Beyond Directing Groups

Transition-Metal-Catalyzed C-H Activation of Simple Arenes

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Supervisor: Yong Huang
2013-01-07

N. Kuhl, M. N. Hopkinson, J. W. Delord, F. Glorius, *Angew. Chem. Int. Ed*. **2012**, *51*, 10236

Contents:

Introduction:

C–H Bond Functionalization/Activation:

R= C or heteroatom
X= FG or H

➢ *(C) is sp^2 or sp^3 carbon atom*

➢ *(C)-H bond is **not a traditionally reactive bond** (i.e. pka > 30-35)*

➢ ***Selectivity** is a large issue due to the ubiquitous presence of C-H bonds in all organic molecules*

reactivity** and **selectivity

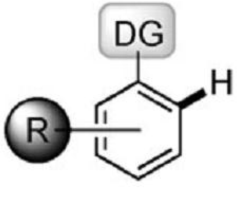
Reactivity *and* ***Selectivity:***

Heterocycles:

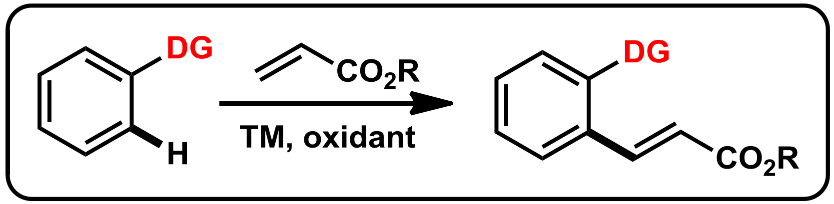
At least ***one position of special reactivity*** *as a result of the presence of one or more* ***heteroatoms***

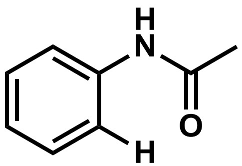
Benzene derivatives:

- *The discrepancy in reactivity between the C-H bonds is generally less pronounced*
- *Using* ***DG*** *such as amides, pyridines, or acetanilides to control site-selectivity*

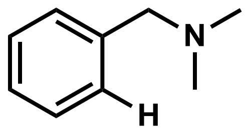


Directing Groups:

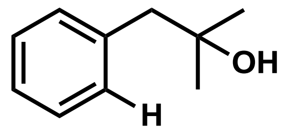




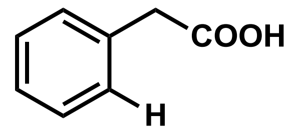
Leeuwen et al.
2002



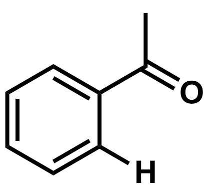
Shi et al.
2007



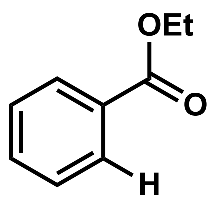
Yu et al.
2010



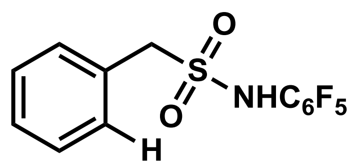
Yu et al.
2010



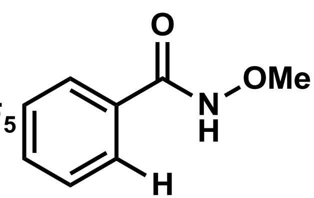
Glorius et al.
2011



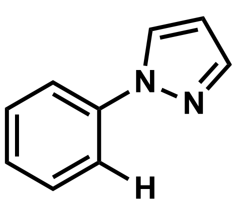
Chang et al.
2011



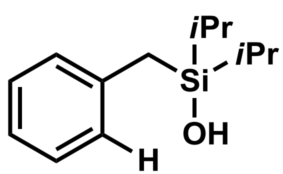
Yu et al.
2011



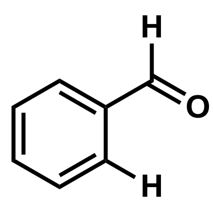
Wang et al.
2011



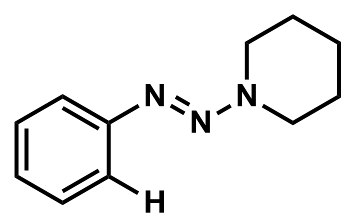
Dixneuf et al.
2011



Ge et al.
2011



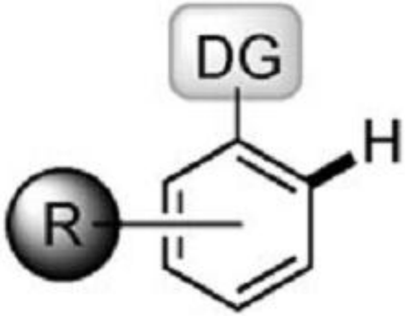
Jeganmohan et al.
2012



Huang et al.
2012

C. Wang, H. Chen, Z. Wang, J. Chen,Y. Huang, *Angew. Chem. Int. Ed*. **2012**, *51*, 7242

Directing Groups:



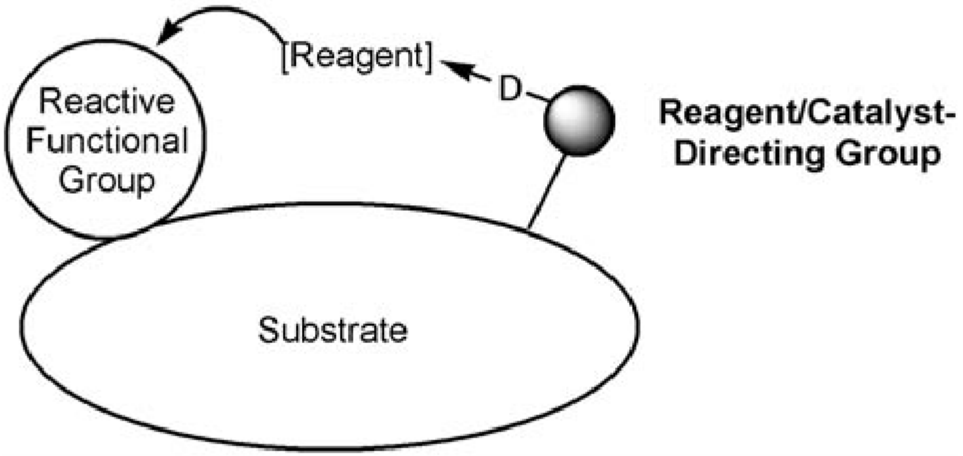
Advantages:

- *Direct the transition metal into* ***close proximity*** *to the C-H bond to be activated*
- ***Higher effective concentration*** *of the catalyst at the site of interest*
- ***High levels of regioselectivity*** *and* ***increased reactivity***

Limitations:

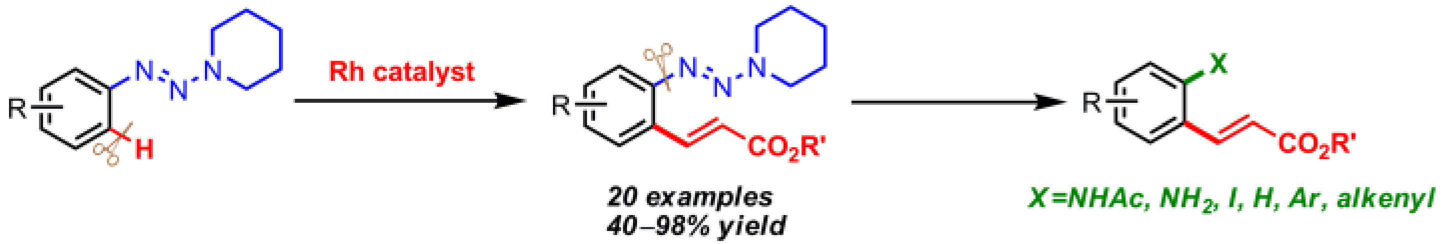
- *In most cases, only at the C-H bond* ***ortho*** *to the DG*
- *Additional synthetic steps:* ***install*** *the DG to SM and* ***remove*** *it*

Easily Modifiable or Removable DG:



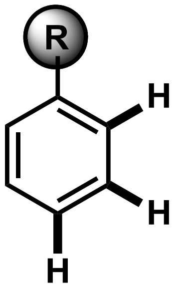
- *Ease of installation of the directing group*
- *Efficient control over the reactivity/selectivity*
- *Ease of removal from the substrate*

G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450



C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7242

C-H Activation of Simple Arenes:



Challenges

Increase of REACTIVITY toward transition metals

Devise new strategies to control REGIOSELECTIVITY

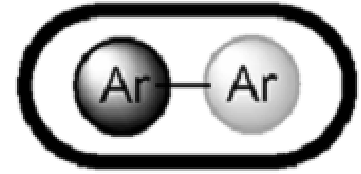
1) no extra steps required to install and/or remove DG
2) possibility of meta or para selectivity

This talk:

•*Activation reactions will be referred to as "**non-chelate-assisted**" rather than "undirected" C-H activation*

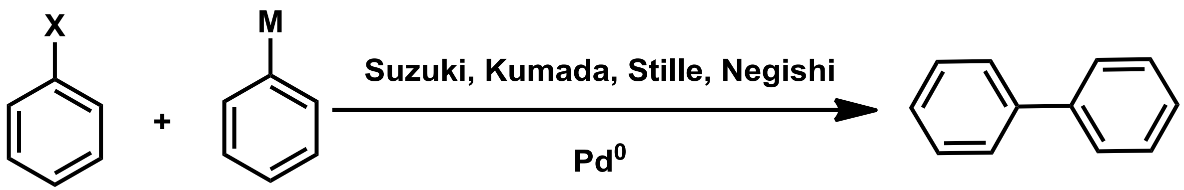
•*Only **homogeneous** processes, distinct **aryl-metal intermediate***

C-C Bond Formation:



Biaryl Formation

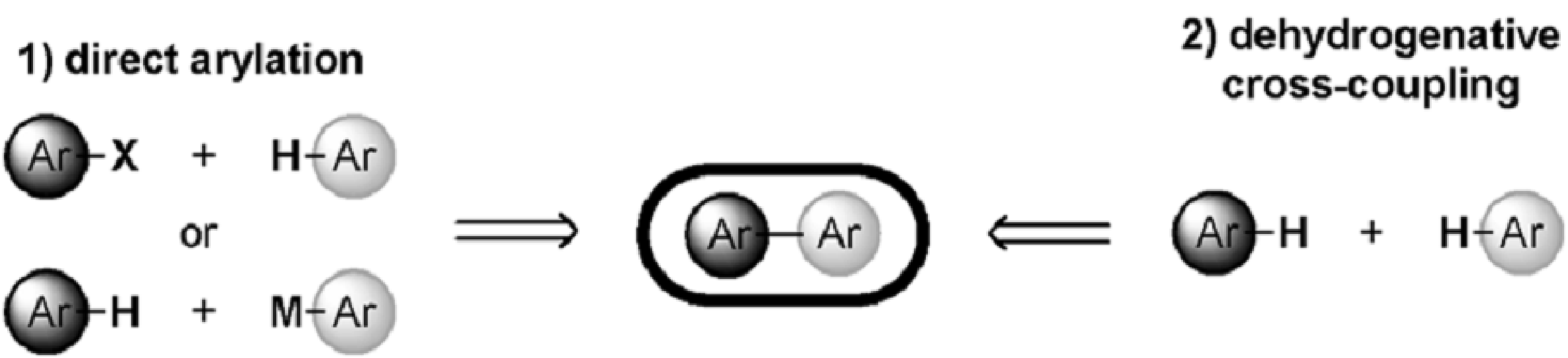
Traditional Cross Coupling Reactions:



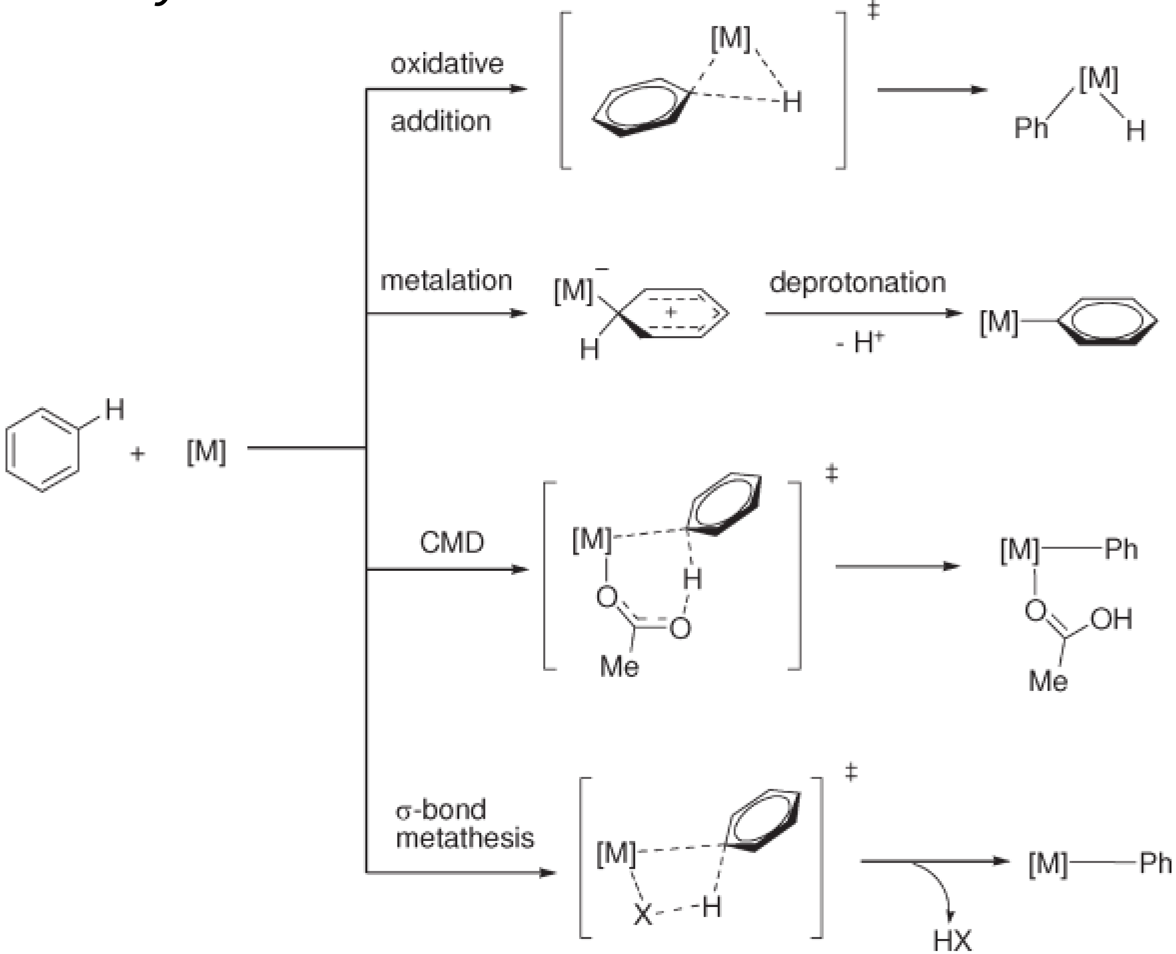
X= Cl, Br, I, OTf   M= Sn, B, Zn, Mg

- *Multiple steps for activation of components*
- *Regioselectivity determined by position of X and M*

C-H Activation Pathways:

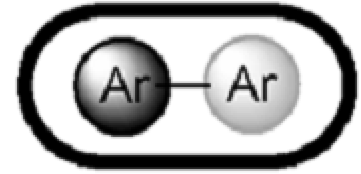


Proposed C-H Activation Mechanism s in Transition Metal Catalysis



S. Zhang, L. Shi, Y. Ding, *J. Am. Chem. Soc.* **2011**, *133* , 20218

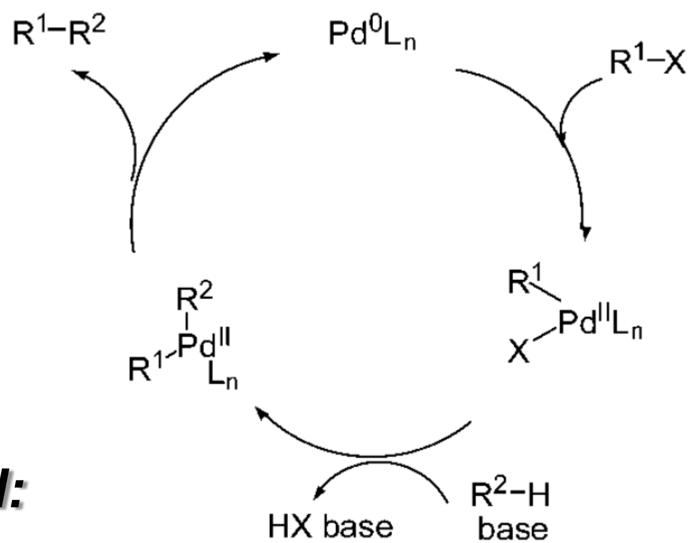
Non-Oxidative Direct Arylation (Ar-X + Ar-H)



Challenge:

Promote C-H activation *of the unreactive arene*
Avoid homocoupling *of the more reactive aryl halide*

Mechanism:

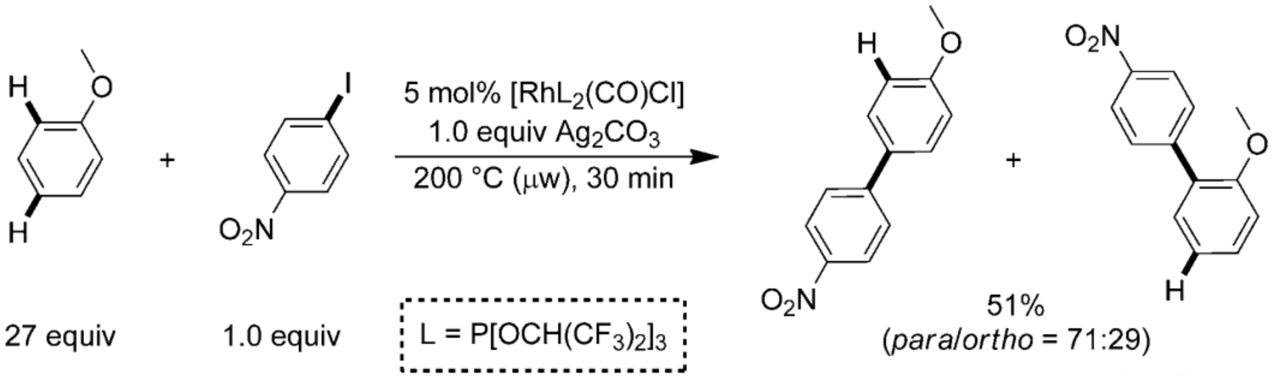


Metal:

Pd, Rh*, Ni, Cu, Co, Fe, etc.*

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

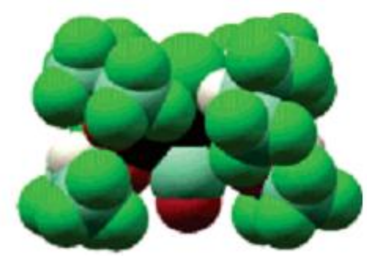
Electron-rich arene:



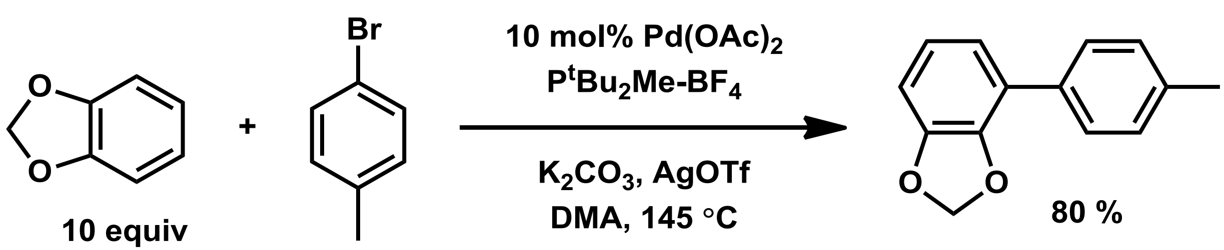
Key:

•*Two **bulky, Π-accepting** phosphite ligands*

•***Electrophilic metalation** pathway*



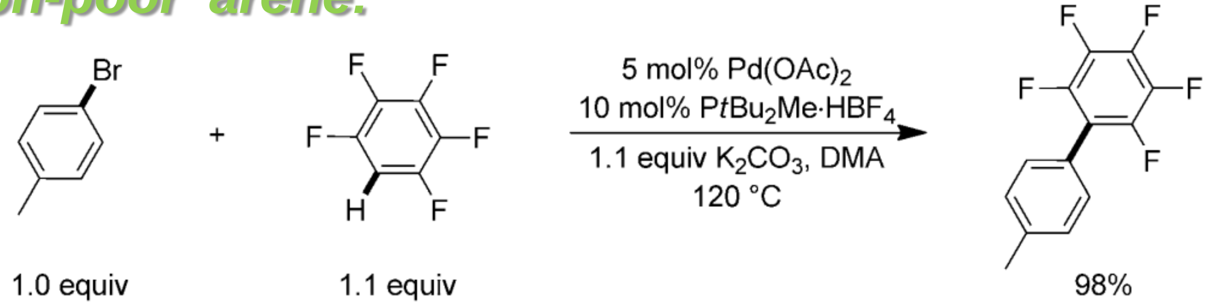
S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748

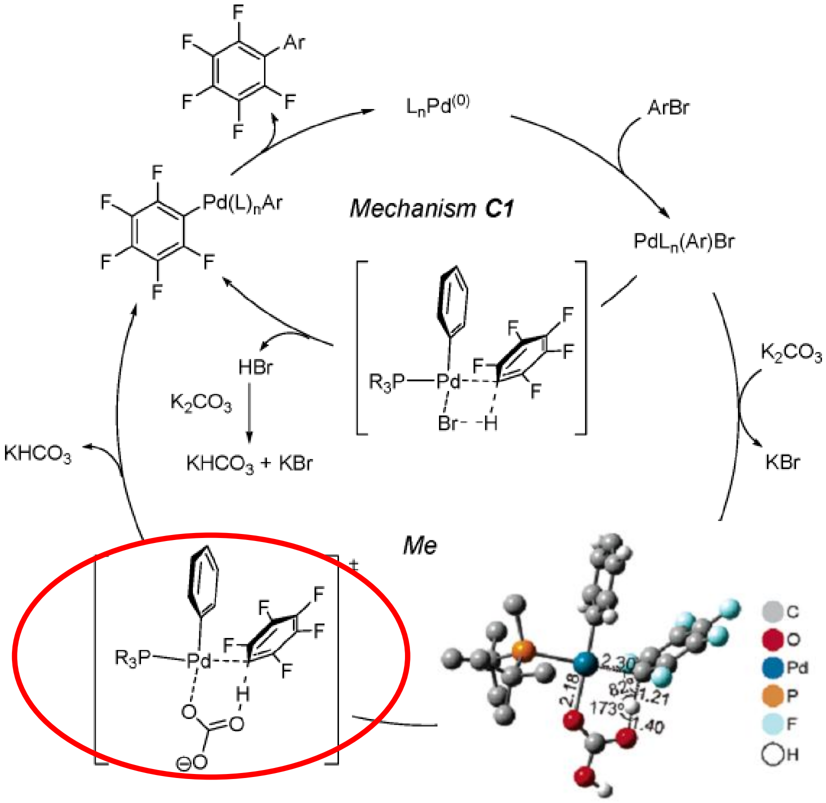


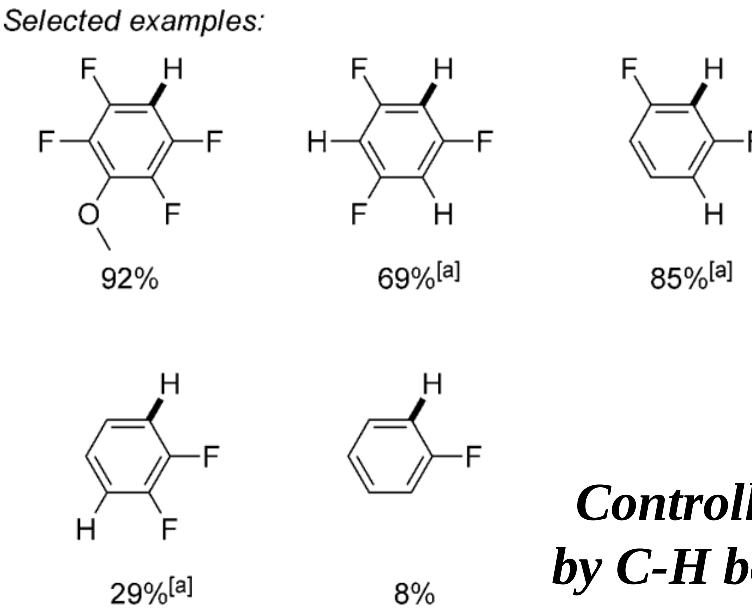
L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581

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

Electron-poor arene:





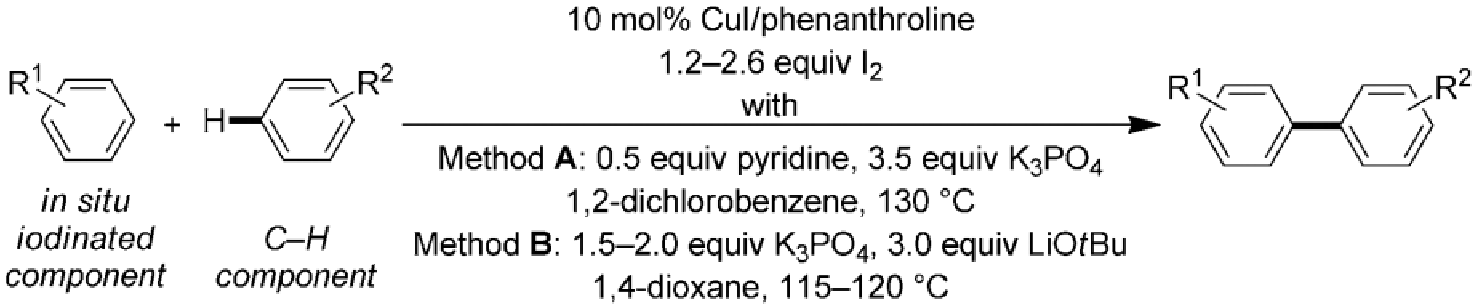


Controlled by C-H bond *acidity*

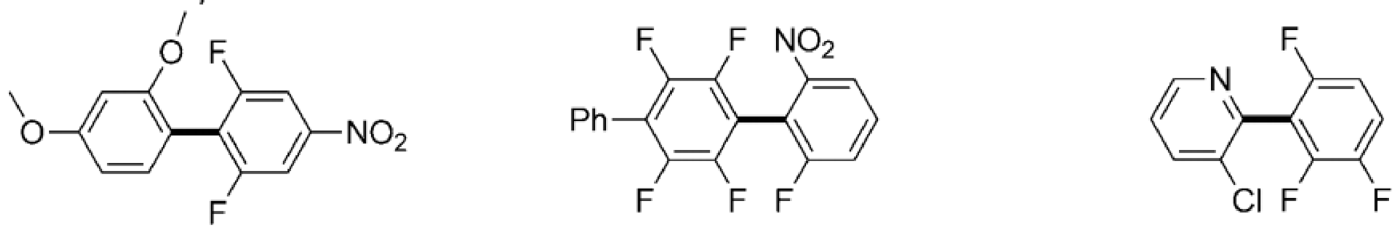
M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc*. **2006**, *128*, 8754

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

Electron-poor arene:



Selected examples:



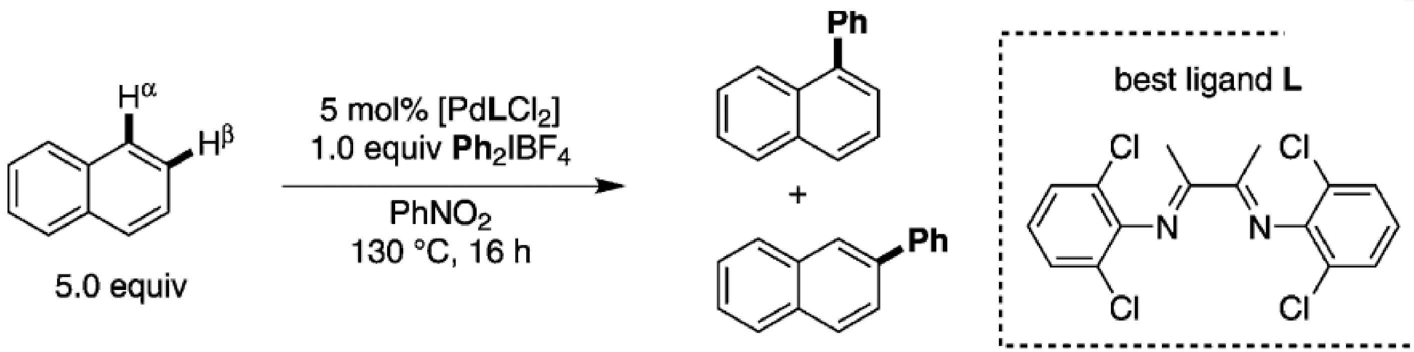
Method **A**	Method **B**	Method **B**
82%	60%	53%
5 days	12 h	5 days

Mechanism:

Ar–H (pKa < 35-37) ⇌ [base; M = Li, K; metallation] Ar–M → [CuI/ligand, -MI; transmetallation] Ar–CuL_n → [Ar'I, -CuI; arylation] Ar–Ar'

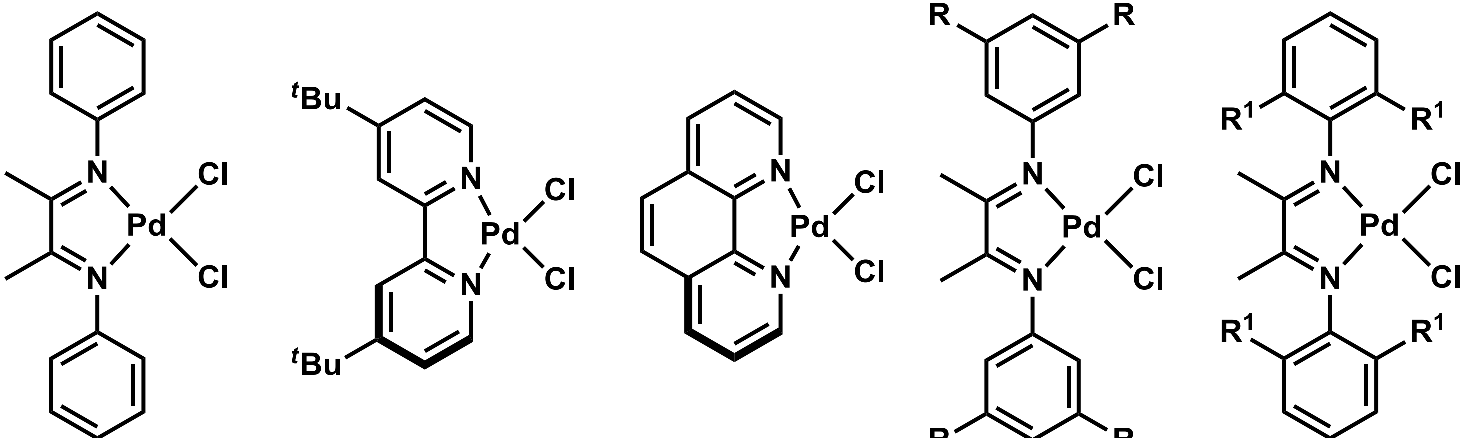
H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc*. **2011**,*133*, 13577
H.-Q. Do, R. M. Kashif Khan, O. Daugulis, *J. Am. Chem. Soc*. **2008**, *130*, 15185

Oxidative Direct Arylation Using Iodonium Salts



Ligand-controlled regioselectivity

70% (α/β = 71:1)



54 % (9:1)

22 % (78:1)

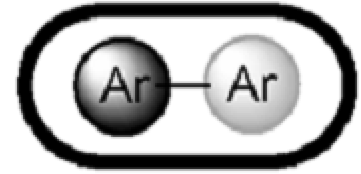
12 % (10:1)

R=CH_3 47 % (9:1)
R=CF_3 50 % (10:1)
R=^{t}Bu 32 % (18:1)
R=Cl 42 % (22:1)

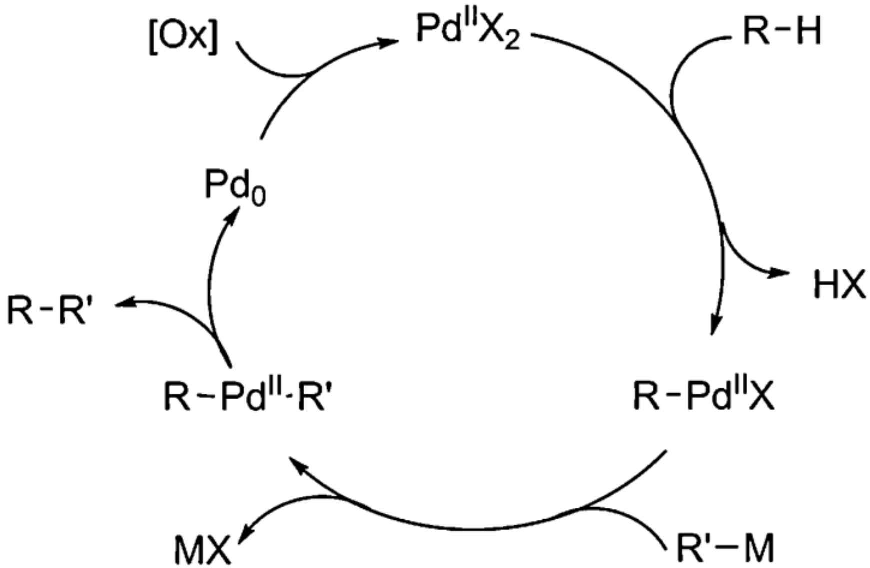
R^1=CH_3 43 % (27:1)
R^1=Cl 70 % (71:1)

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

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



General mechanism:



Key: (oxidative cross-coupling)

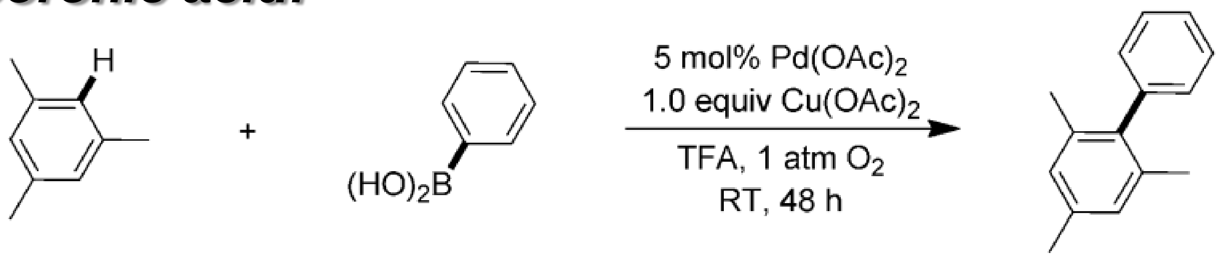
- *Appropriate* ***oxidants*** *are necessary*
- ***Acidic conditions*** *promote these processes*

Challenge:

- ***homo-coupling*** *of organometallic reagent*
- *the* ***incompatibility*** *of reaction conditions*
- *the* ***stability*** *of organometallic reagents*

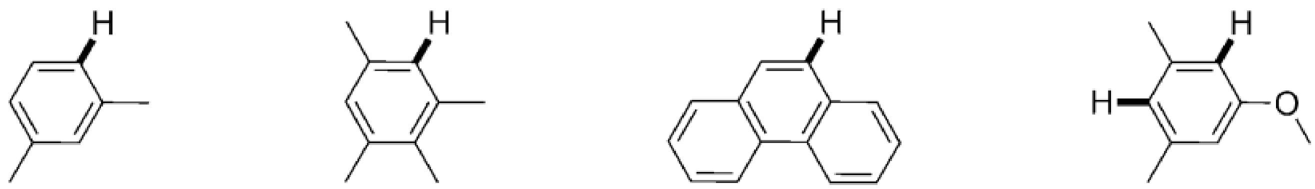
Oxidative Direct Arylation (Ar-H + Ar-M)

With Boronic acid:



2.0 equiv | 1.0 equiv | 83%[a]

Selected examples:



48%[a] | 78%[a] | 54% | 68% (*ortho*/*para* = 2:1)

Electron-rich arene

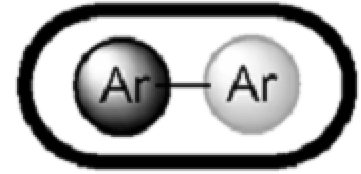
S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, Angew. Chem. Int. Ed. 2008, 47, 1473

Polyfluoroarene + $ArB(OH)_2$ $\xrightarrow[Ag_2CO_3,\ DMA,\ 110\text{-}120\ ℃,\ 10\ h]{Pd(OAc)_2,\ base,\ acid}$ Ar_F-Ar **3**

Electron-poor arene

Y. Wei, J. Kan, M. Wang, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 3346

Cross-Dehydrogenative Coupling (CDC)



Challenge:

•*How* ***reactivity*** *of an unreactive arene*

•*How catalyst* ***differentiates*** *between the two C-H bond*

Key & Strategies:

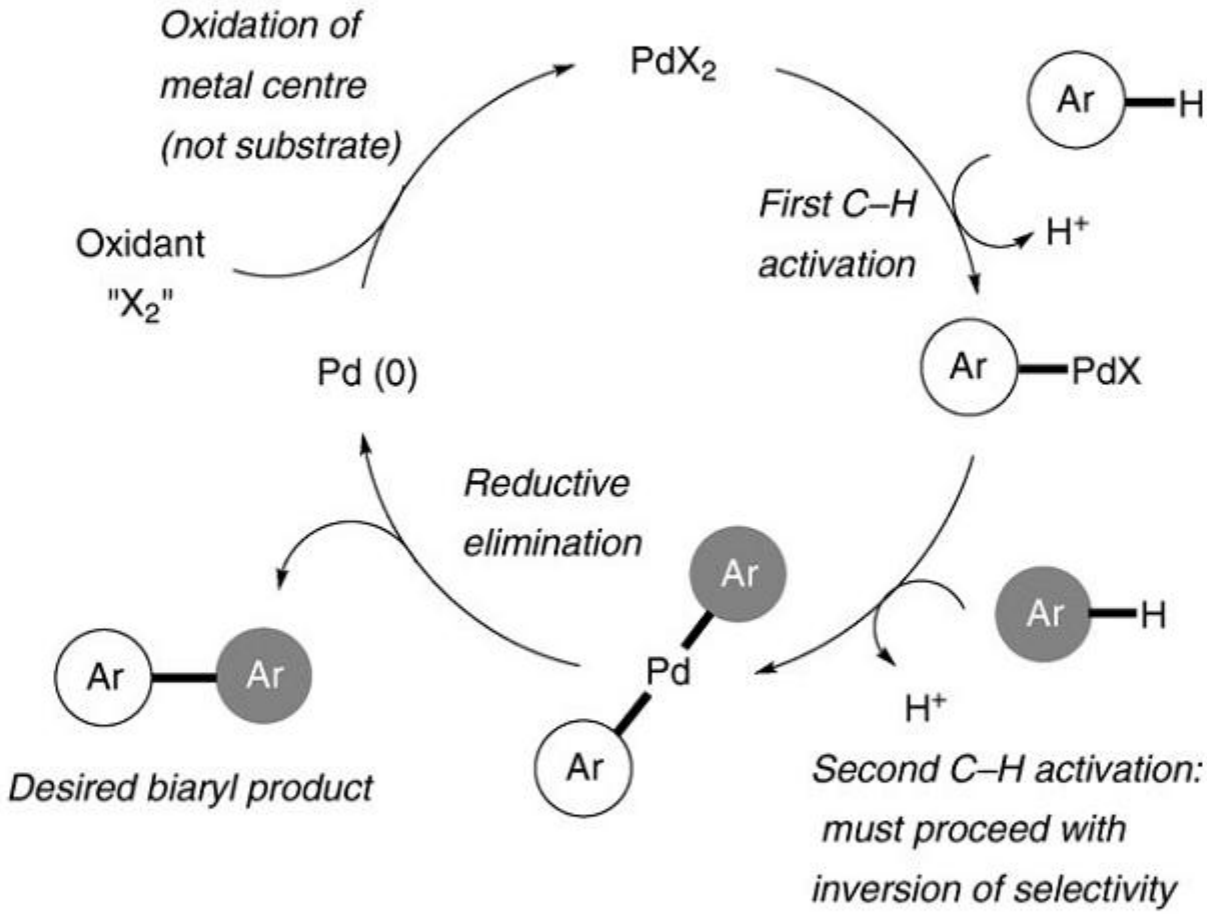
•*Regioselectivity determined by the* ***electronic*** *and* ***steric*** *preferences*

•***Selective oxidation*** *of one arene partner generates an electrophilic arene species*

•*Achieve* ***two successive palladium-catalyzed C–H activations*** *with orthogonal selectivity*

Cross-Dehydrogenative Coupling (CDC)

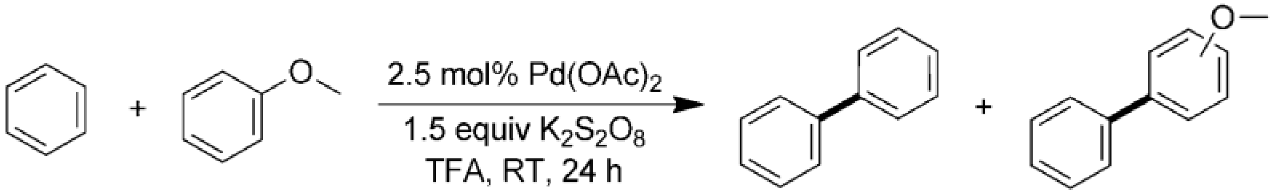
General mechanism:



J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540

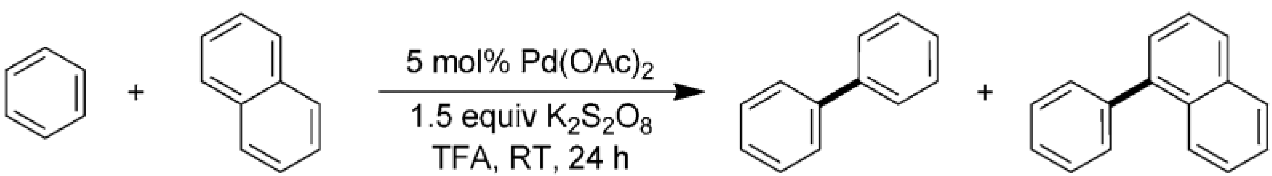
Cross-Dehydrogenative Coupling (CDC)

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

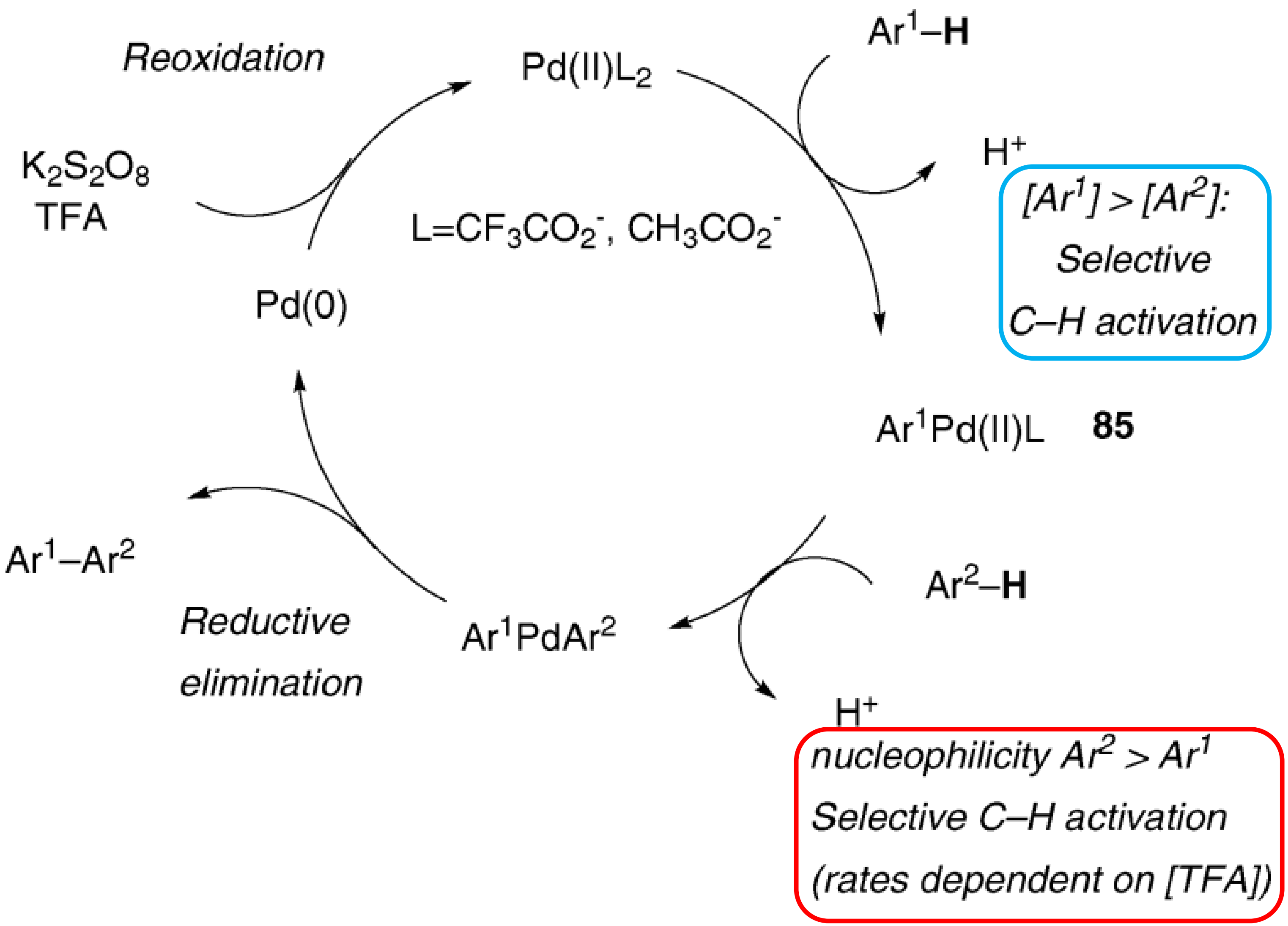
2) Selected example showing the effect of the arene ratio:



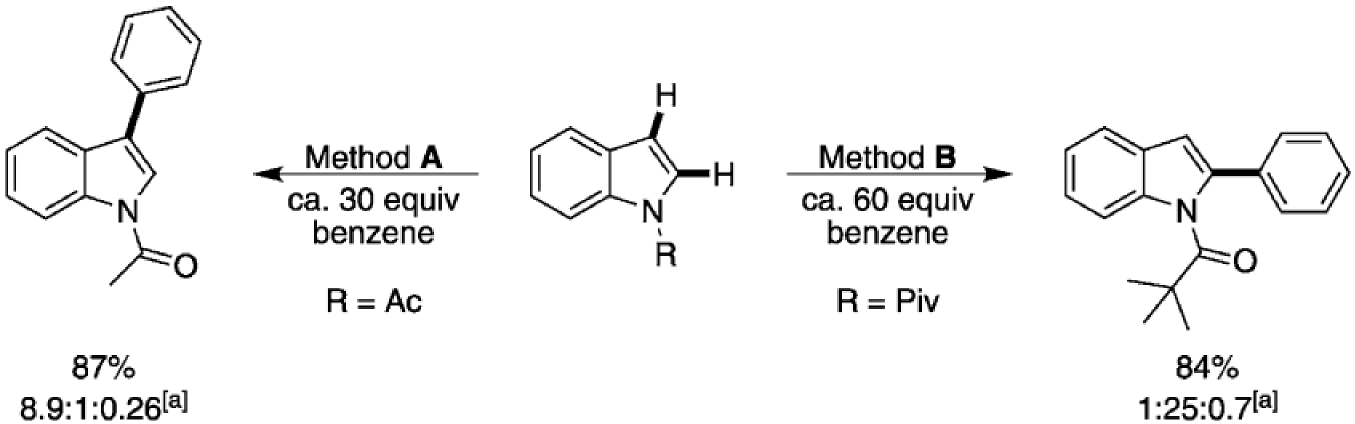
25 equiv	1 equiv	0.5 equiv TFA	not observed	15% (93%[b])	TON = 3.1
100 equiv	1 equiv	1.3 equiv TFA	not observed	32% (>99%[b])	TON = 3.2

R. Li, L. Jiang, W. Lu, *Organometallics* **2006**, *25*, 5973

Cross-Dehydrogenative Coupling (CDC)



Cross-Dehydrogenative Coupling (CDC)

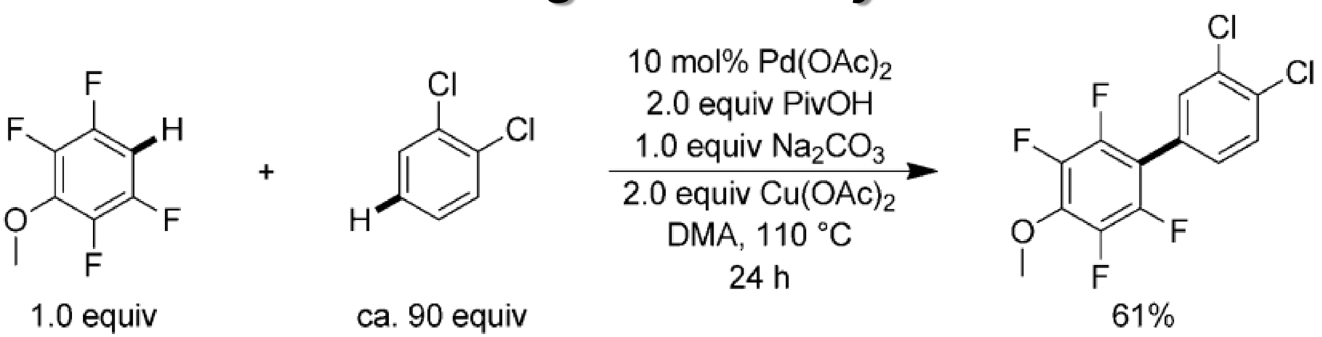


Method A:
10 mol% $Pd(TFA)_2$, 10 mol% 3-nitropyridine
40 mol% CsOPiv, PivOH, 3.0 equiv $Cu(OAc)_2$
140 °C (μw), 5 h

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

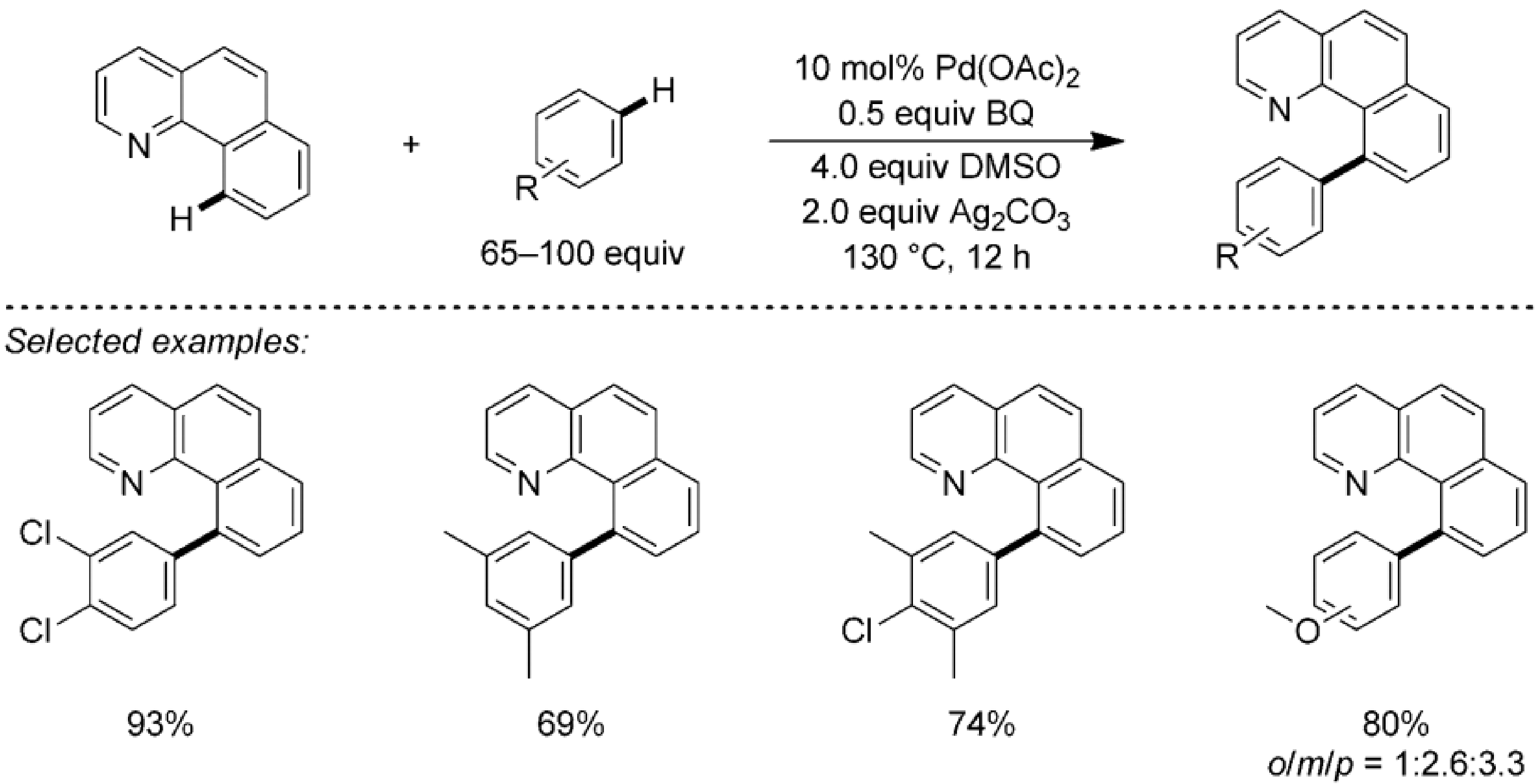
D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172

Steric factors controlled regioselectivity:



Y. Wei, W. Su, *J. Am. Chem. Soc.* **2010**, *132*, 16377

Chelate-Assisted Cross-Dehydrogenative Couplings

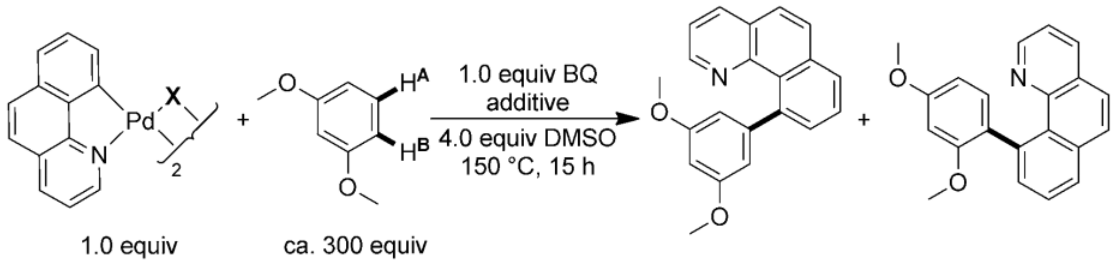


K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904

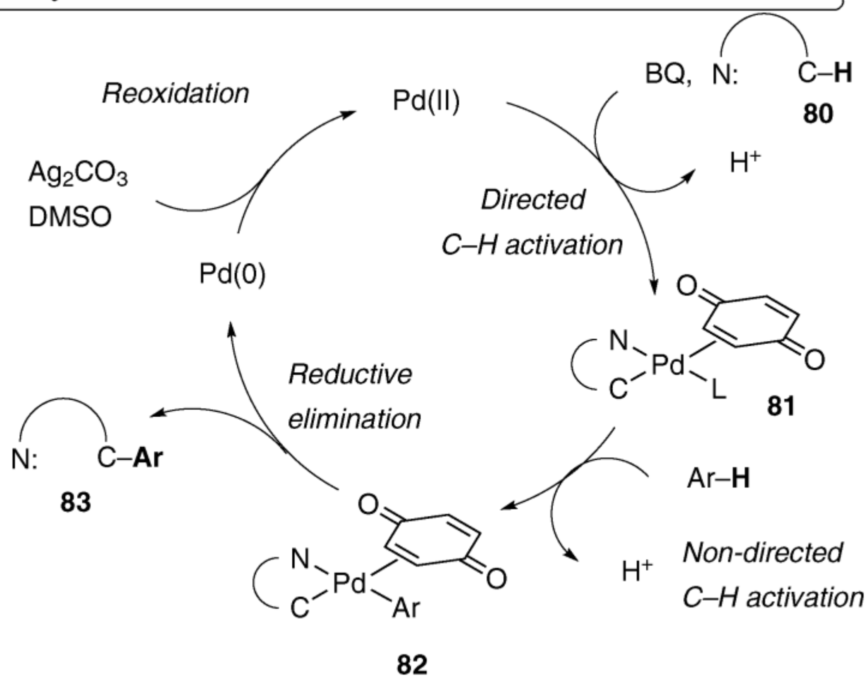
Chelate-Assisted Cross-Dehydrogenative Couplings

Key:

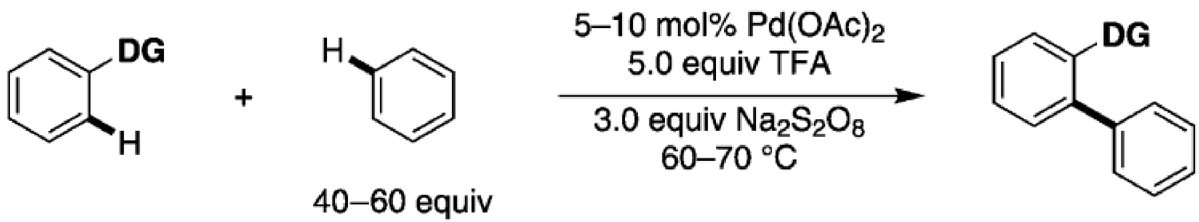
1) Amount of BQ, 2) Acid additive, 3) Nature of a ligand X on the metal center

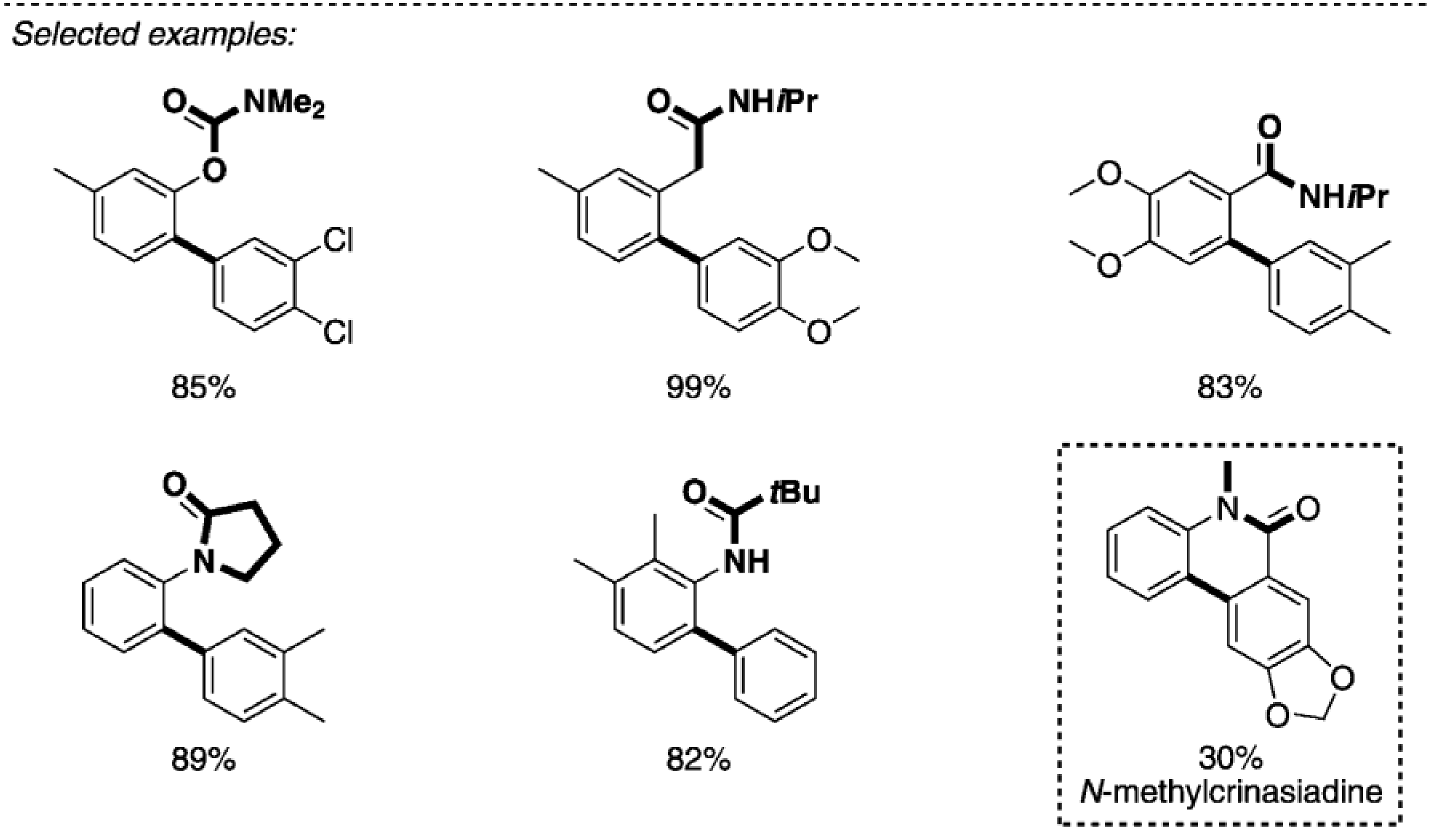


X = OAc	3.0 equiv AcOH	15 : 1
X = CO_3^{2-}	no additive	1 : 11



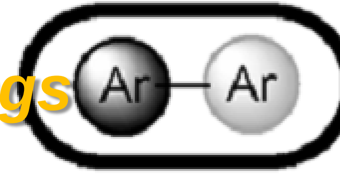
Chelate-Assisted Cross-Dehydrogenative Couplings

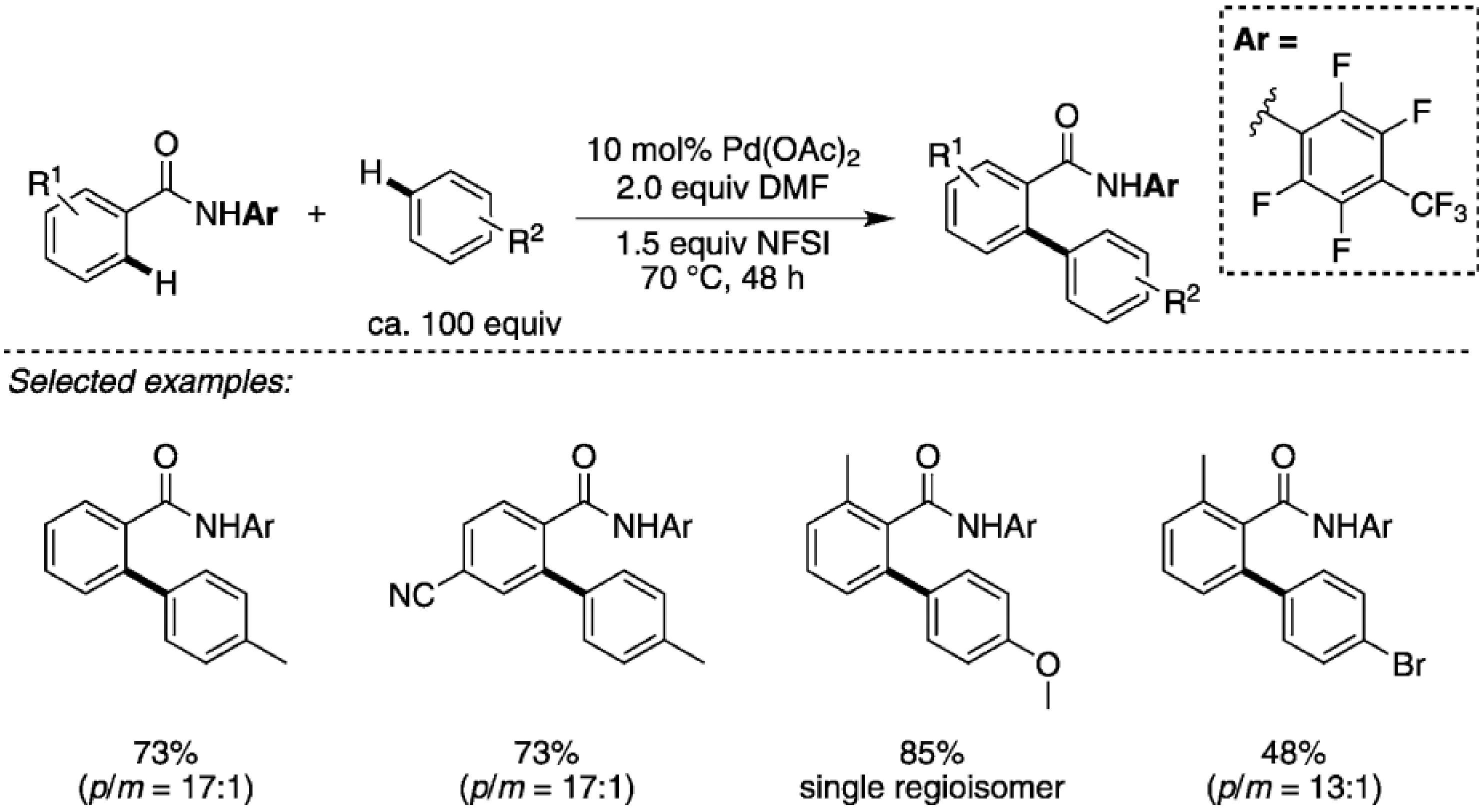




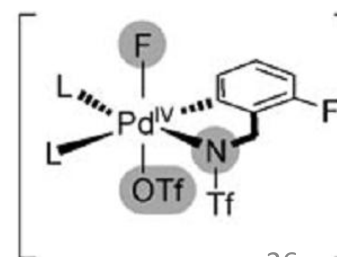
X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837
C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331

Chelate-Assisted Cross-Dehydrogenative Couplings

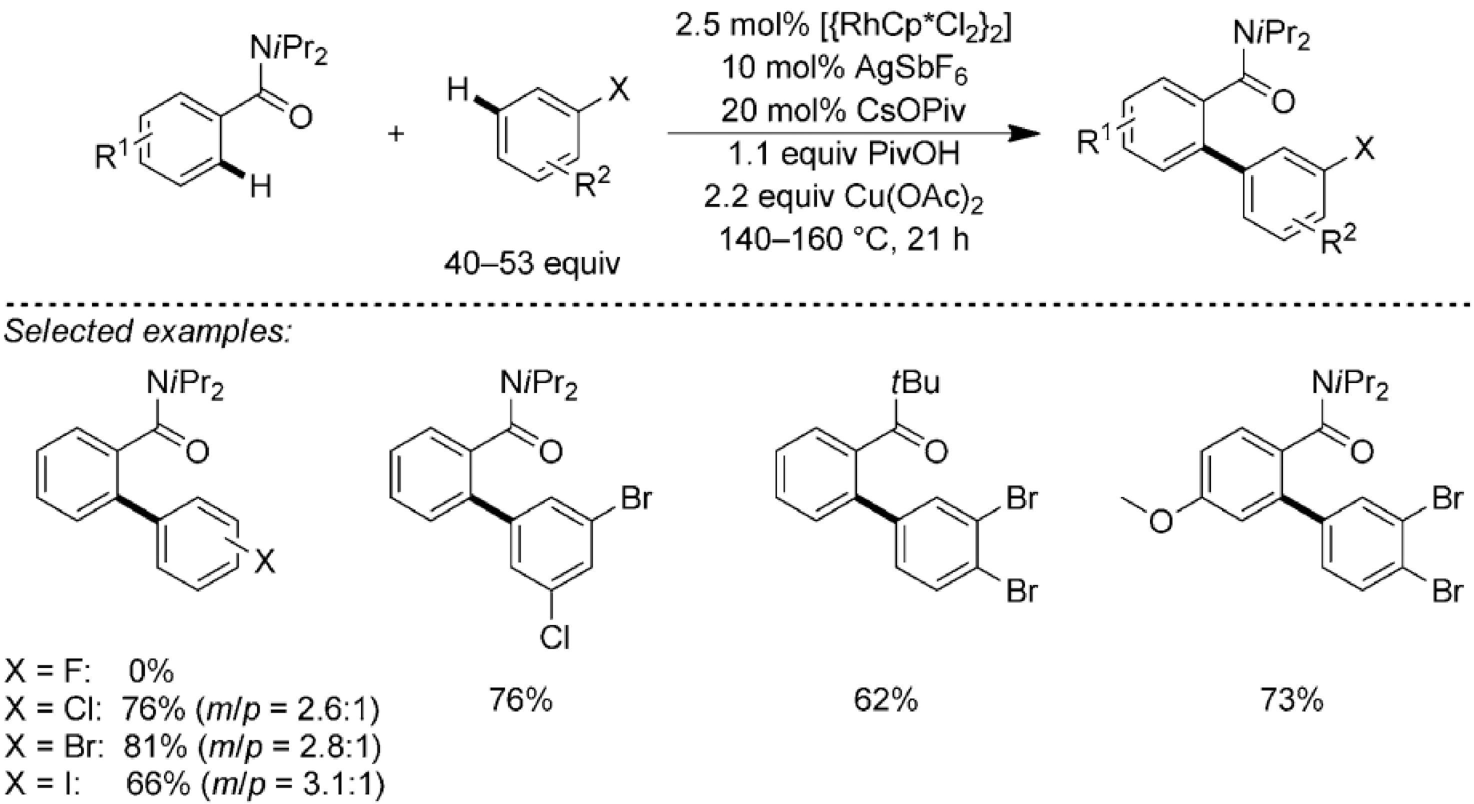




X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864
K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 1478

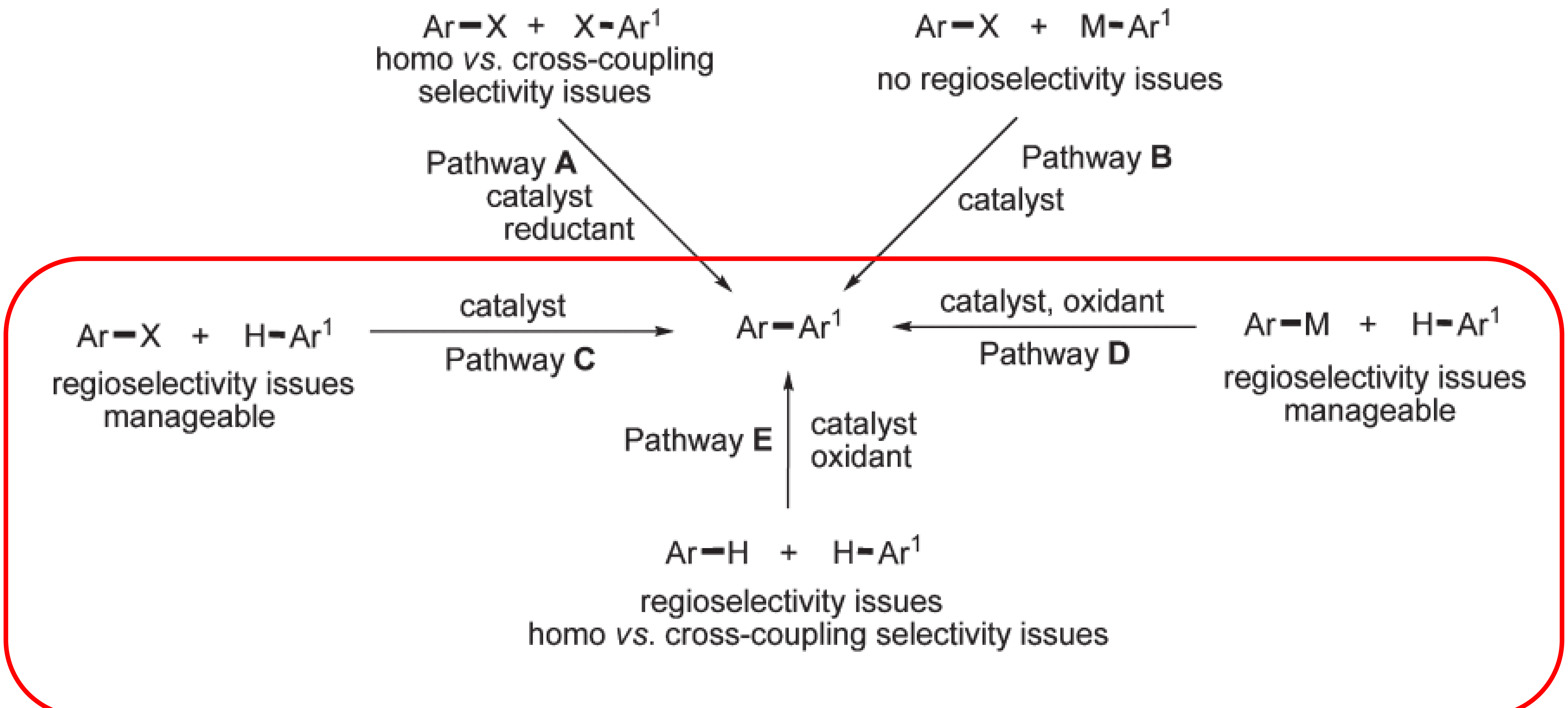


Chelate-Assisted Cross-Dehydrogenative Couplings



J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 2247
J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Chem. Asian J.* **2012**, *7*, 1208

Biaryl Formation

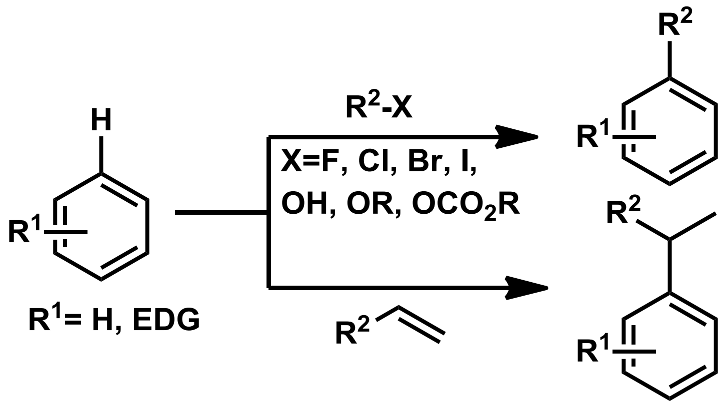


X = halogen, OSO_2R; M = SnR_3, $B(OR)_2$, CO_2H, etc.

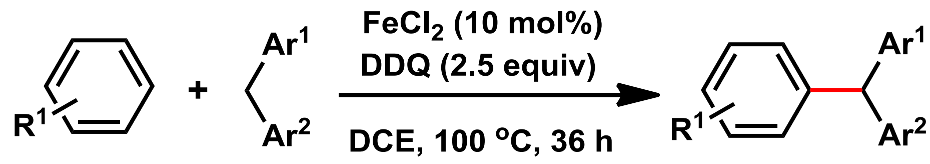
C-C Bond Formation:

Alkylation of Simple Arenes

Friedel-Crafts Alkylation:

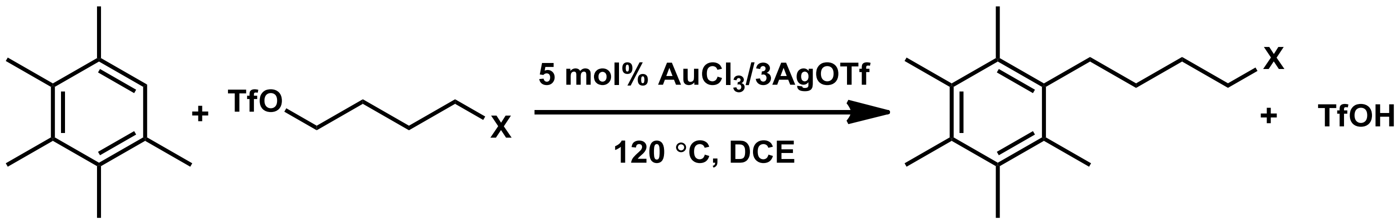


Dehydrogenative Coupling:



Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2009**, *48*, 3817.

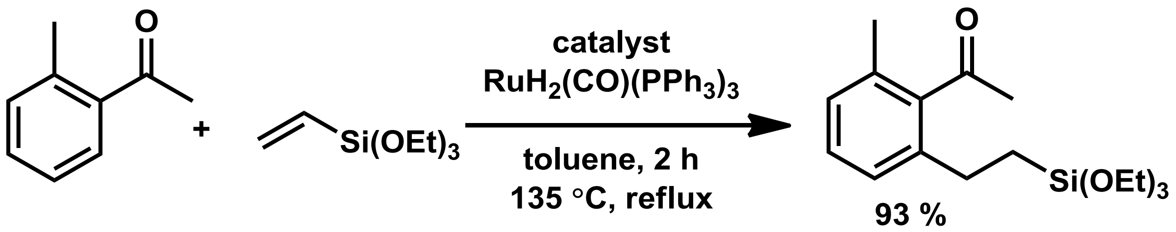
Direct Alkylation



Z.-J. Shi, C. He, *J. Am. Chem. Soc.* **2004**, *126*, 13596

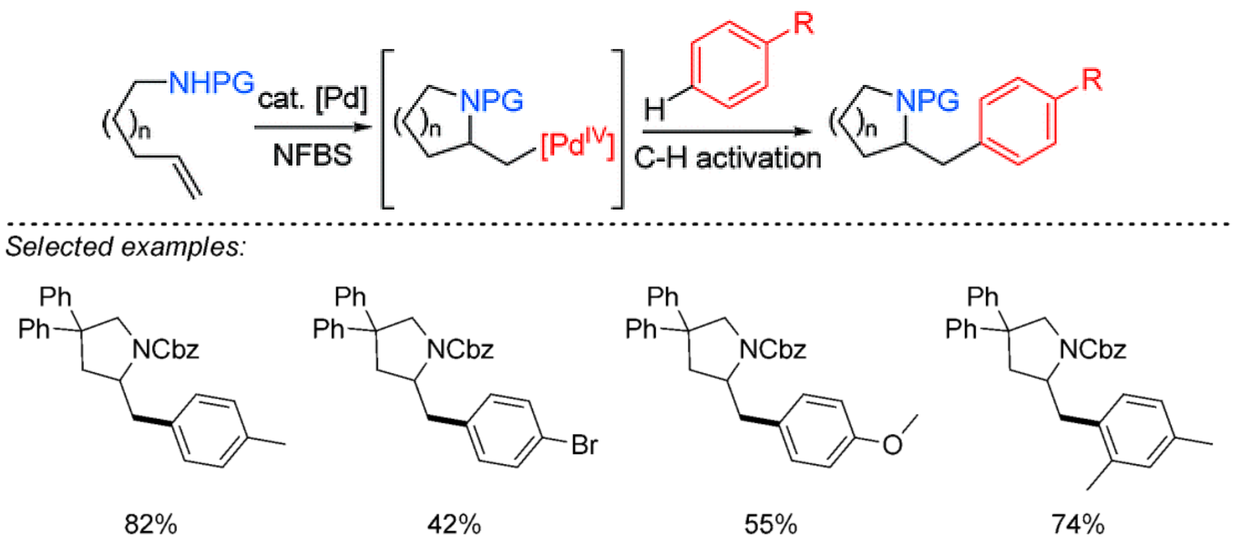
Alkylation of Simple Arenes

Olefin Hydroarylation:



S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529

Carboamination of Olefin

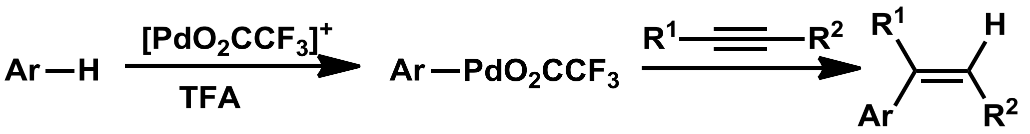


C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488

C-C Bond Formation:

Alkenylation of Simple Arenes

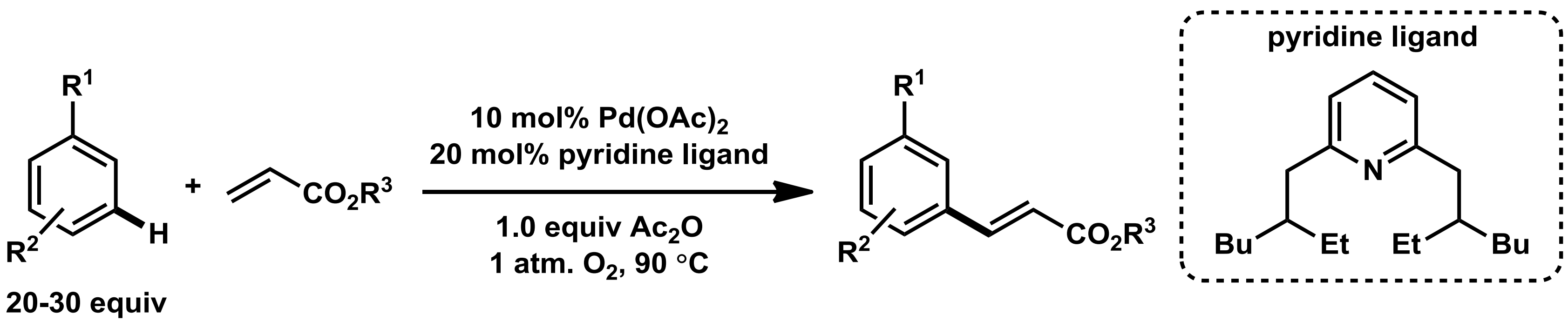
Hydroarylation of Alkyne:



C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992

Other metal: Ni, Rh, Fe, Au, etc

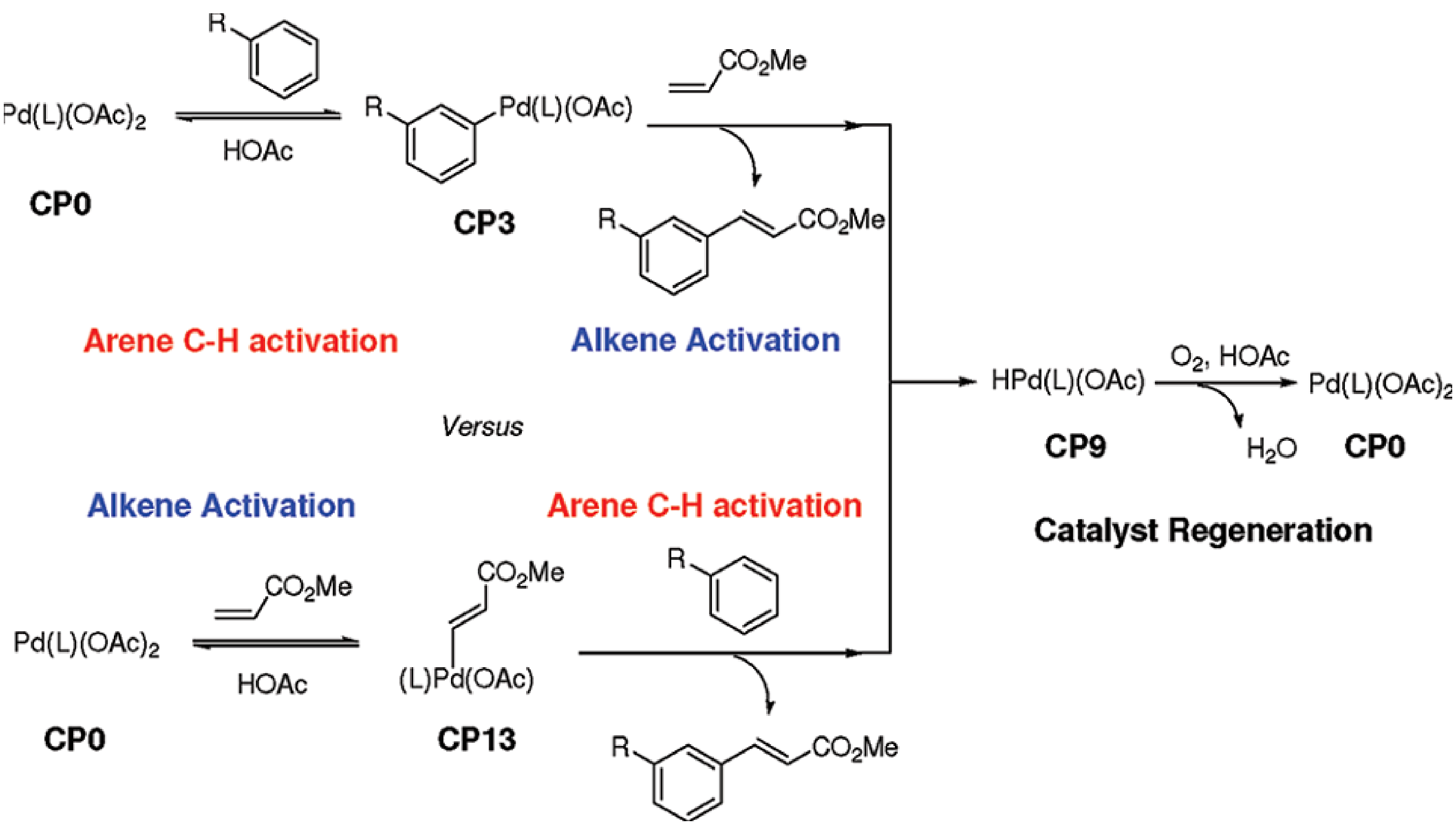
Oxidative Heck Reaction:



Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072

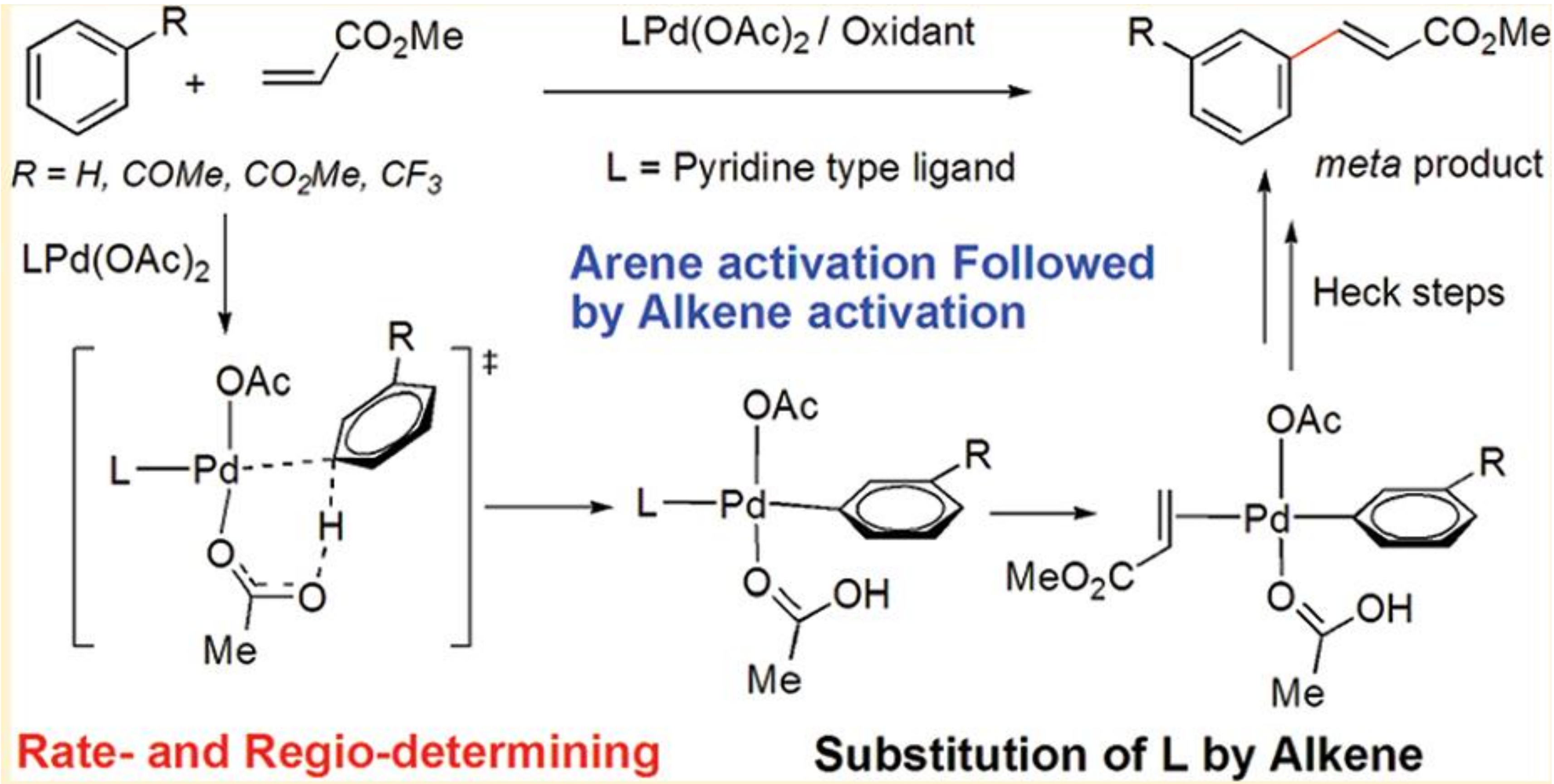
Alkenylation of Simple Arenes

Pathways of Oxidative Heck Reaction:



Alkenylation of Simple Arenes

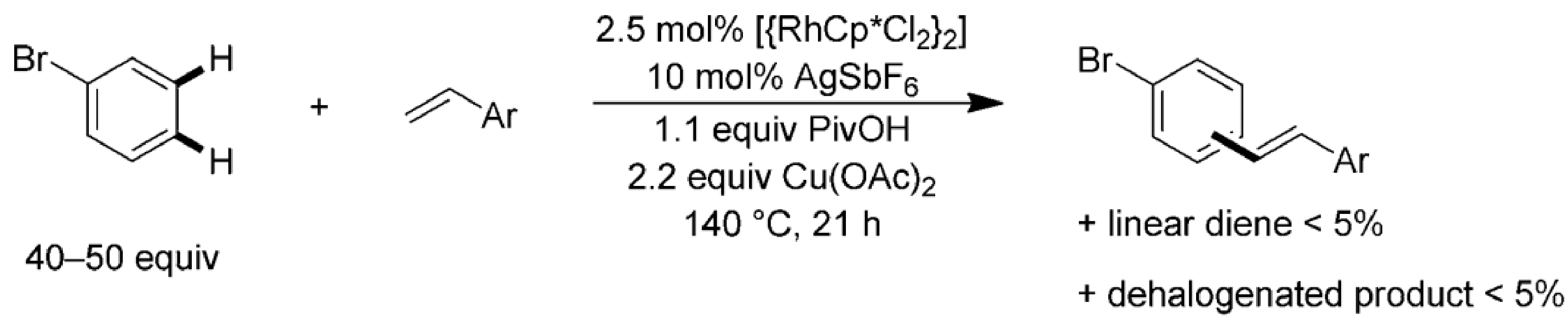
Oxidative Heck Reaction:



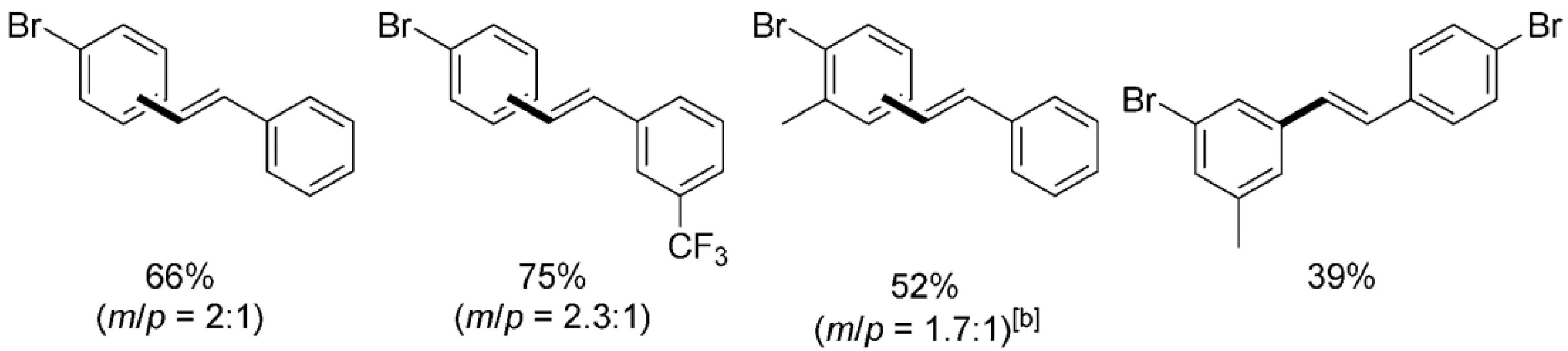
Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072
S. Zhang, L. Shi, Y. Ding, *J. Am. Chem. Soc.* **2011**, *133* , 20218

Alkenylation of Simple Arenes

Oxidative Heck Reaction:



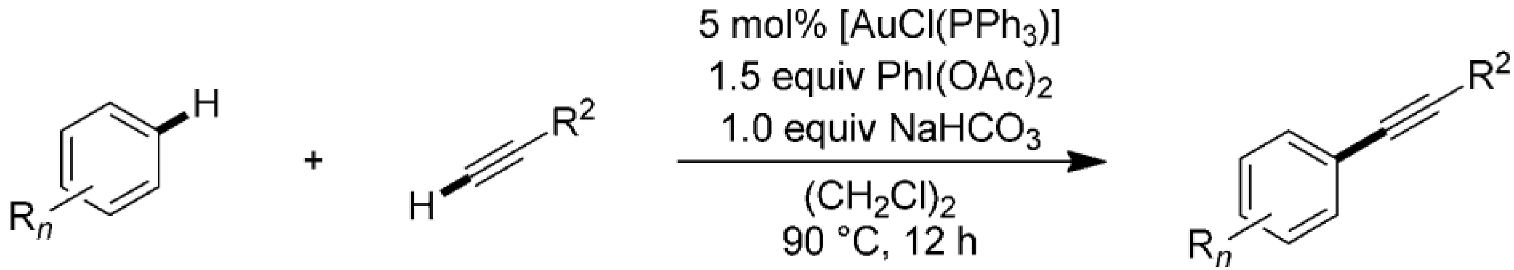
Selected examples:[a]



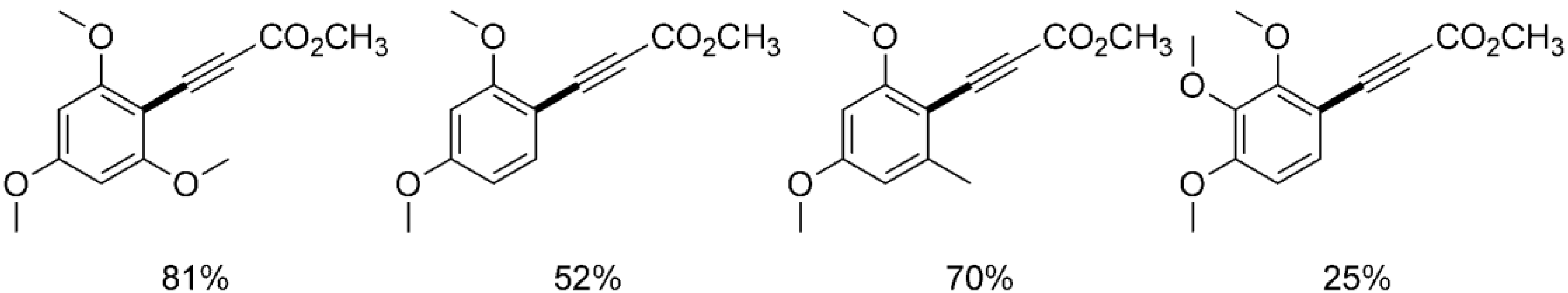
F. W. Patureau, C. Nimphius, F. Glorius, *Org. Lett.* **2011**, *13*, 6346

C-C Bond Formation:

Alkynylation of Simple Arenes



Selected examples:



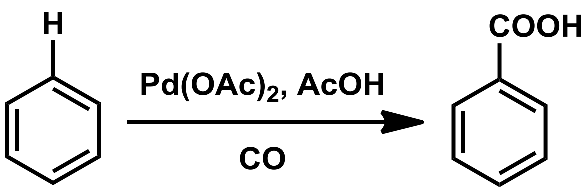
Regioselectivity is controlled by ***mesomeric*** *and* ***inductive effects***

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

C-C Bond Formation:

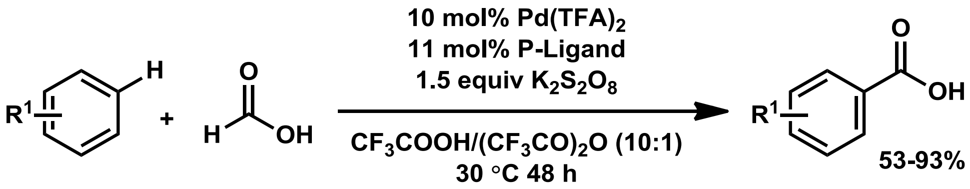
Carboxylation of Simple Arenes

Reaction with CO:



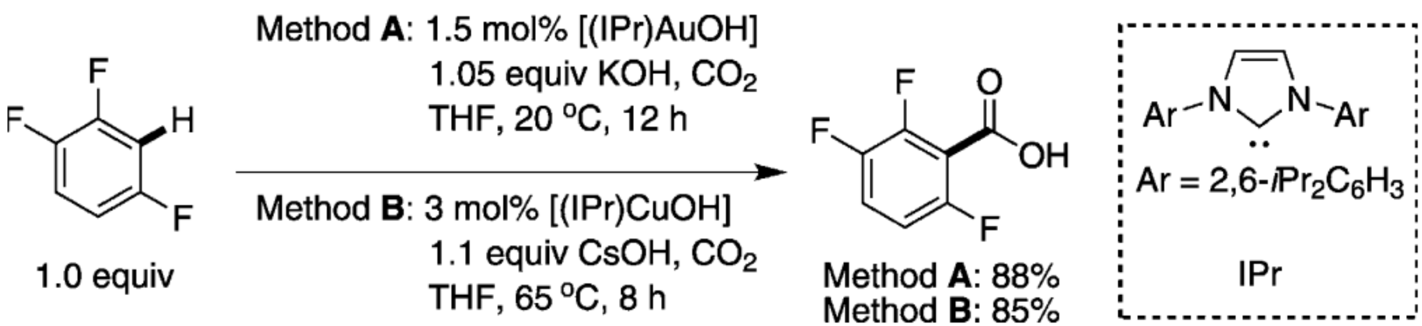
Y. Fujiwara, T. Kawauchi, H. Taniguchi,
J. Chem. Soc. Chem. Commun. **1980**, 220

Reaction with Formic Acid:



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

Reaction with CO2:

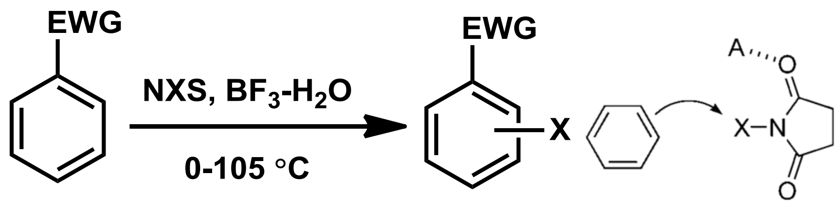


I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858

C-Heteroatom Bond Formation:

C-Halogen Bond Formation

Electrophilic Aromatic Halogenation



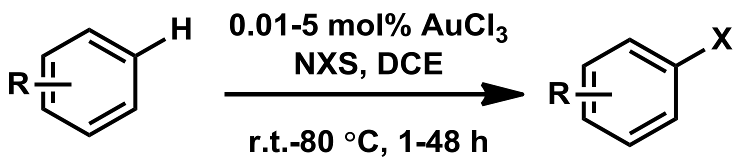
X= Cl, Br or I

Selectivity:

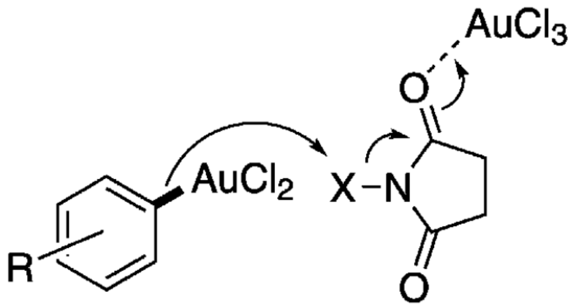
- *strong BrΦnsted or Lewis acid*
- *high temperature*
- *catalyst loadings*

G. K. S. Prakash, T. Mathew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul, G. A. Olah, *J. Am. Chem. Soc.* **2004**, *126*, 15770

Gold(III) as Catalyst



Proposed mechanism

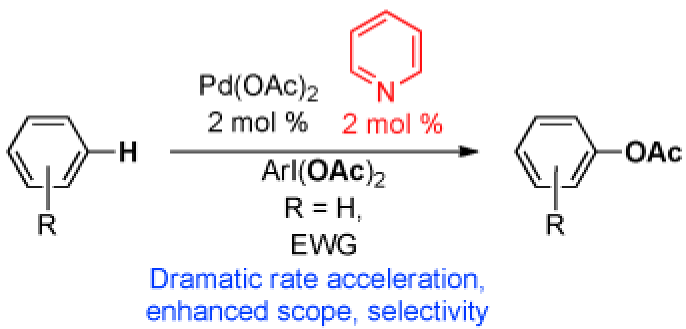


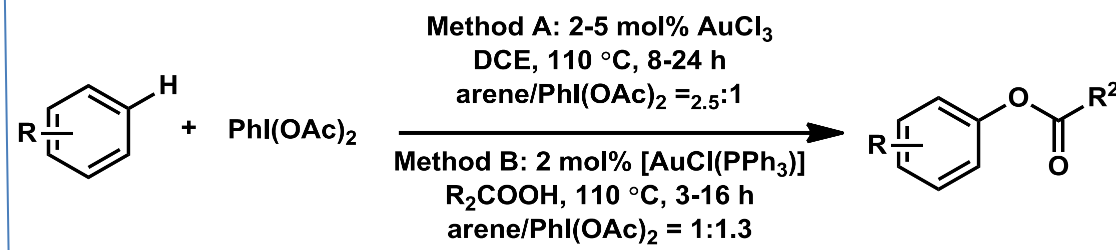
F. Mo, J. M. Yan, D. Qiu, F. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 2028

C-Heteroatom Bond Formation:

C-O Bond Formation

Acetoxylation



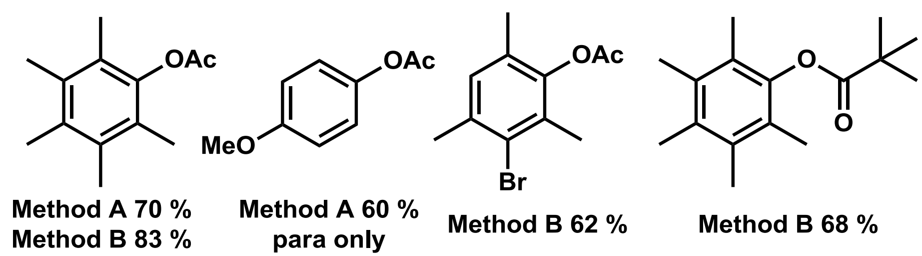


Key:

- The equivalent of pyridine:

In situ formation of $[(py)Pd^{II}(OAc)_2]$, improve regioselectivity

- The nature of the hypervalent iodine



M. H. Emmert, A. K. Cook, Y. J. Xie, M. S. Sanford, *Angew. Chem. Int. Ed.* **2011**, *50*, 9409

D. Qiu, Z. Zheng, F. Mo, Q. Xiao, Y. Tian, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 4988

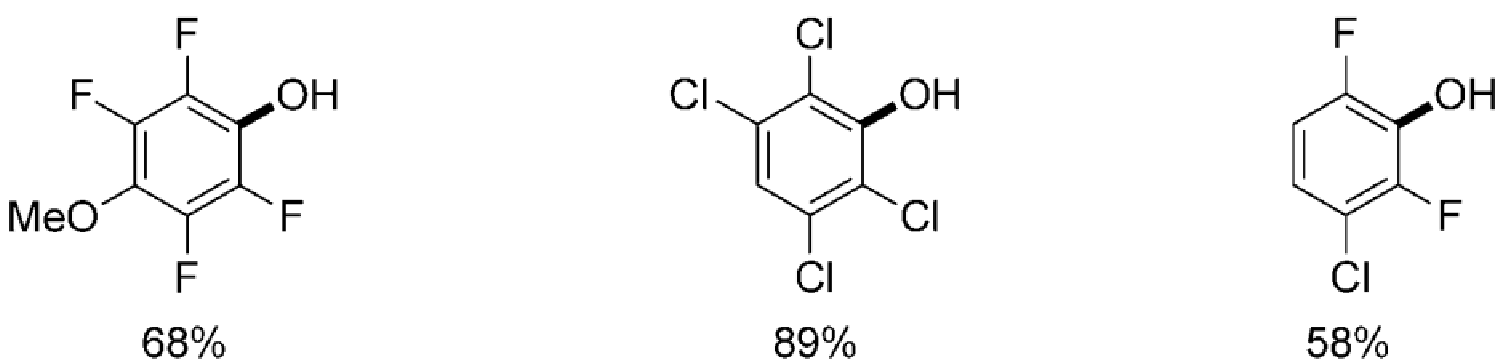
A. Pradal, P. Y. Toullec, V. Michelet,

B. *Org. Lett.* **2011**, *13*, 6086

C-O Bond Formation

Hydroxylation

Selected examples:

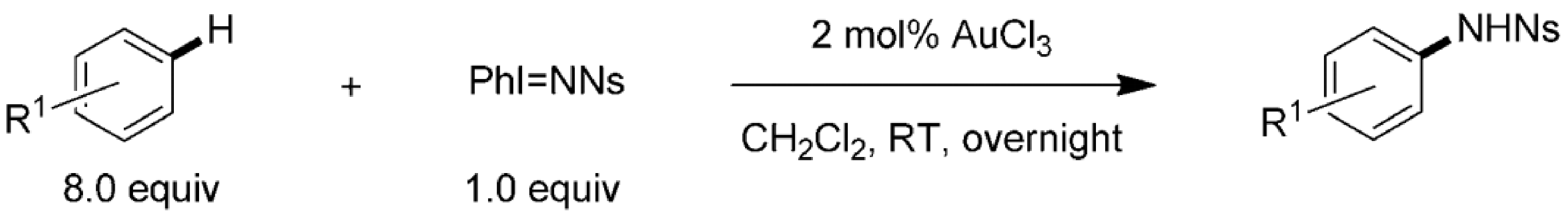


Q. Liu, P. Wu, Y. Yang, Z. Zeng, J. Liu, H. Yi, A. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 4666

C-Heteroatom Bond Formation:

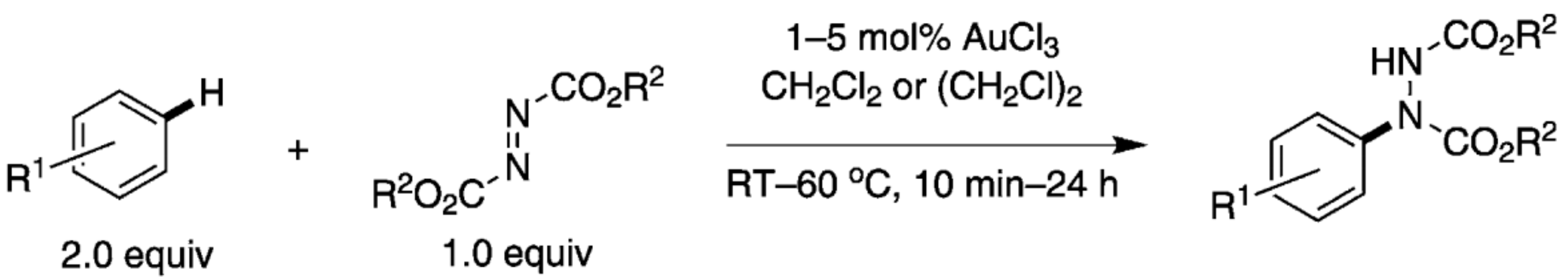
C-N Bond Formation

PhI=NNs as N source



Z. Li, D. A. Capretto, R. O. Rahaman, C. He, *J. Am. Chem. Soc.* **2007**, *129*, 12058

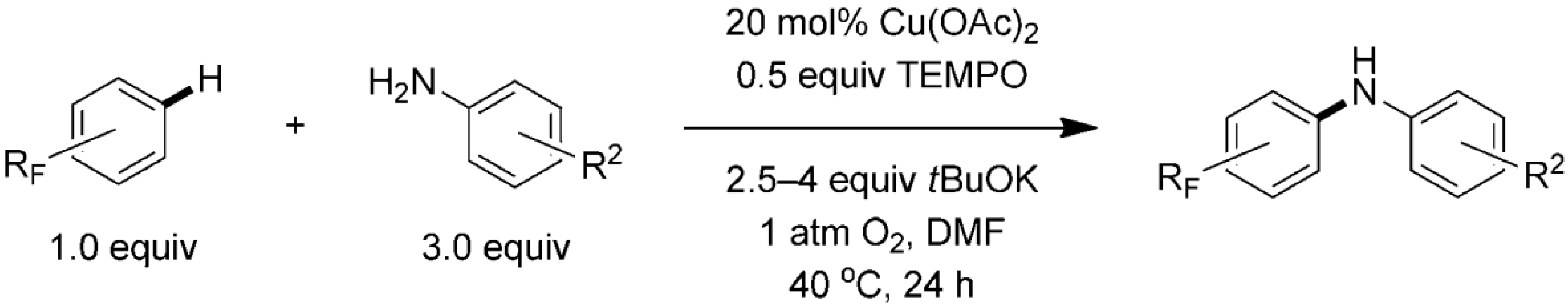
Azodicarboxylates as N source



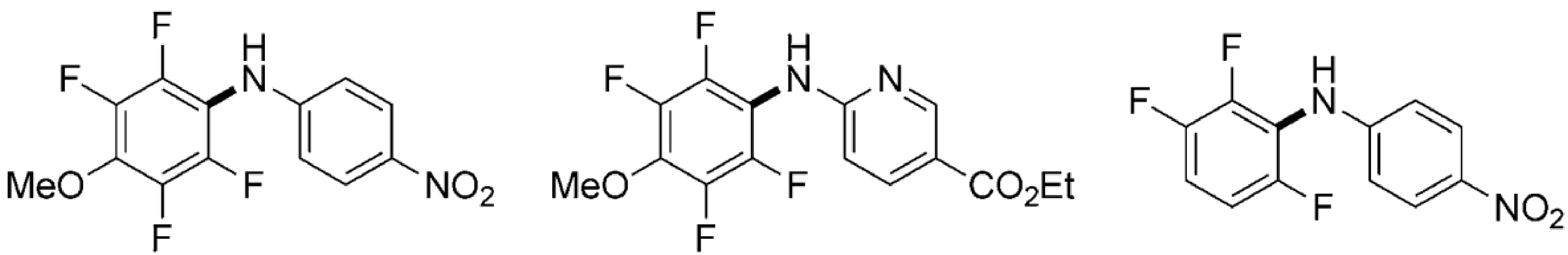
L. Gu, B. S. Neo, Y. Zhang, *Org. Lett.* **2011**, *13*, 1872

C-N Bond Formation

Simple Amine as N Source



Selected examples:



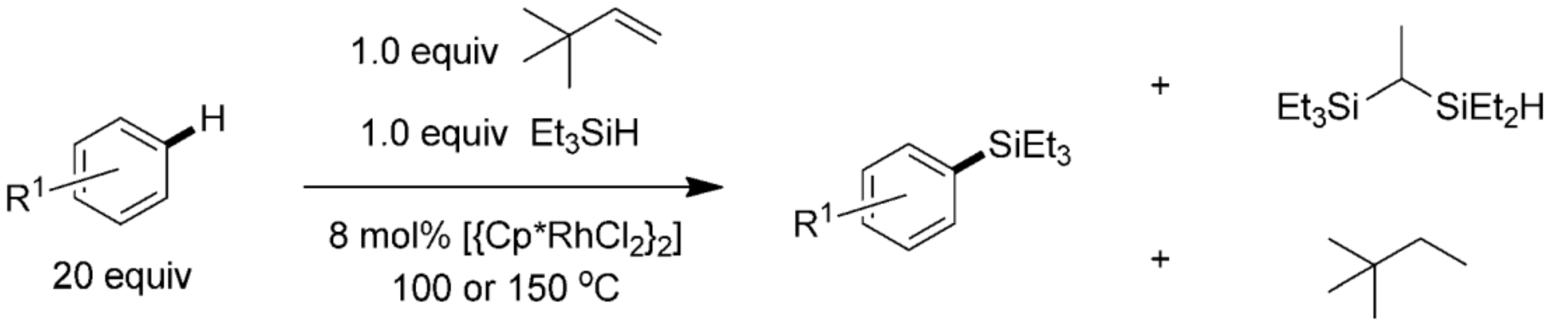
83% 34% 35%
single regioisomer

H. Zhao, M. Wang, W. Su, M. Hong, *Adv. Synth. Catal.* **2010**, *352*, 1301

C-Heteroatom Bond Formation:

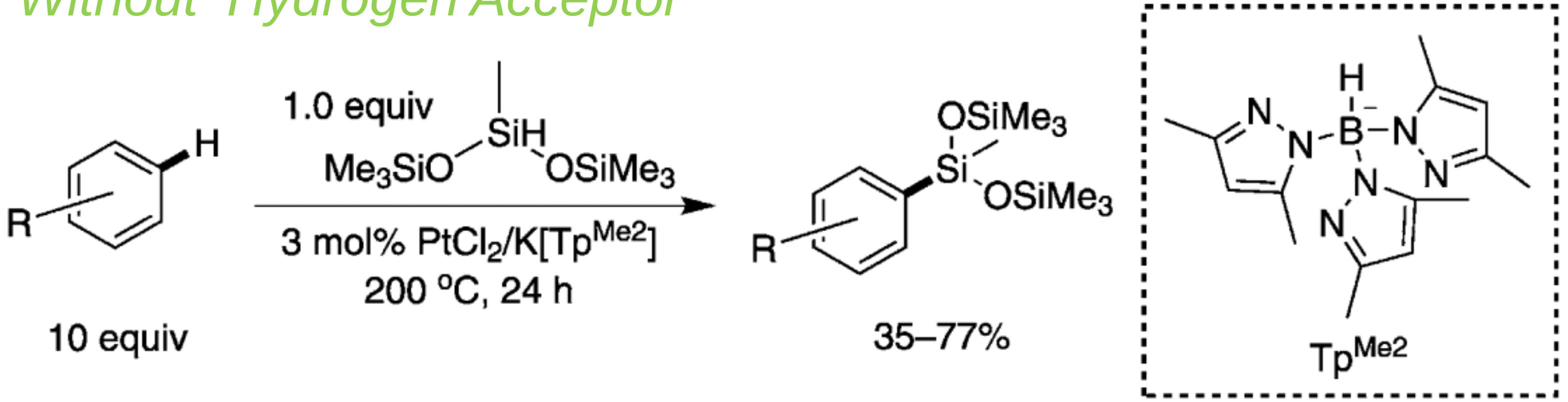
C-Si Bond Formation

Hydrogen Acceptor needed



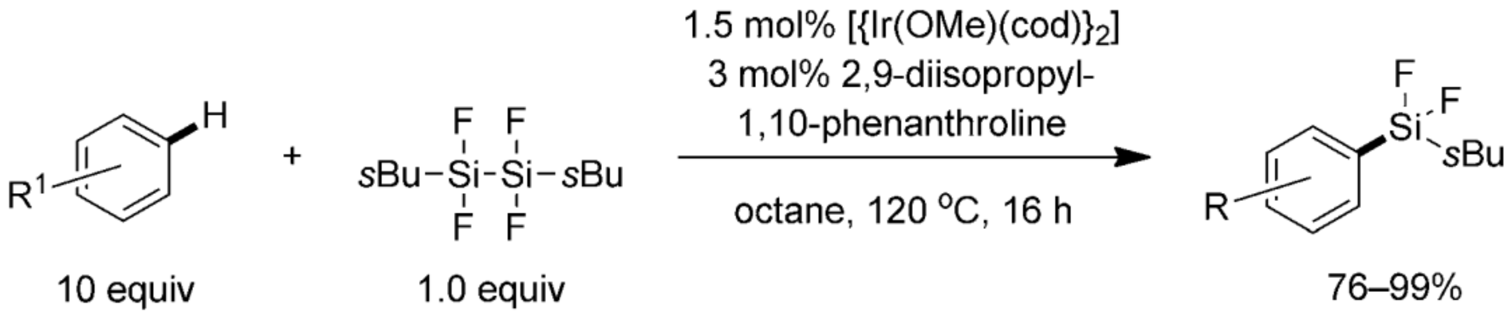
K. Ezbiansky, P. I. Djurovich, M. LaForest, D. J. Sinning, R. Zayes, D. H.Berry, *Organometallics* **1998**, *17*,1455

Without Hydrogen Acceptor

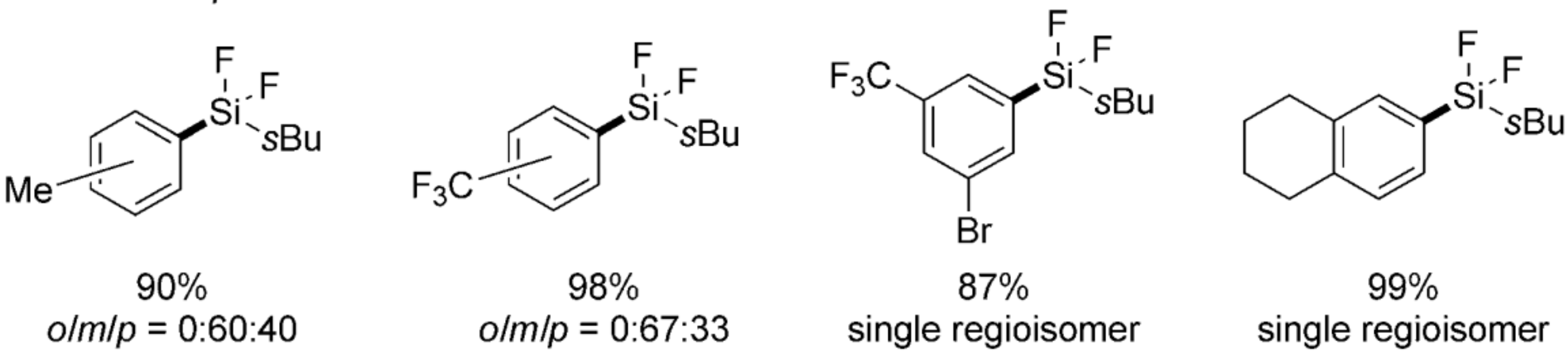


M. Murata, N. Fukuyama, J. Wada, S. Watanabe, Y. Masuda, *Chem. Lett.* **2007**, *36*, 910

C-Si Bond Formation



Selected examples:



T. Saiki, Y. Nishio, T. Ishiyama, N. Miyaura,*Organometallics* **2006**, *25*, 6068

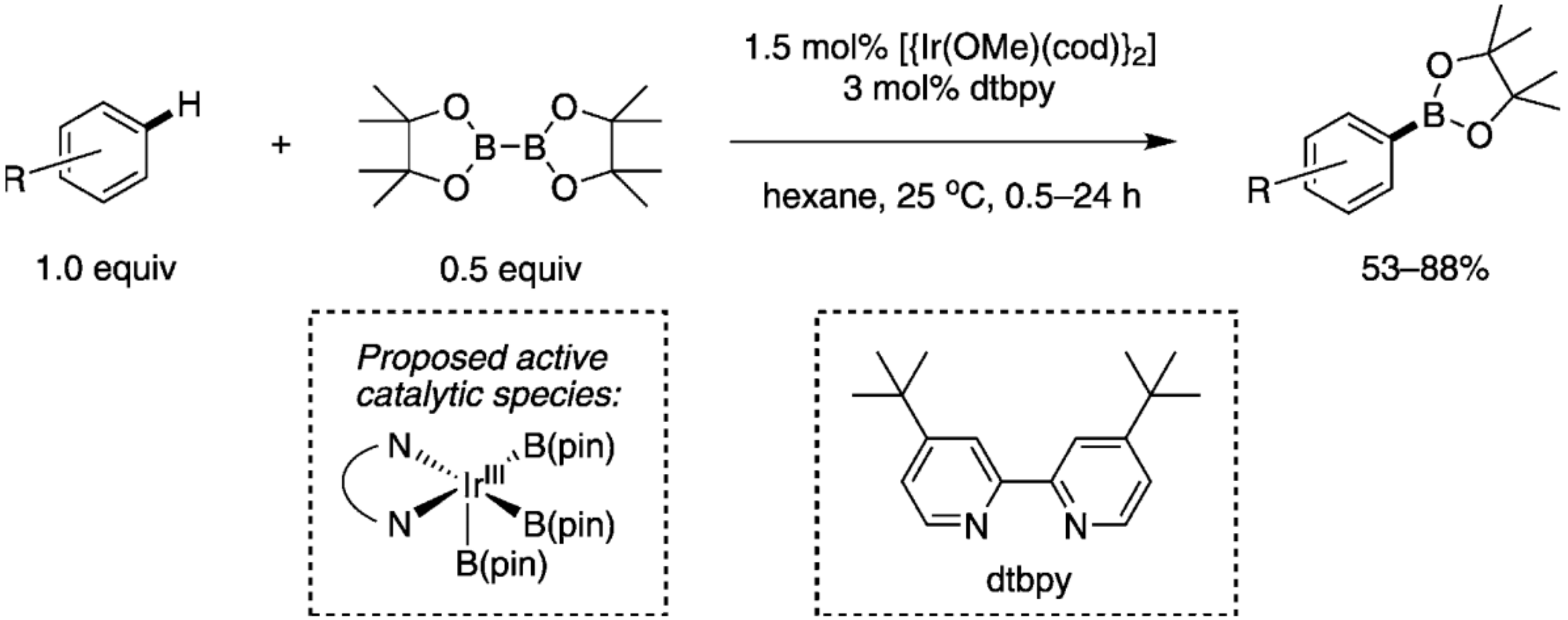
C-Heteroatom Bond Formation:

C-B Bond Formation

General Catalyst: *Rhodium, Iridium (Cp*Ir, Ir^{I} dimer ($[Ir(OMe)(cod)]_2$/dtppy)*

Borylating Reagent: *HB(pin) or $B_2(pin)_2$ (pin=pinacol)*

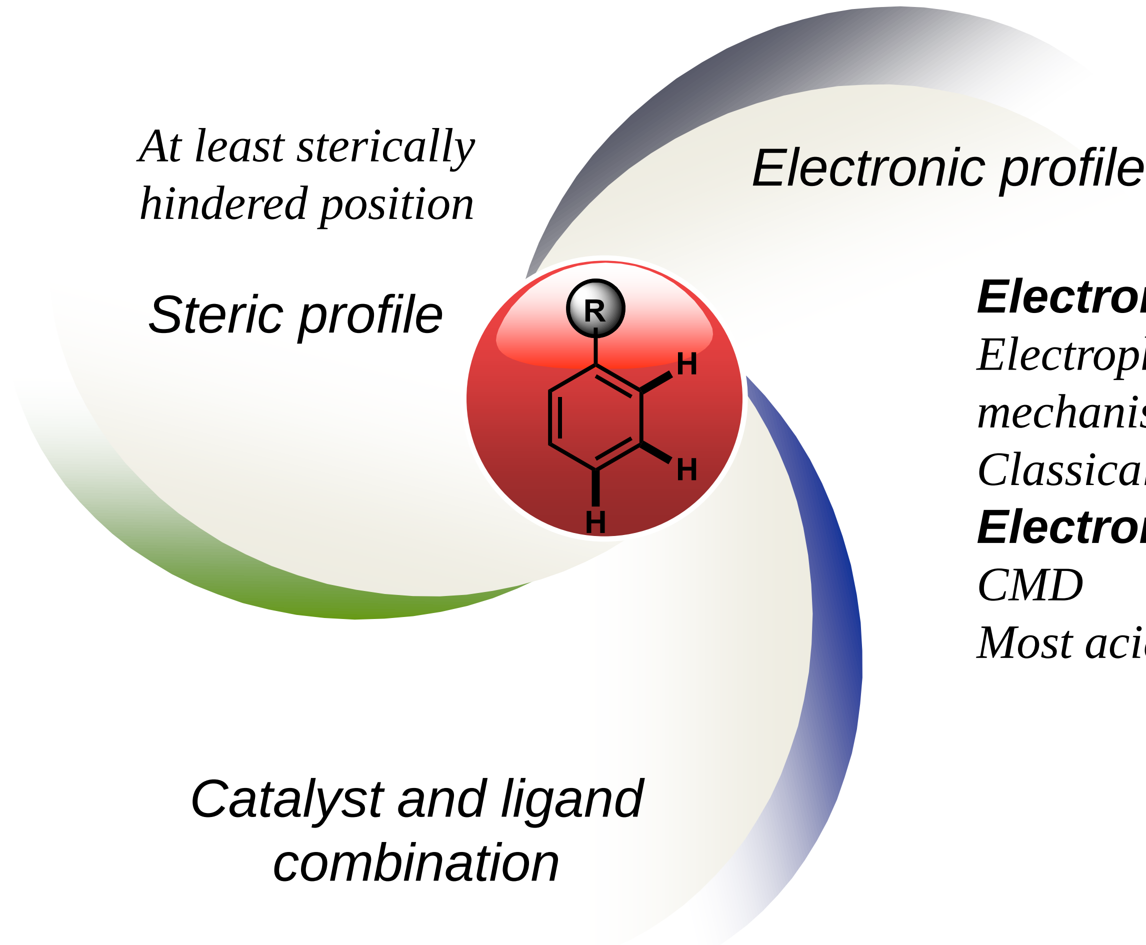
Regioselectivity: *steric effect*



T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390

Conclusion:

At least sterically hindered position



Electron-rich:
Electrophilic metalation mechanism
Classical Friedel-Crafts type
Electron-poor:
CMD
Most acidic position

Acknowledgement:

- *Prof. Yong Huang*
- *Cheng-Ming Wang*
- *All members here*