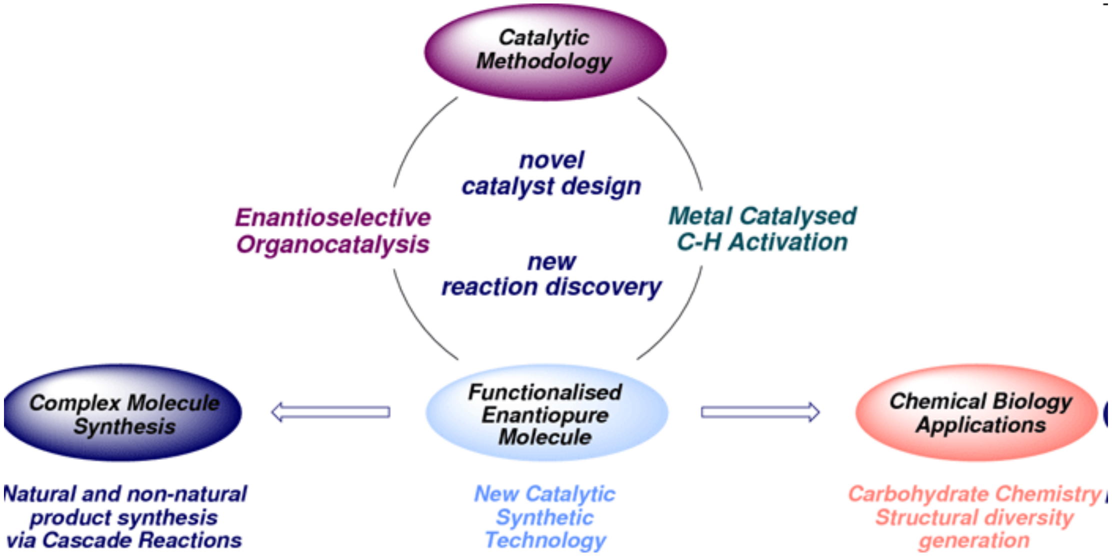
A Meta Selective Copper-Catalyzed C-H Bond Arylation

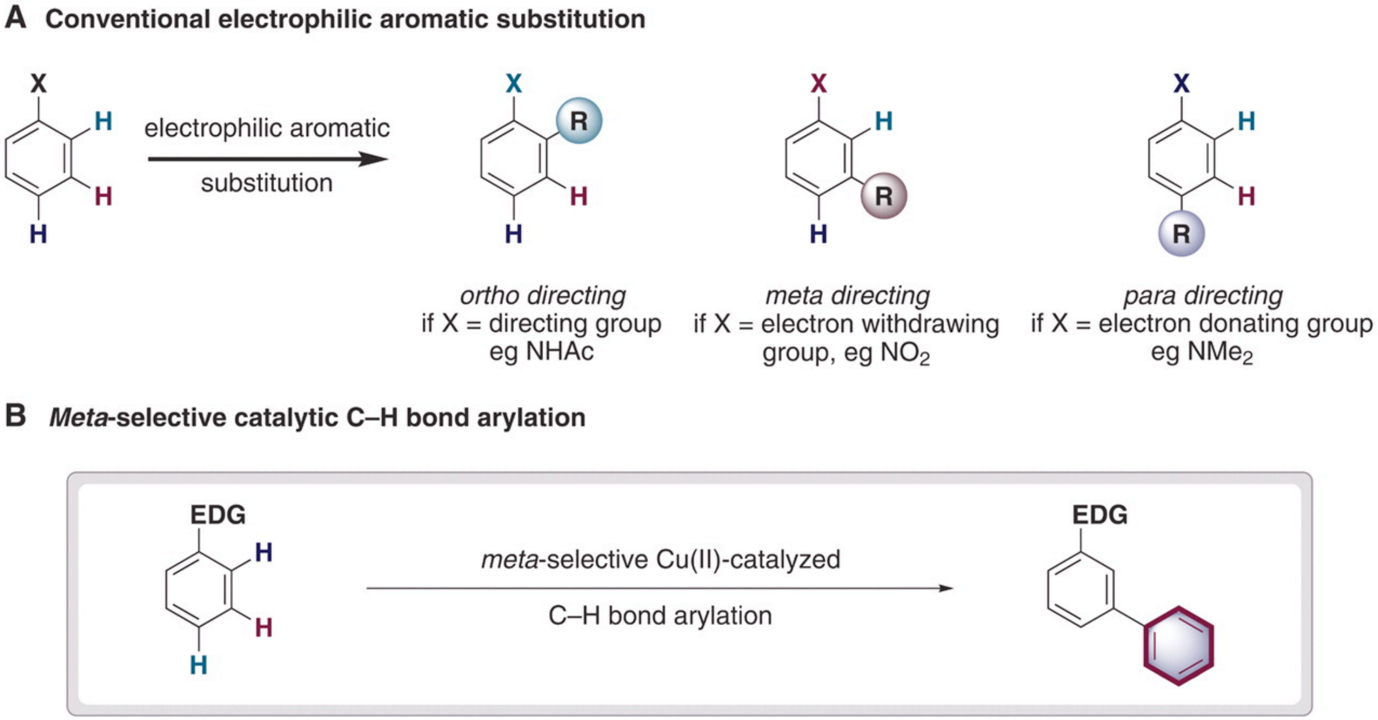
Robert J. Phipps and Matthew J. Gaunt
Science **2009**, *323*, 1593.



Marija Manojlović

Wipf Group Current Literature Meeting
4-11-09

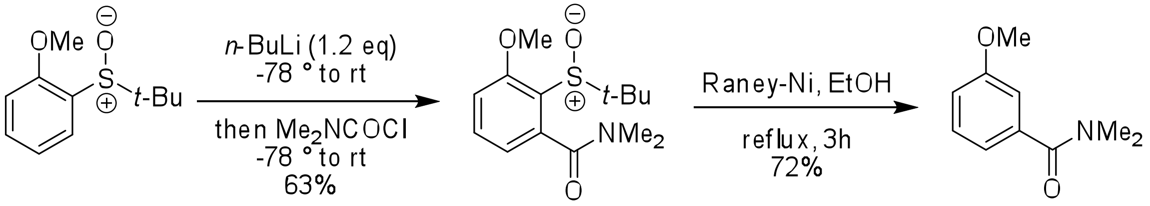
Electrophillic Aromatic Substitution



Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

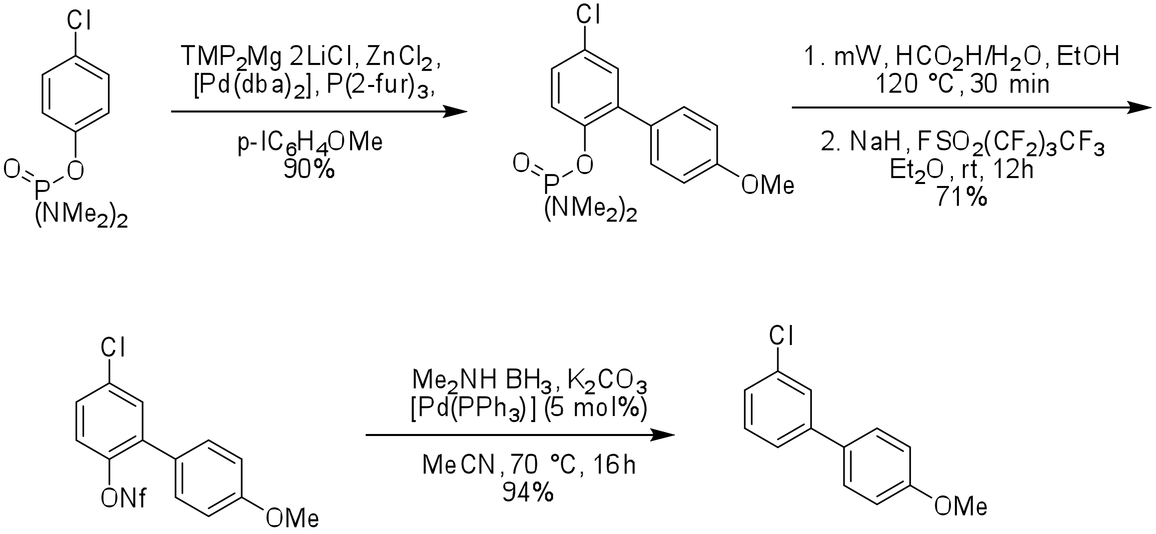
Indirect meta-substitution

Sulfoxide as a relay:



Brown, J. M. *et al. Org. Biomol. Chem.* **2008**, *6*, 1215.

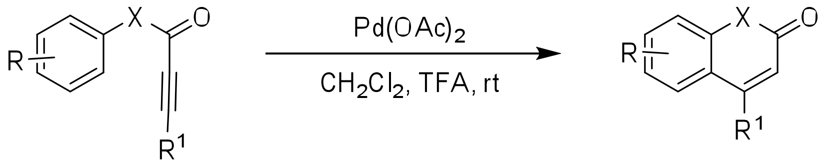
Metallation using TMP_2Mg 2LiCl:



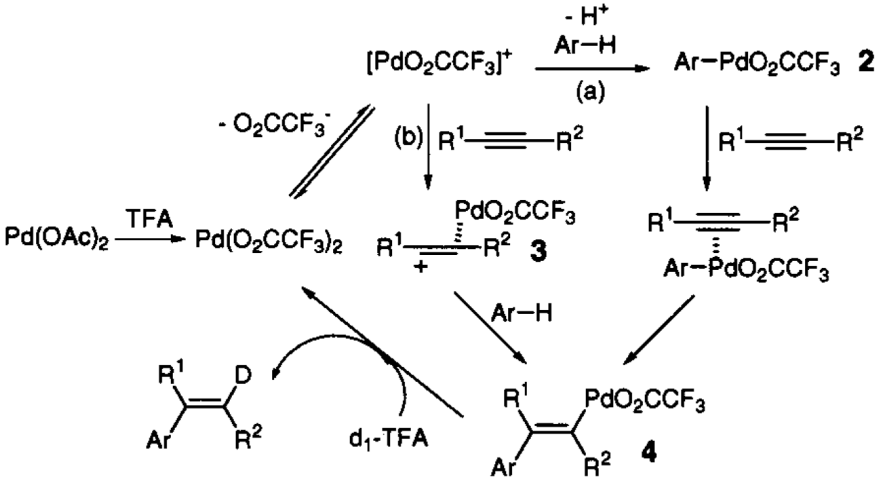
Knochel, P. *et al. ACIE* **2008**, *47*, 1503.

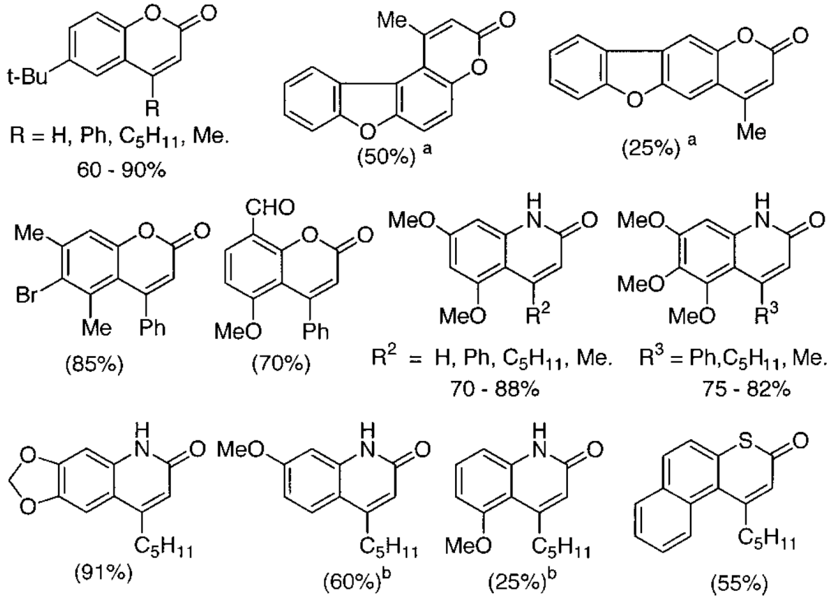
Mechanism of C-H Activation
EAS on e$^-$-rich arenes

Pd-catalyzed hydroarylation:



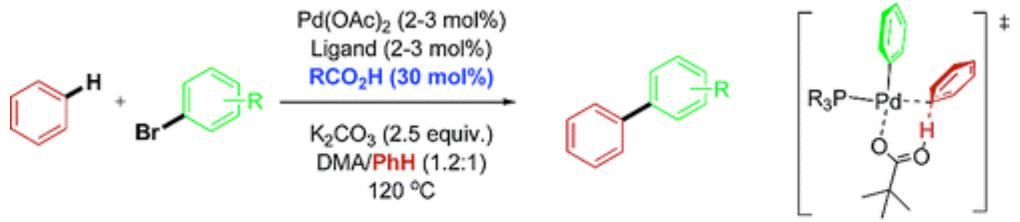
X = O, NH, S
50-91 % yield



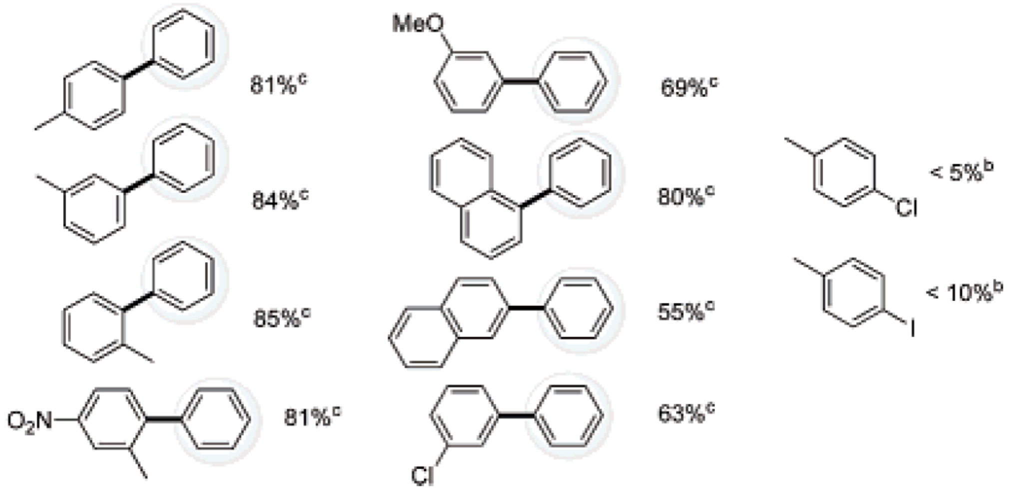


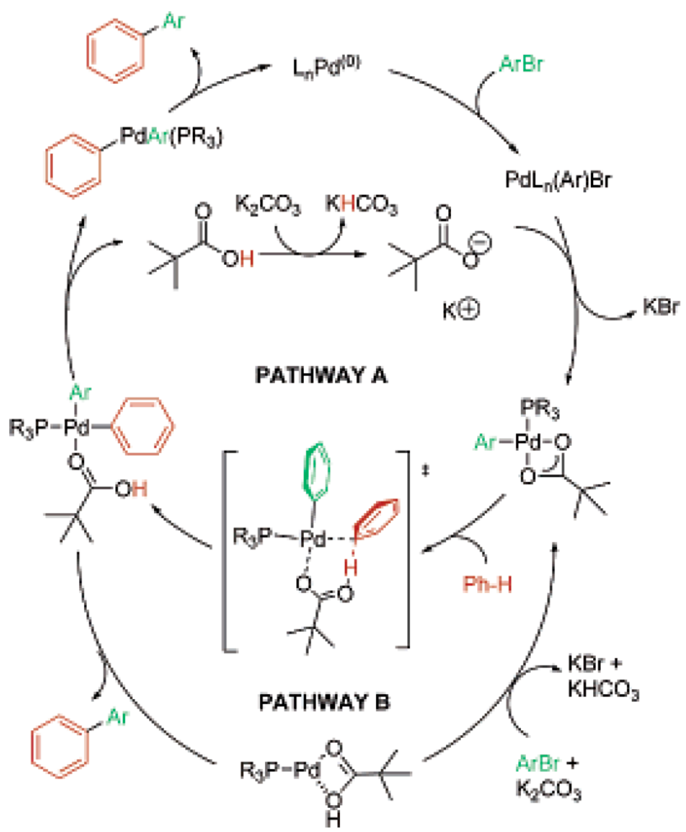
Fujiwara, Y. *et al. Acc. Chem. Res.*, **2001**, *34*, 633.

Mechanism of C-H Activation
Concerted metallation-deprotonation on e$^-$-poor and neutral arenes



- *Direct Arylation of an Unfunctionalized Arene*
- *Unprecedented Reactivity from a Palladium-Pivalic Acid Co-Catalyst System*
- *Pivalic Acid as a Catalytic Proton Shuttle and a Key Element in Catalyst Design*

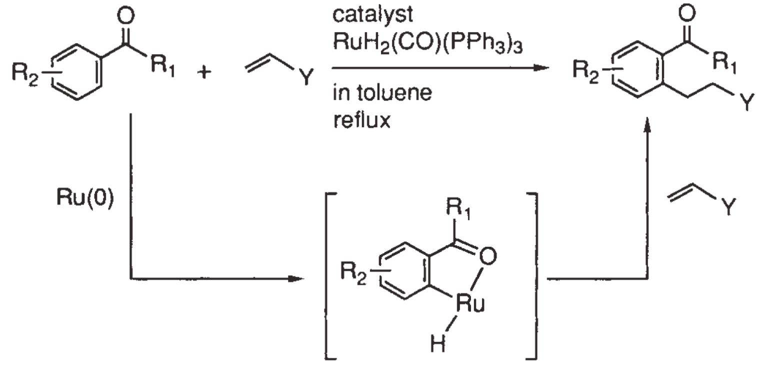


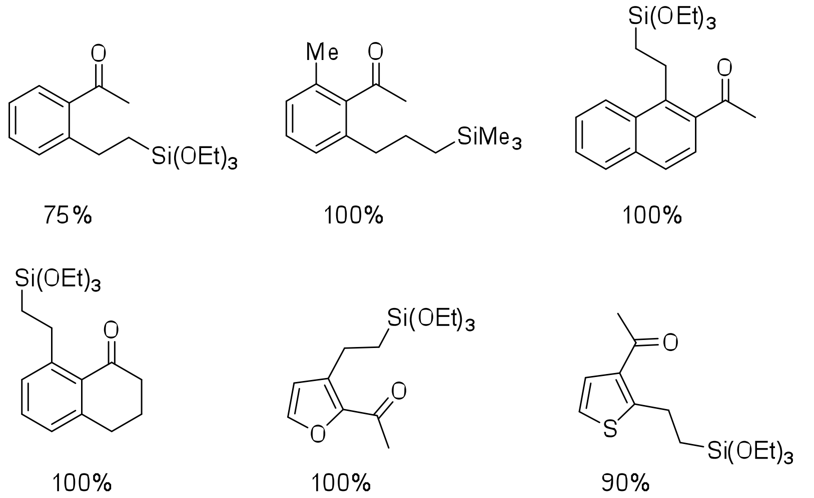


Fagnou, K.; Lafrance, M. *JACS* **2006**, *128*, 16496.

Mechanism of C-H Activation
Directed cyclometallation

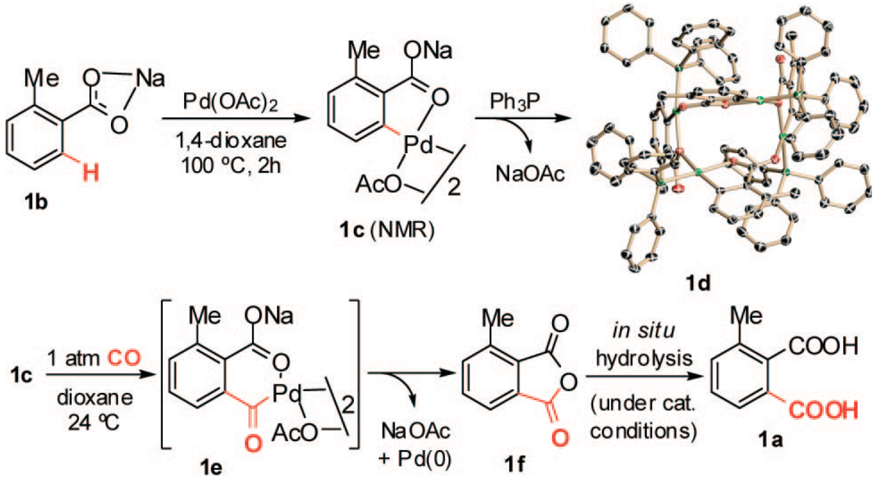
Ketone directed cyclometallations:

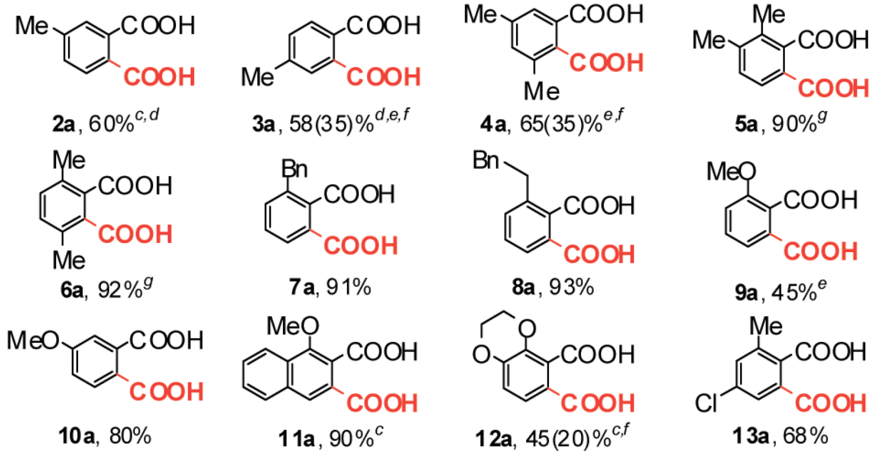




Chatani N. *et. Al. Nature* **1993**, *366*, 529.

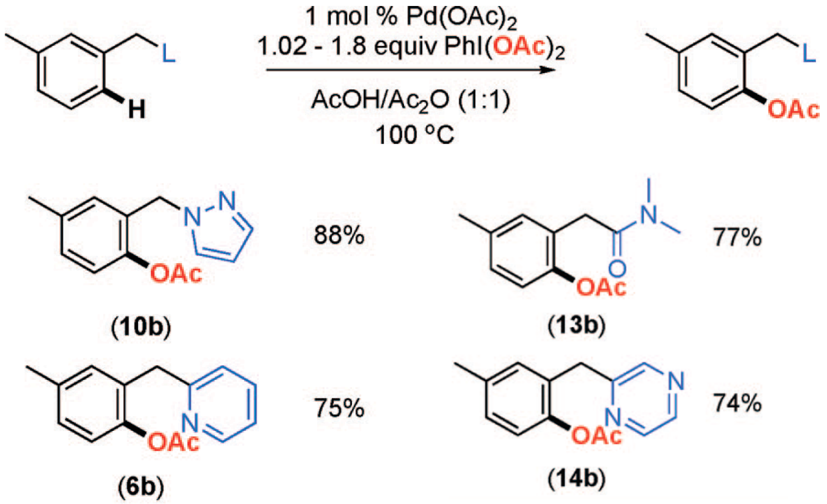
Carboxilate directed cyclometallations:

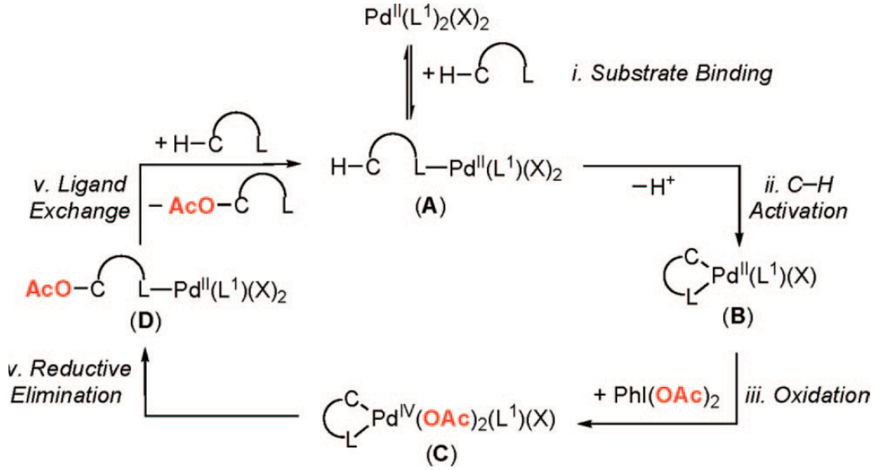




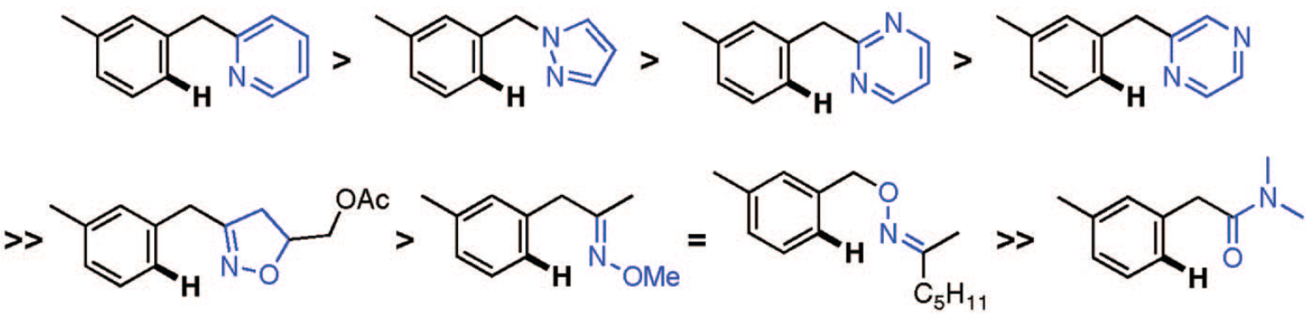
Giri, R.; Yu, J.-Q. *JACS* **2008**, *130*, 14082.

Mechanism of C-H Activation
Directed cyclometallation



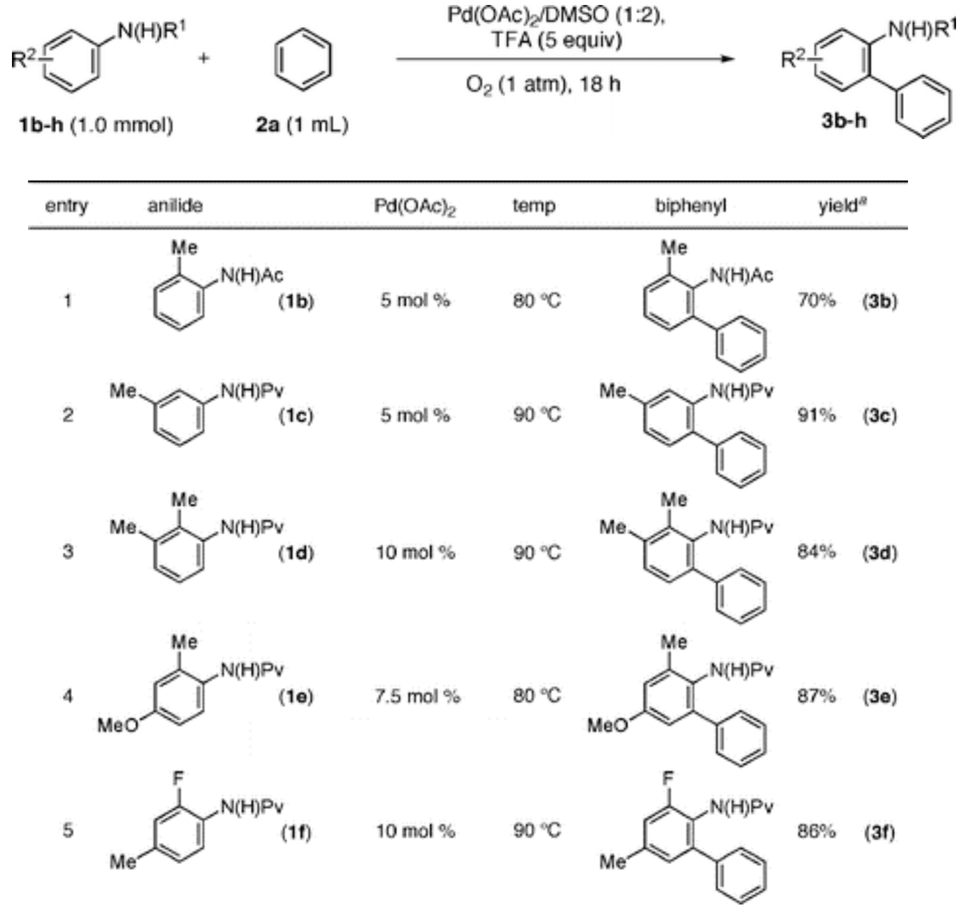


Trend in AcOH/Ac_2O

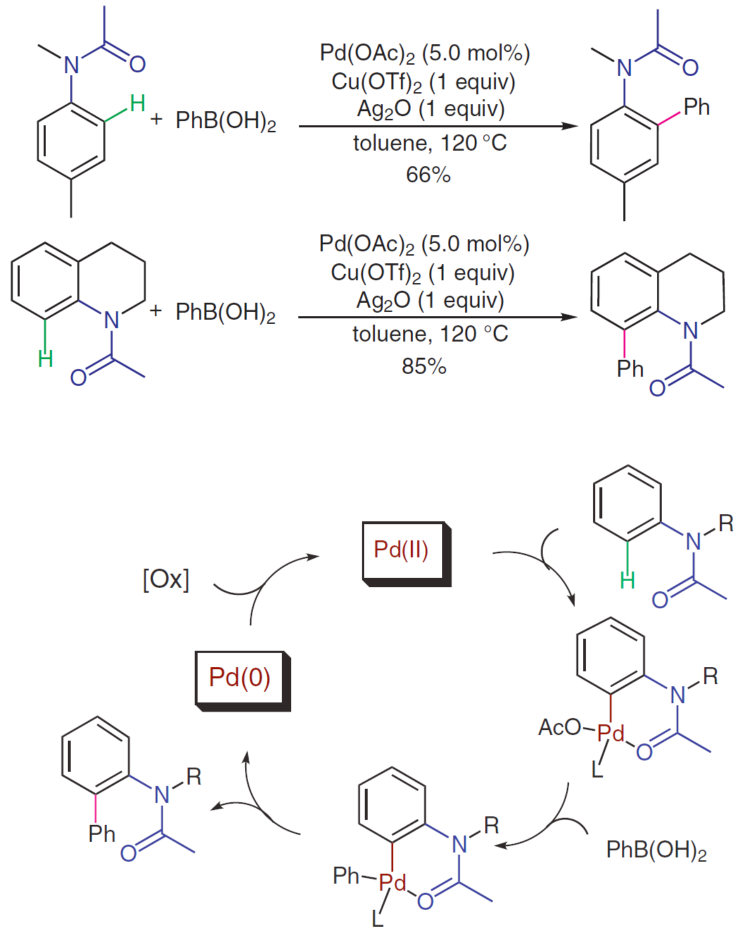


Sanford, M. S. *et al. JACS* **2008**, *130*, 13285.

Mechanism of C-H Activation
Acetanilide directed cyclometallations



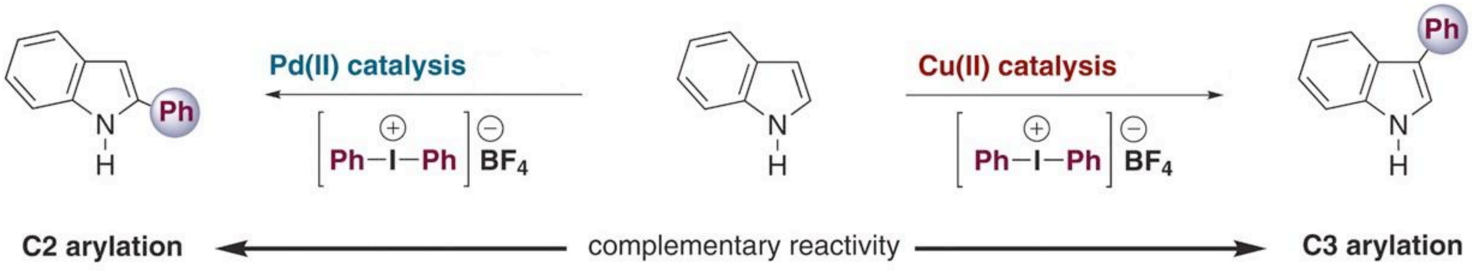
entry	anilide	Pd(OAc)$_2$	temp	biphenyl	yield^a
1	(1b)	5 mol %	80 °C	(3b)	70%
2	(1c)	5 mol %	90 °C	(3c)	91%
3	(1d)	10 mol %	90 °C	(3d)	84%
4	(1e)	7.5 mol %	80 °C	(3e)	87%
5	(1f)	10 mol %	90 °C	(3f)	86%

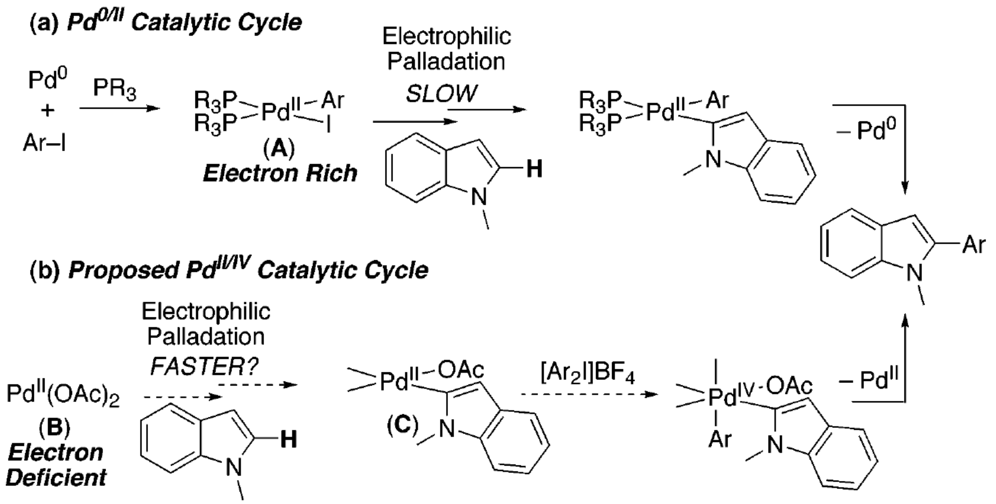


Buchwald, S. L. *et al. OL* **2008**, *10*, 2207.

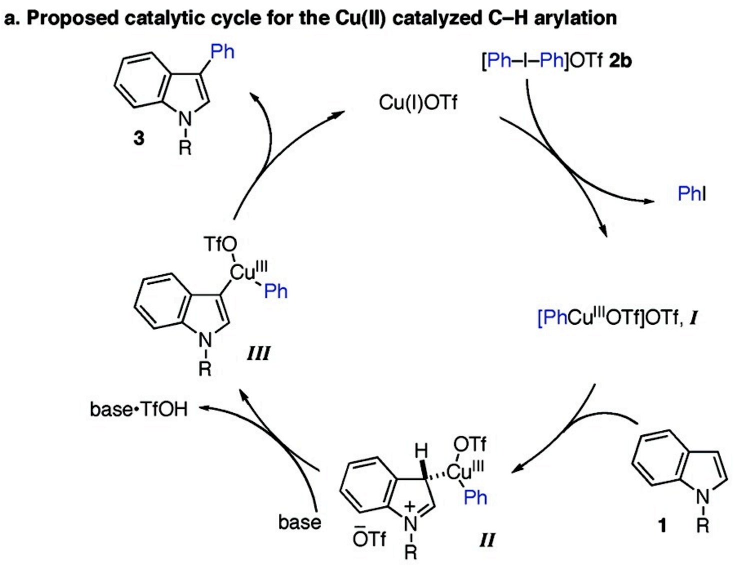
Shu, Z.-J. *et al. Synlett* **2008**, 949.

Arylation of Indoles



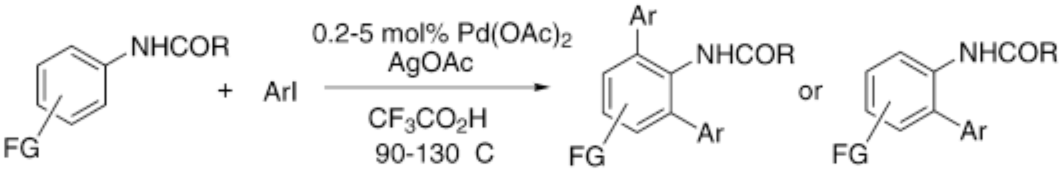


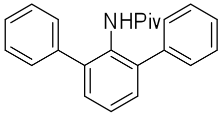
Sanford, M. S. *et al. JACS* **2006**, *128*, 4972.



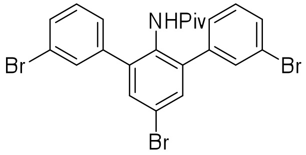
Gaunt, M. J. *et al. JACS* **2008**, *130*, 8172.

o-Arylation of Acetanilides

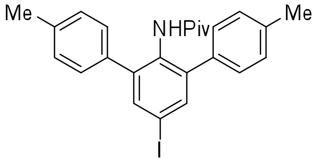




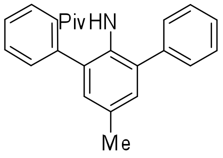
91%



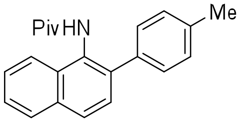
95%



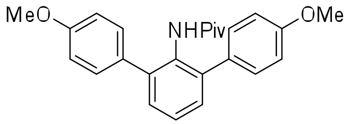
92%



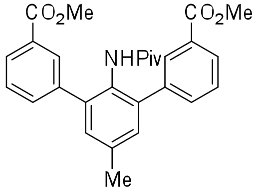
79%



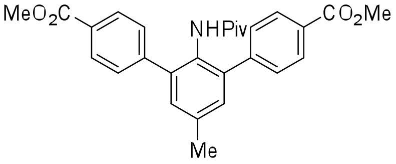
62%



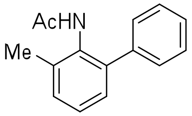
67%



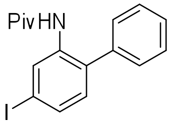
85%



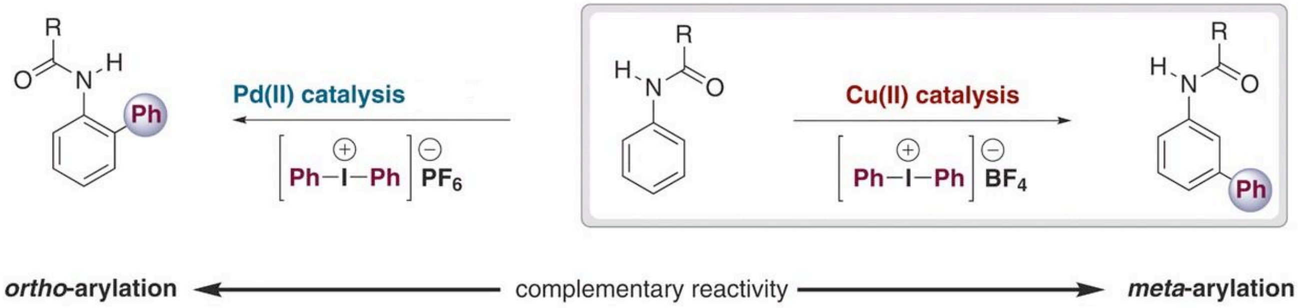
96%



76%

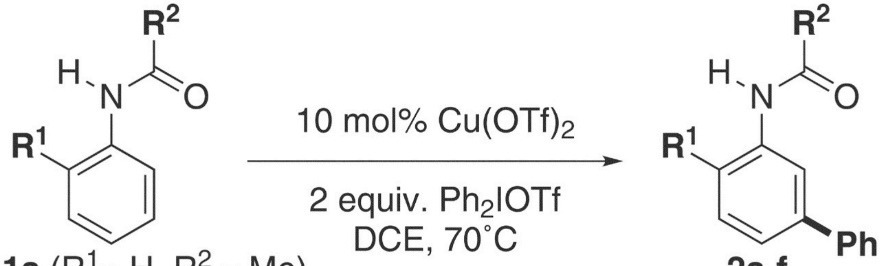


83%



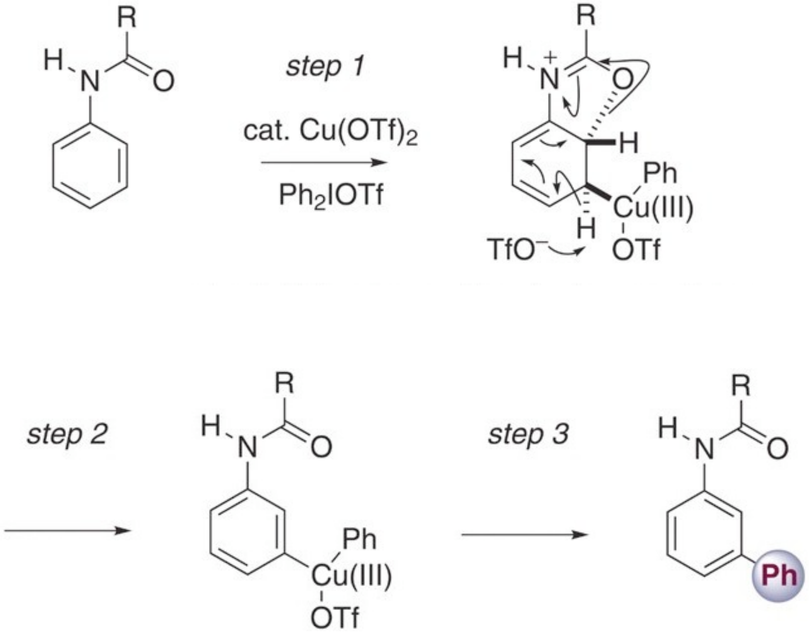
Daugulis, O.; Zaitsev, V. G. *ACIE*, **2005**, *44*, 4046.

Reaction Optimization and Mechanistic Proposal



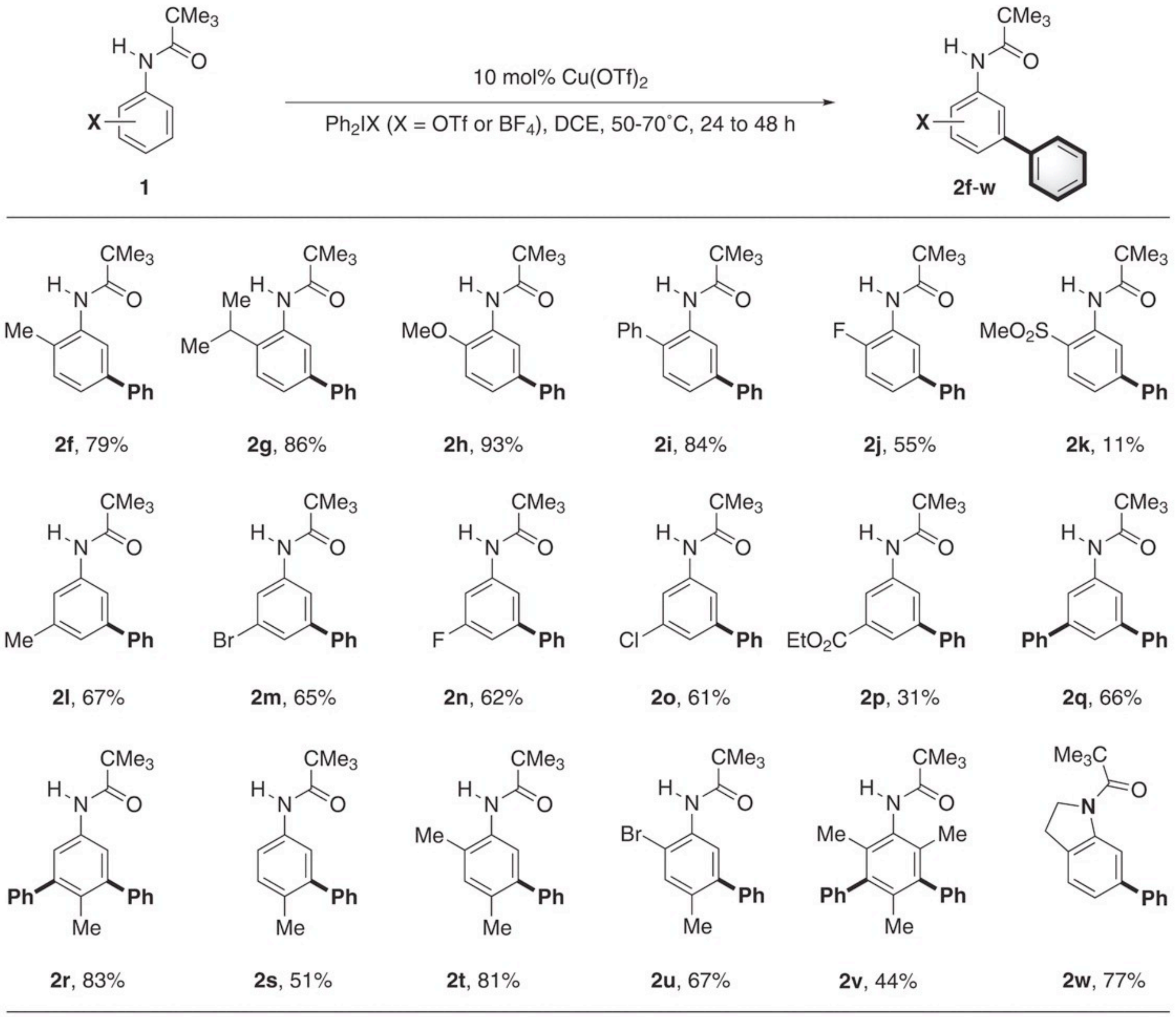
1a (R^1= H, R^2 = Me)
1b (R^1= Me, R^2 = Me)

entry	R^1	R^2	product	yield %
1	H	Me	**2a**	14
2	Me	Me	**2b**	43
3	Me	OMe	**2c**	45
4	Me	NEt_2	**2d**	31
5	Me	Ph	**2e**	73
6	Me	CMe_3	**2f**	79



Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

Substrate Scope



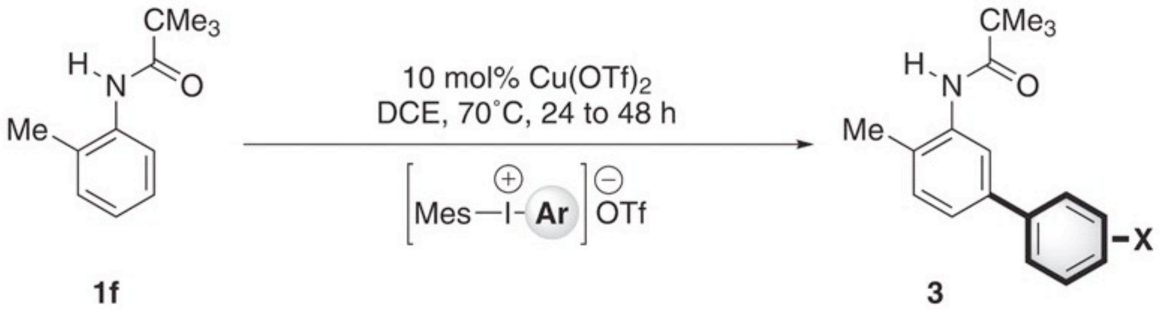
1

2f-w

2f, 79%
2g, 86%
2h, 93%
2i, 84%
2j, 55%
2k, 11%
2l, 67%
2m, 65%
2n, 62%
2o, 61%
2p, 31%
2q, 66%
2r, 83%
2s, 51%
2t, 81%
2u, 67%
2v, 44%
2w, 77%

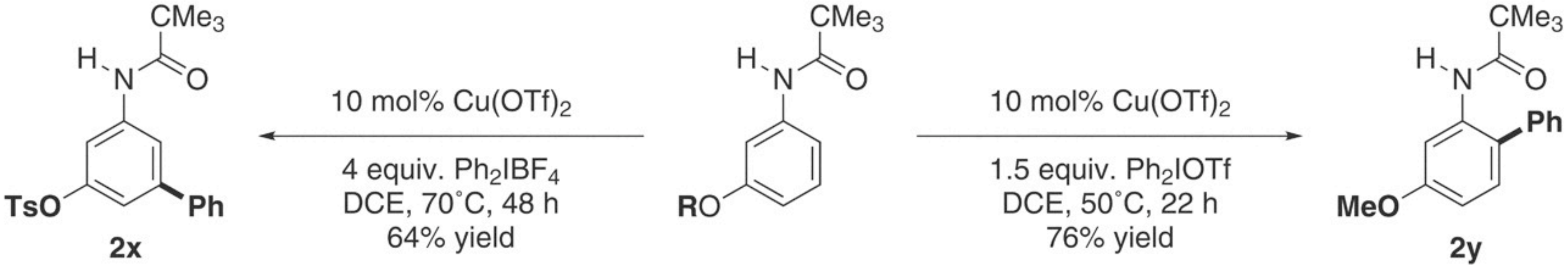
Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

Scope of the Aryl Group Transfer



	X	yield
3a	4-Me	82%
3b	4-F	78%
3c	4-I	49%
3d	4-CO_2Et	82%
3e	4-NO_2	60%
3f	3-CF_3	70%
3g	3-Br	72%
3h	2-Me	44%

Controlling the Site Selectivity



Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

Conclusions

- Mild copper-catalyzed highly meta-selective arylation of acylanilides was developed
- Broad range of substrates is compatible with this reaction, though the best results were obtained with electron-rich substrates
- Meta-selectivity can be overridden by strongly electron-donating substituents
- Reaction is proposed to proceed through oxazoline-like intermediate
- Further mechanistic work is ongoing