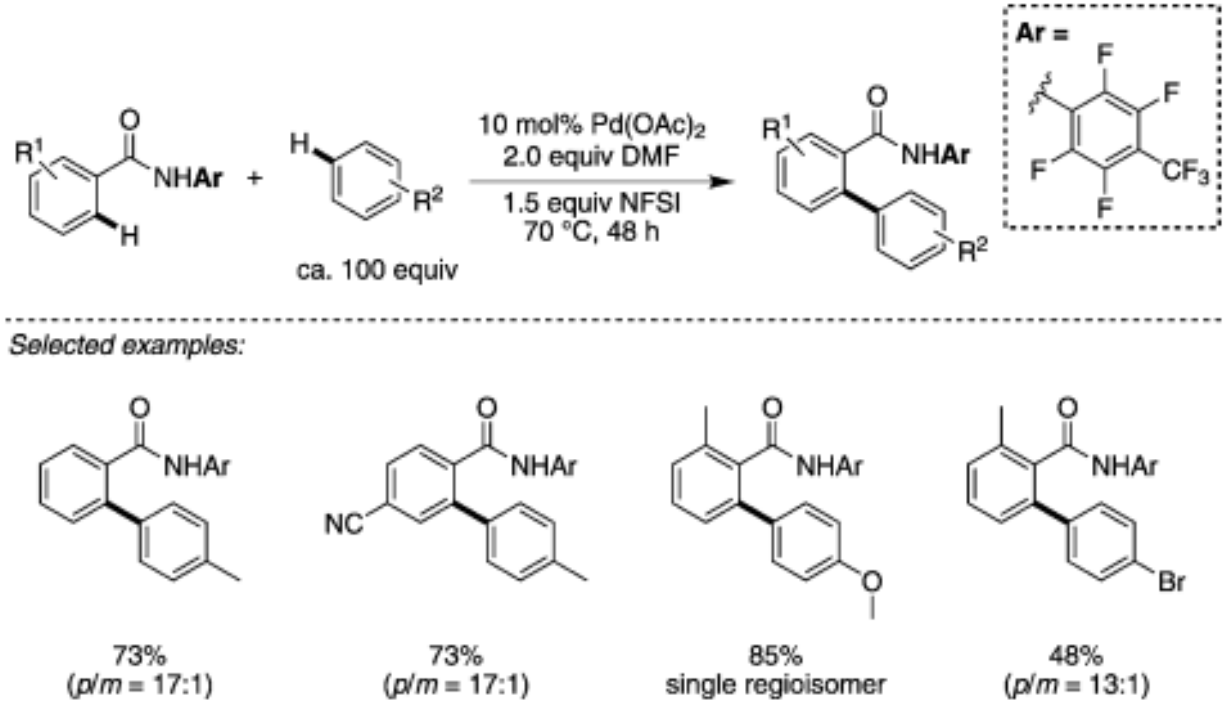
The reaction can be influenced by three parameters:
1) the amount of BQ,
2) the acid additive,
3) the nature of a ligand X on the metal center.

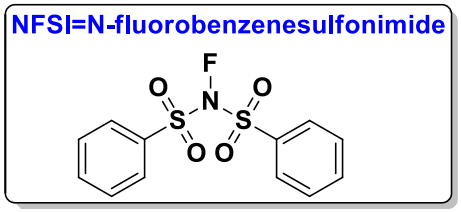
When one equivalent of BQ was used, C-H activation was reversible and complexation of BQ to the intermediary palladium diaryl species was proposed to be rate and selectivity determining.

Under these conditions, arylation occurred predominantly at the sterically less-hindered position of 1,3-dimethoxybenzene. This effect could become further pronounced by the addition of acetic acid.

*T. W. Lyons, K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2011, 133, 4455–4464;*
*K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2007, 129, 11904–11905.*

# Para-selective arylation of mono-substituted arenes



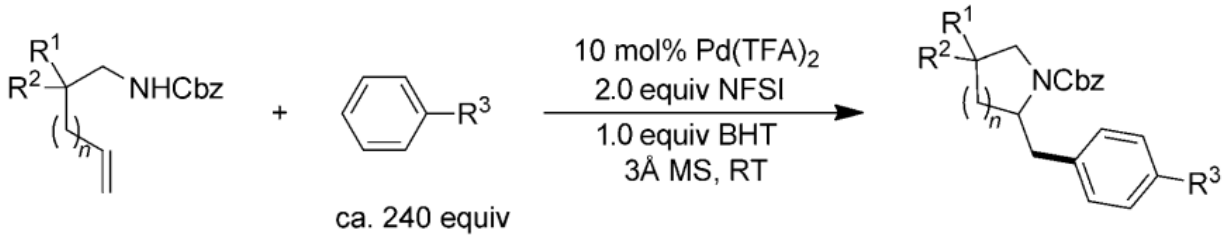




**T**he crucial reagents that afforded this reactivity and selectivity were $F^+$ oxidants, which recently have been proven to promote otherwise difficult reductive eliminations from $Pd^{IV}$ intermediates.

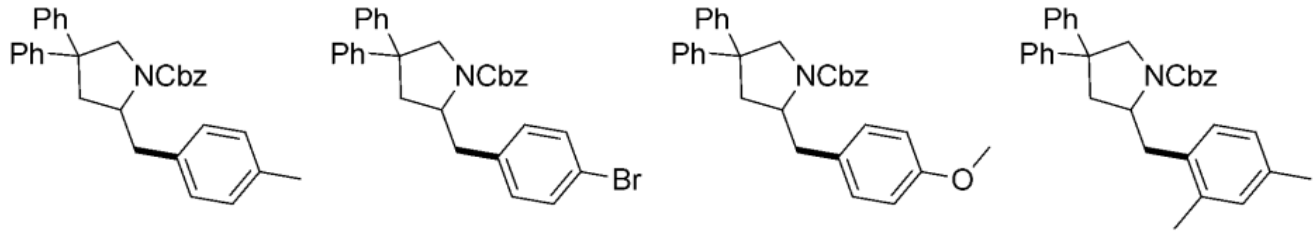
**A** mechanism involving electrophilic palladation was proposed, as a KIE of 1.0 was observed.

*X. Wang, D. Leow, J.-Q. Yu, J. Am. Chem. Soc. 2011, 133, 13864–13867.*

# Alkylation of Simple Arenes

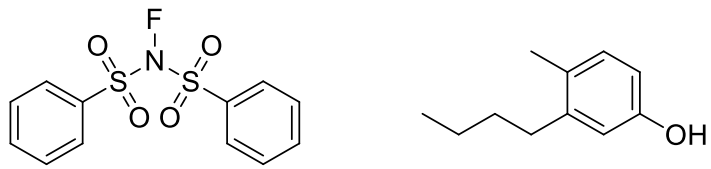



*Selected examples:*




82% 42% 55% 74%

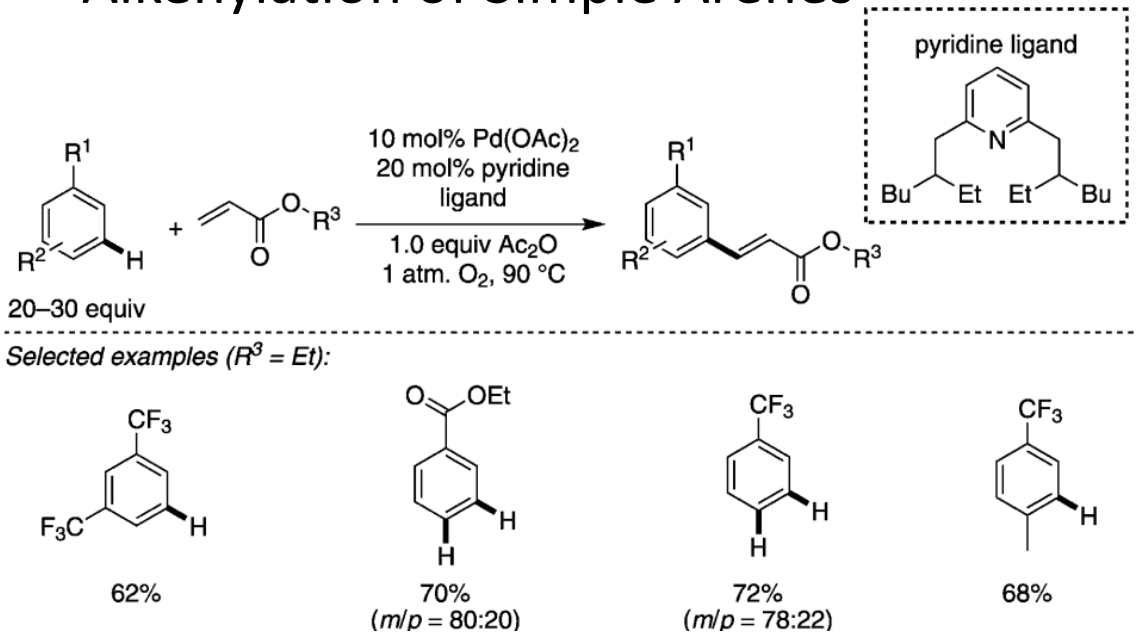
NFSI=N-fluorobenzenesulfonimide, BHT=butylhydroxytoluene



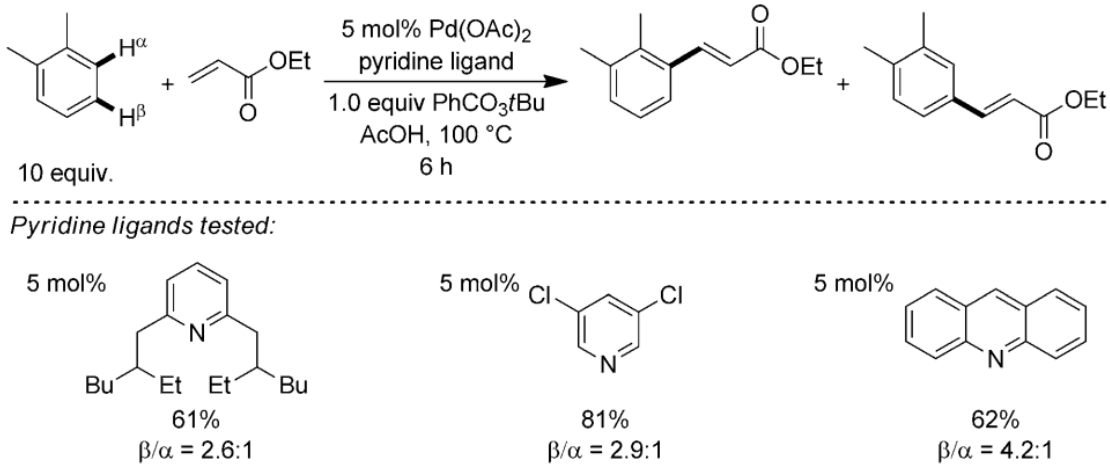

**M**ono-substituted arenes were alkylated with exclusive para selectivity

*C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, J. Am. Chem. Soc. 2009, 131, 9488–9489.*

# Alkenylation of Simple Arenes



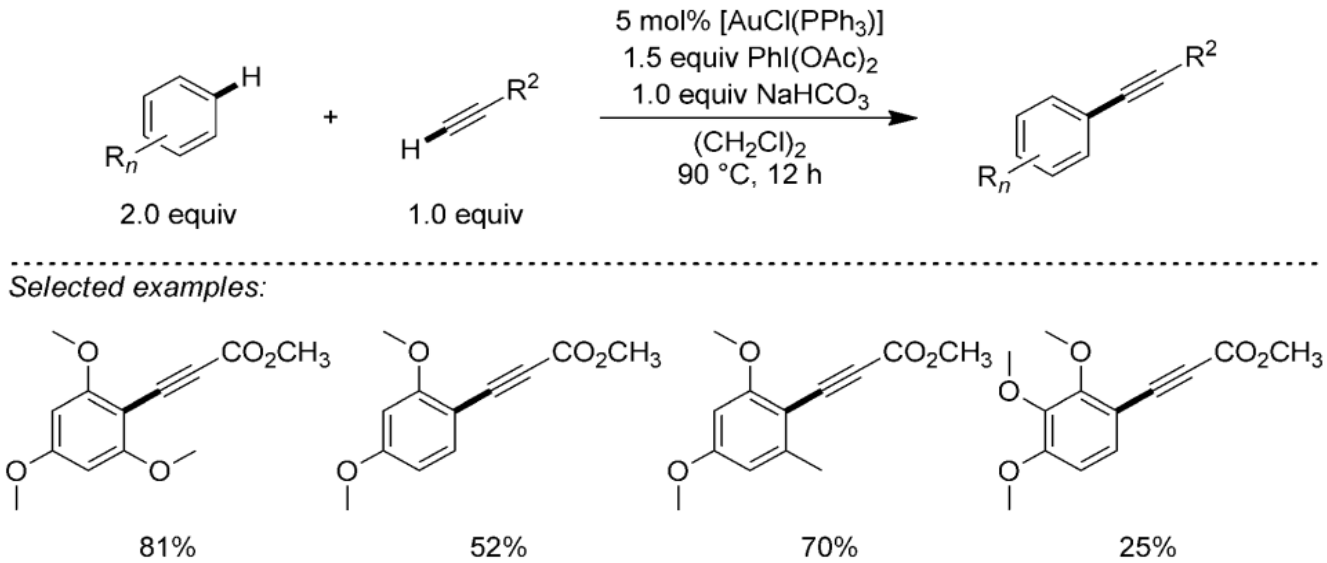

The ligand was found to be crucial for sufficient reactivity (it is bound to the palladium catalyst by a single bond, thus leaving free coordination sites for substrate) and selectivity.

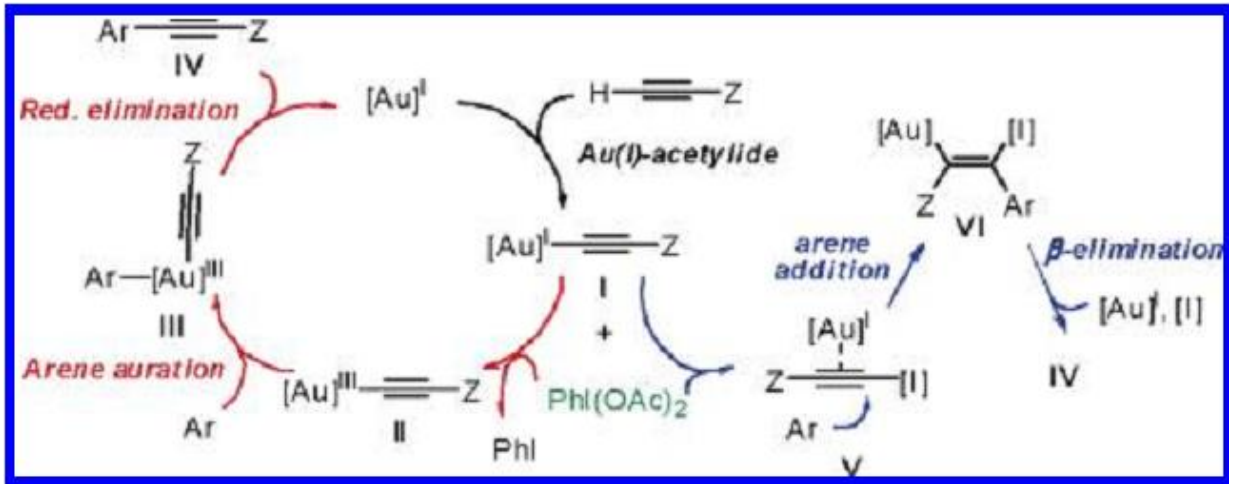



Appropriate catalyst design virtually permits site-selective C-H activation reactions

*Y.-H. Zhang, B.-F. Shi, J.-Q. Yu,J. Am. Chem. Soc.2009,131,5072 – 5074*
*A. Kubota, M. H. Emmert, M. S. Sanford,Org. Lett.2012, 14,1760 – 1763.*

# Alkynylation of Simple Arenes



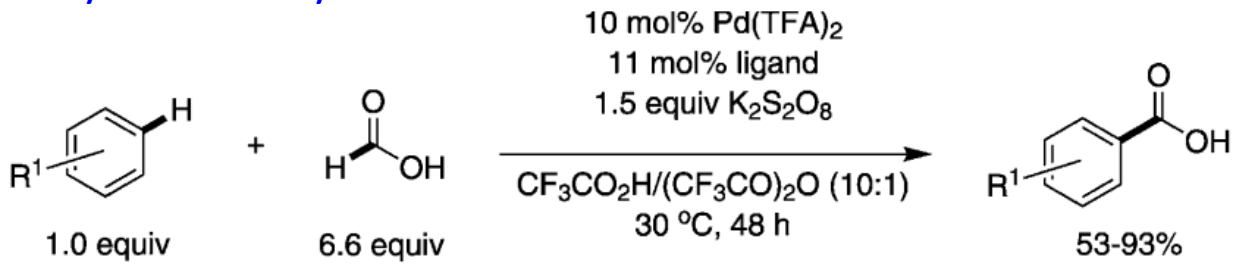




This regioselectivity is consistent with an electrophilic-type C-H activation mechanism that involves nucleophilic attack of the arene onto either a gold-activated alkyne species or onto gold(III) itself.

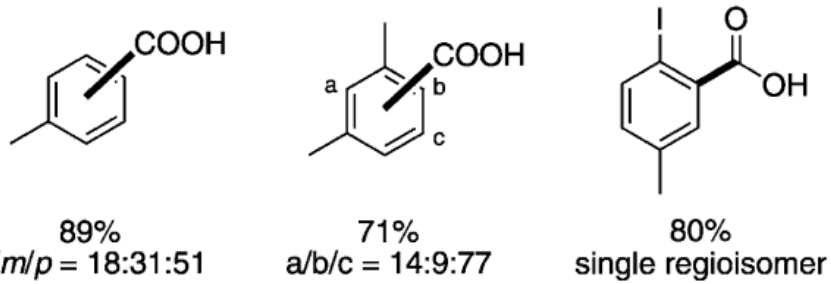
*T. de Haro, C. Nevado, J. Am. Chem. Soc. 2010, 132, 1512 –1513.*

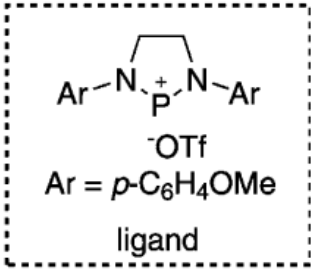
# Carboxylation of Simple Arenes

## Palladium-catalyzed carboxylation of arenes with formic acid



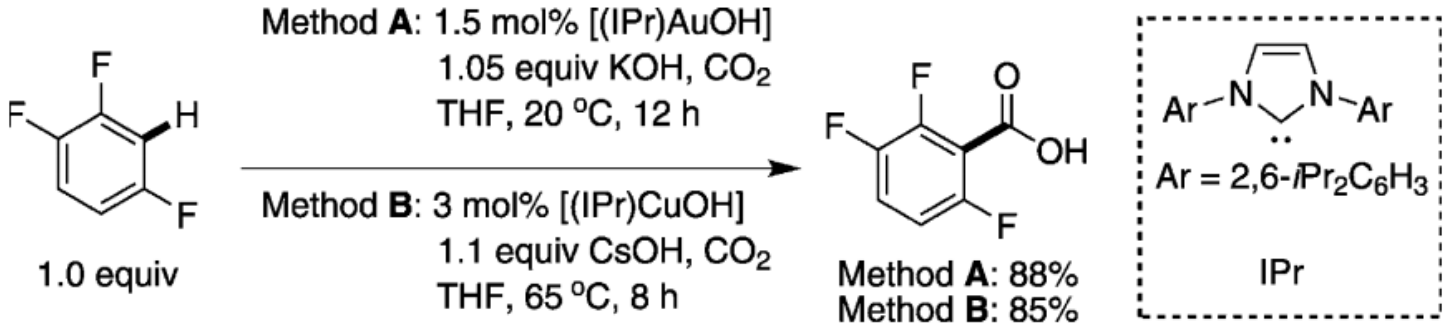

*Selected examples:*




*K. Sakakibara, M. Yamashita, K. Nozaki, Tetrahedron Lett. 2005, 46, 959–962.*

## Gold- or copper-catalyzed carboxylation of polyfluorobenzenes with $CO_2$




*I. I. F. Boogaerts, S. P. Nolan, J. Am. Chem. Soc. 2010, 132, 8858–8859.*

## C-Heteroatom Bond Formation

*To be continued next time … …*