Remote *Meta*-Selective C–H Functionalization of Arenes

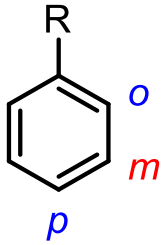
Reporter: Cong Liu
Checker: Mu-Wang Chen
Date: 2015/10/27

Motomu Kanai *et al*,
Nature Chem. **2015**, *7*, 712.

Motomu Kanai
University of Tokyo

Regioselective C-H Functionalizations of Arenes

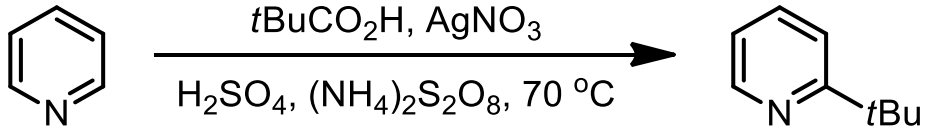
Friedel-Crafts Reaction:



R = electron-donating group; *o*, *p*-orientation;
R = electron-withdrawing group; *m*-orientation.

Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392.

Minisci Reaction:



Minisci, F. *et al*, *Tetrahedron* **1971**, *27*, 3575.

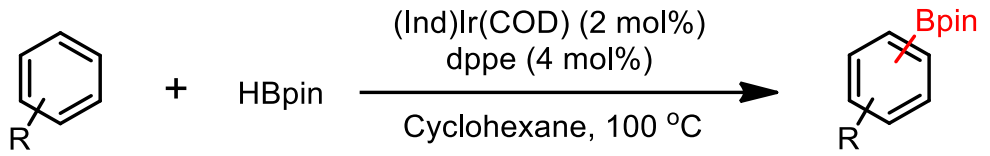
DOI: 10.1002/anie.201206568

***meta*-Directing Groups**

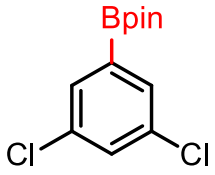
Directed Functionalization of C–H Bonds: Now also *meta* Selective

*Thanh Truong and Olafs Daugulis**

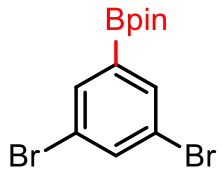
Steric-Sensitive Borylation and Silylation



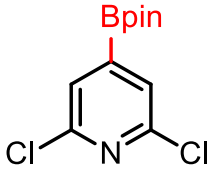
Hartwig:
$[Ir(OMe)(COD)]_2$ (1.5 mol%)
dtbpy (3 mol%)
B_2pin_2 or HBpin (0.5-1.1 equiv)
Hexane, 25 °C, 2-24 h



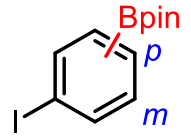
14 h, 89% yield



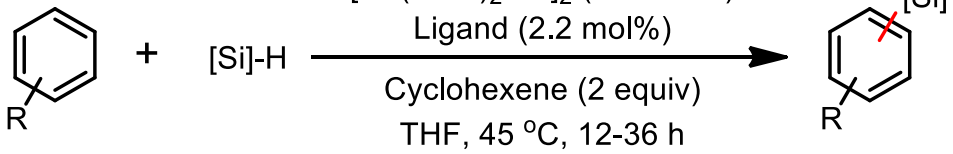
17 h, 92% yield



4 h, 69% yield

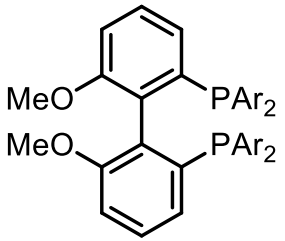


57 h, 77% yield, *m*/*p* = 79:21
$(MesH)Ir(Bpin)_3$ as catalyst

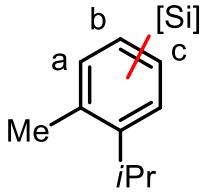


[Si] = $SiMe(OTMS)_2$

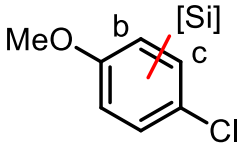
Ligand



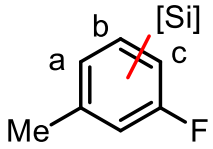
Ar = $3,4,5\text{-}(MeO)_3C_6H_2$



E = [Si]: 69% yield (b/c = 82:18)
E = [B]: 78% yield (b/c = 42:58)



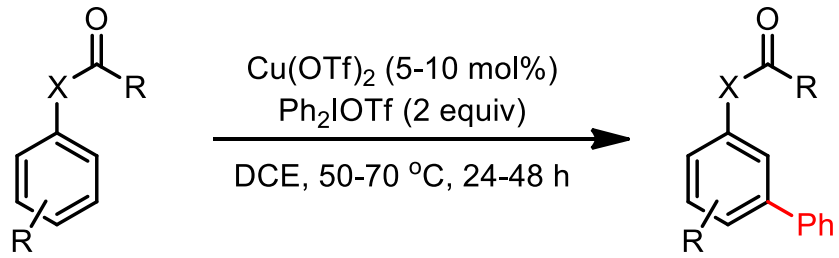
E = [Si]: 83% yield (b/c = 98:2)
E = [B]: 88% yield (b/c/di = 43:19:38)

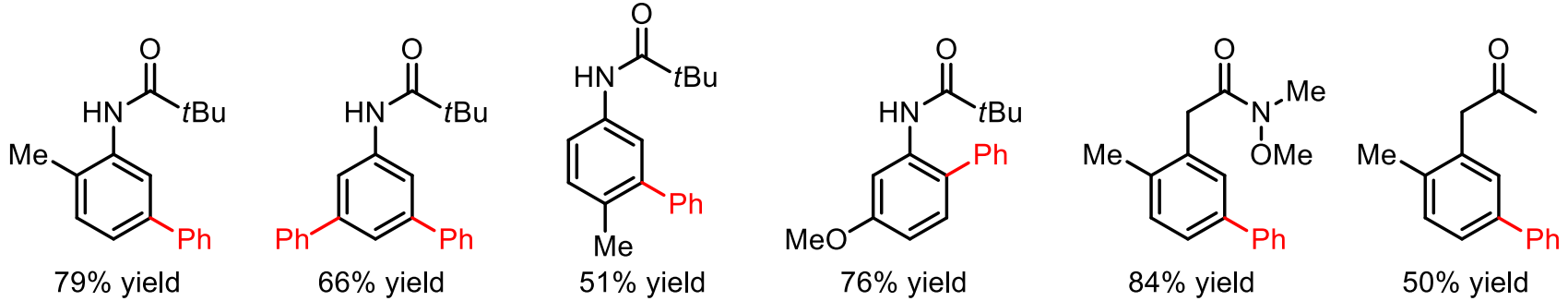


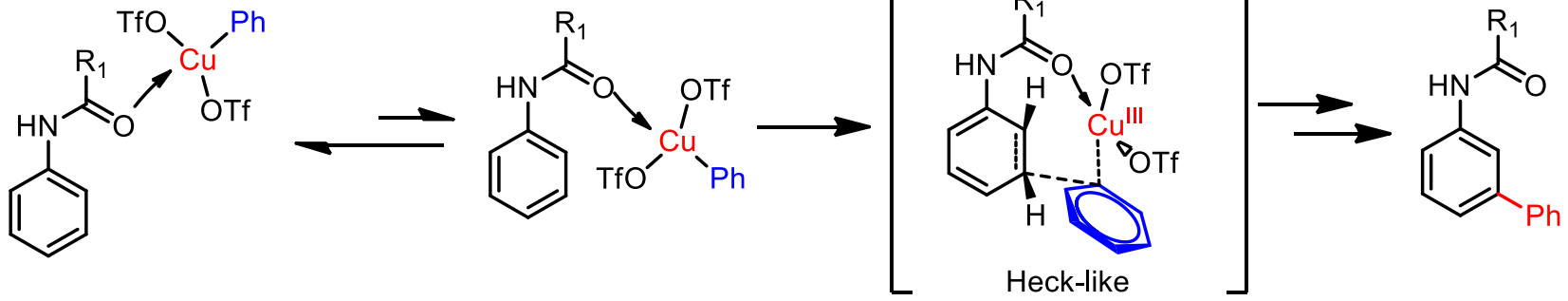
E = [Si]: 72% yield (b/c = 89:11)
E = [B]: >95% yield (b/c/di = 49:41:10)

Science **2002**, *295*, 305; *Angew. Chem. Int. Ed.* **2002**, *41*, 3056; *Science* **2014**, *343*, 853.

Diaryliodonium Salt-Mediated Arylation



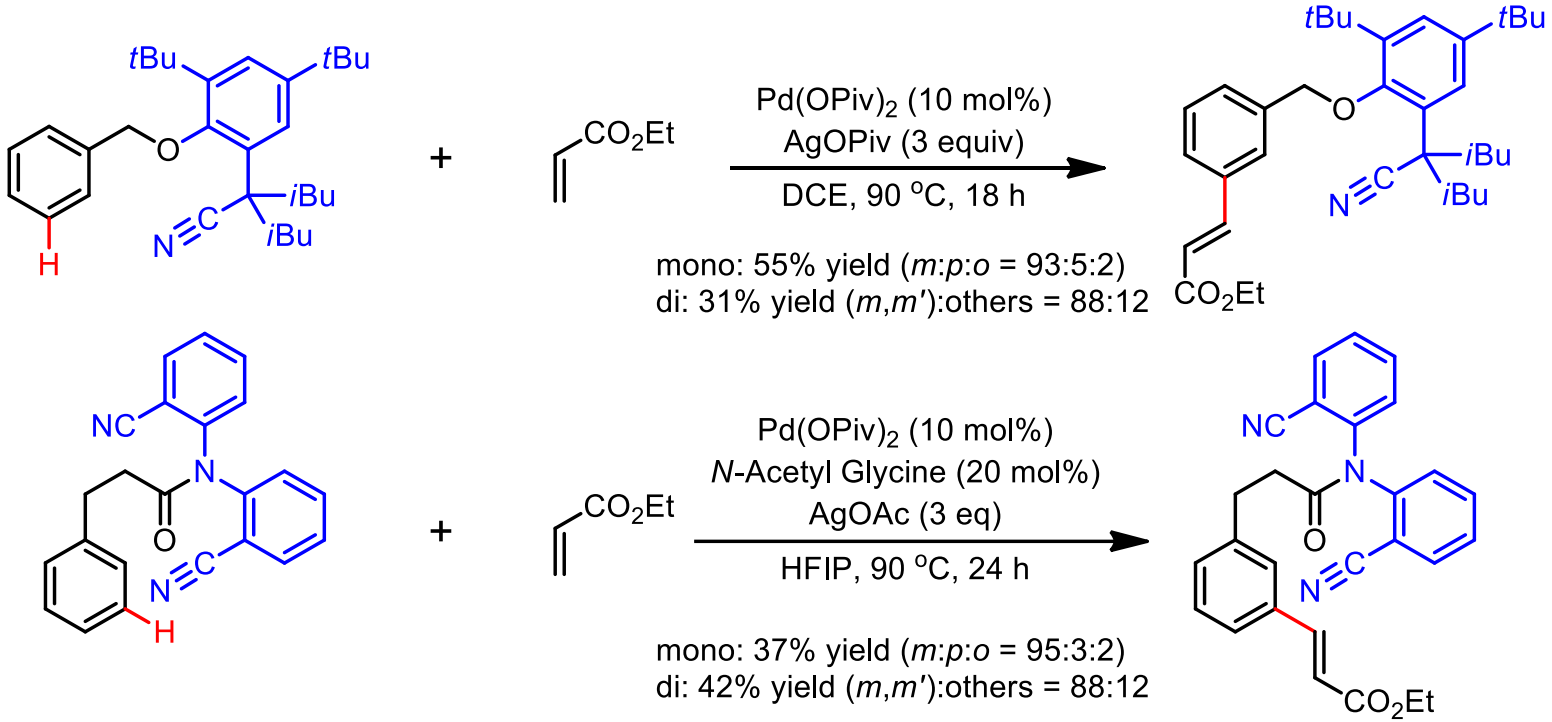


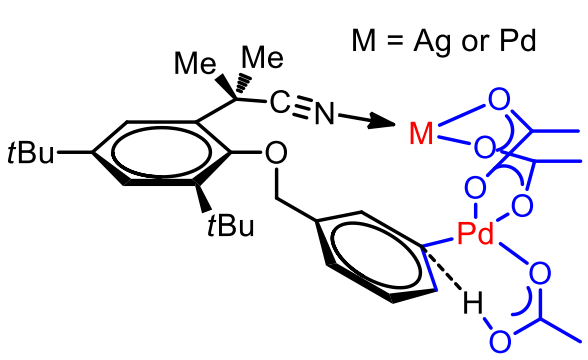


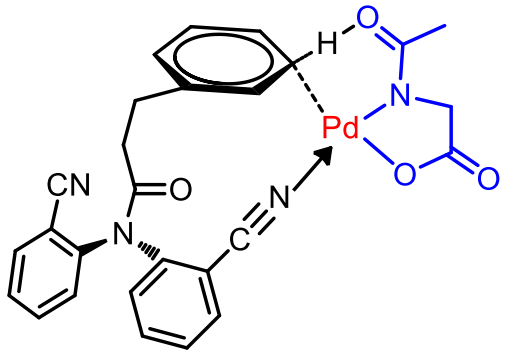
Science **2009**, *323*, 1593; *Angew. Chem. Int. Ed.* **2011**, *50*, 463; *J. Am. Chem. Soc.* **2011**, *133*, 7668; *Chin. J. Chem. Phys.* **2011**, *24*, 711.

Meta C–H Fuctionalizations with End-on Templates

- Cyclophane-like pretransition state: ≥12-membered ring

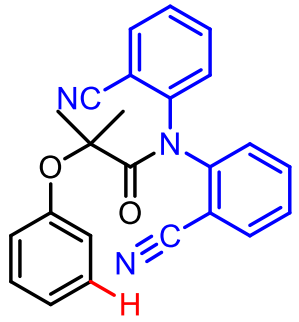




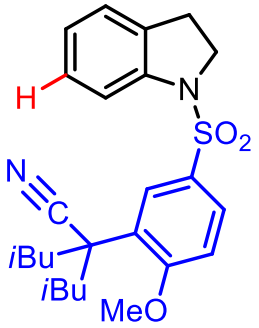


Nature **2012**, *486*, 518; *J. Am. Chem. Soc.* **2014**, *136*, 344; *J. Am. Chem. Soc.* **2014**, *136*, 894.

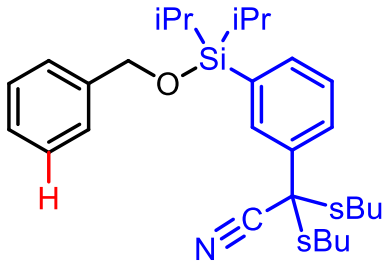
The Use of U Shaped Templates



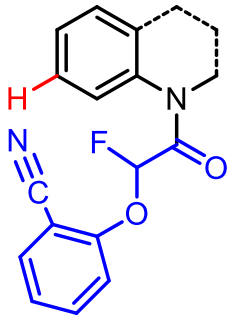
Yu, **2013**



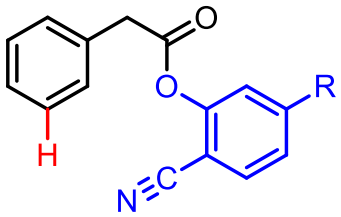
Yu, **2014**



Tan, **2013**

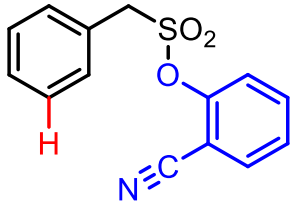


Yu, **2014**

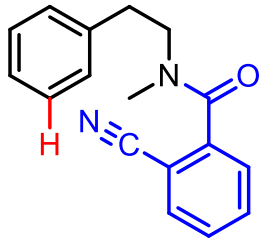


R = H or OMe

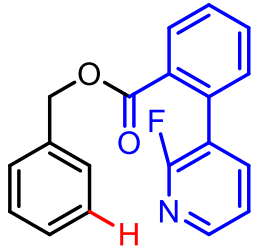
Maiti, **2014**



Maiti, **2015**



Li, **2015**

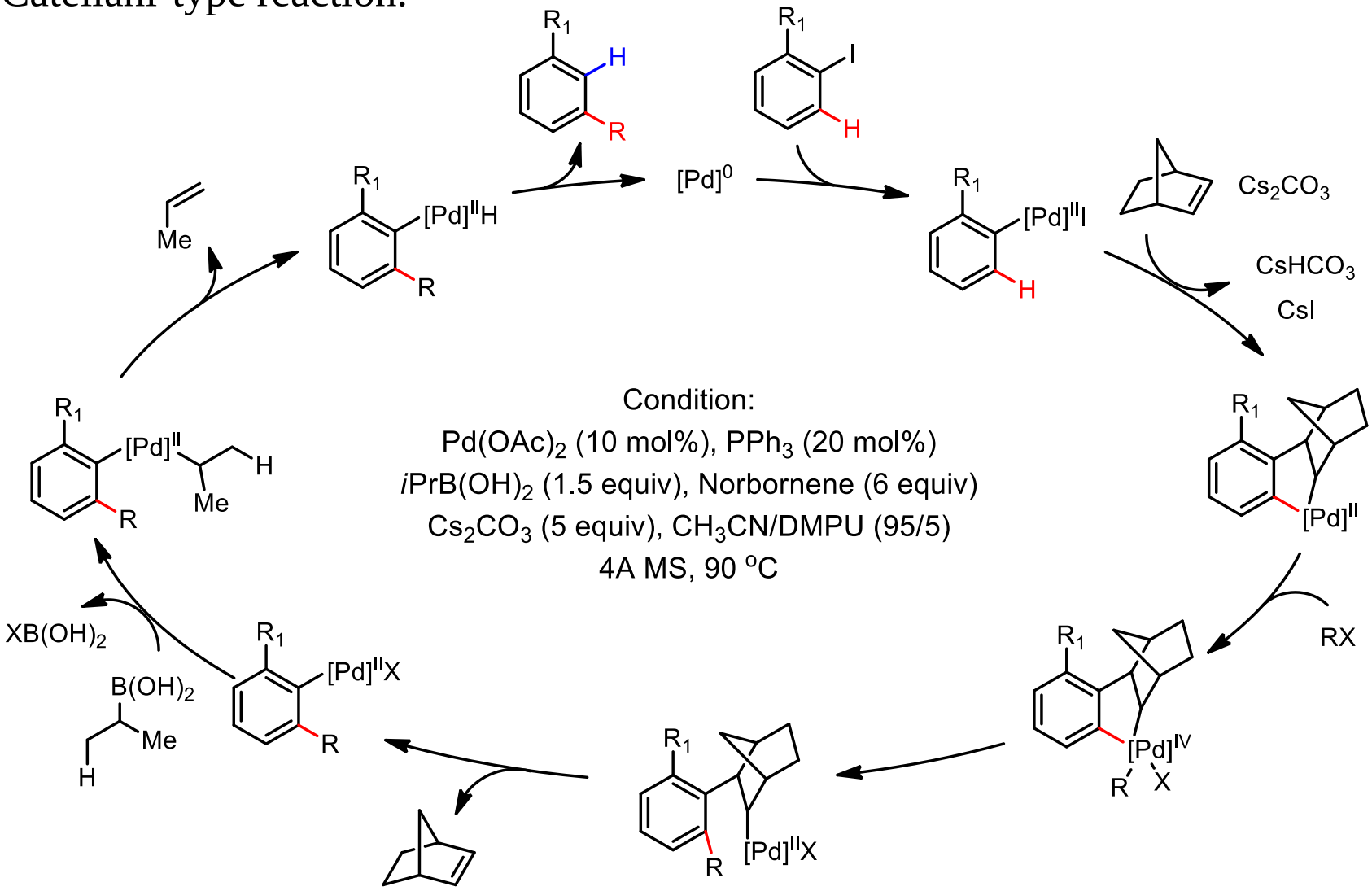


Yu, **2015**

J. Am. Chem. Soc. **2013**, *135*, 7567; *J. Am. Chem. Soc.* **2013**, *135*, 18778; *J. Am. Chem. Soc.* **2014**, *136*, 10807; *Nature* **2014**, *507*, 215; *Org. Lett.* **2014**, *16*, 5760; *Angew. Chem. Int. Ed.* **2015**, *54*, 8515; *Chem. Sci.* **2015**, *6*, 5595; *ACS Cent. Sci.* **2015**, asap. (10.1021/acscentsci.5b00312)

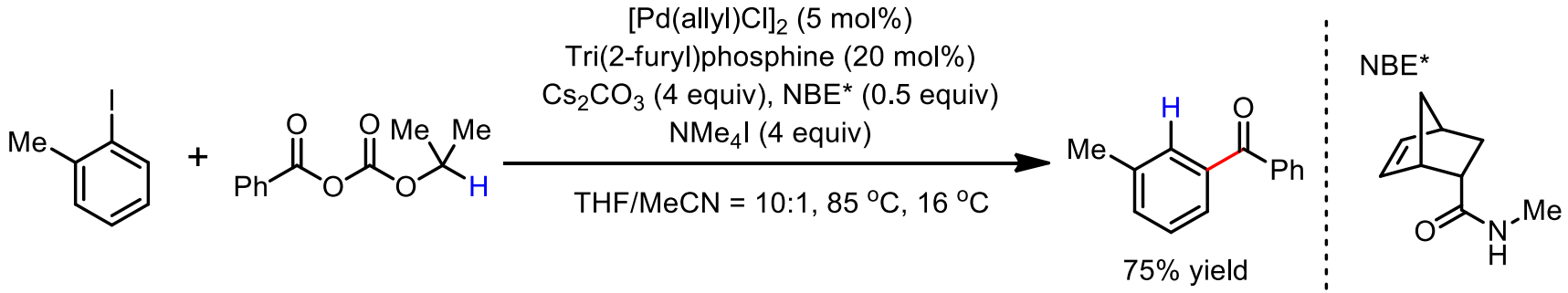
Norbornene-Mediated *Meta* C–H Functionalization

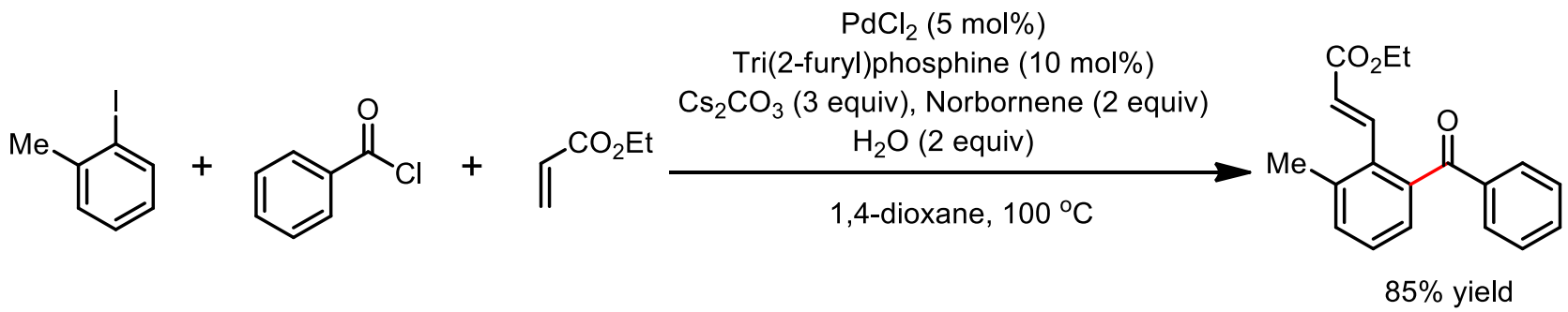
- Catellani-type reaction.



Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053.

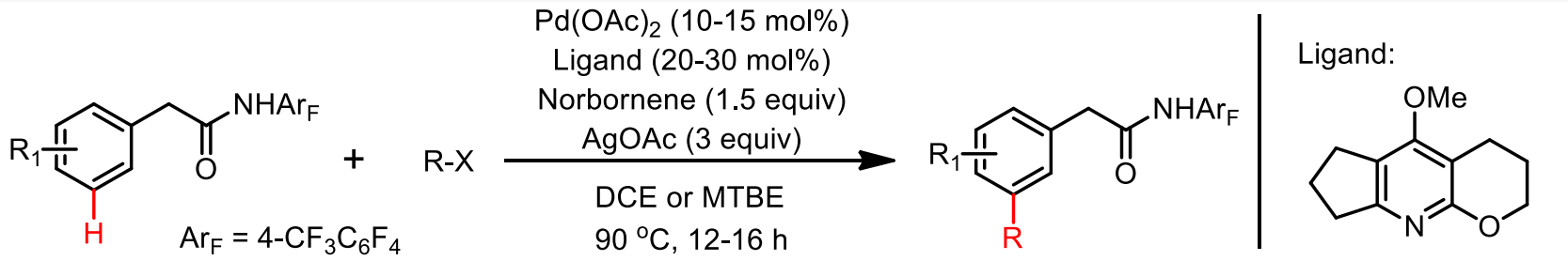
Meta-Selective C–H Acylation *via* Pd/NBE Catalysis

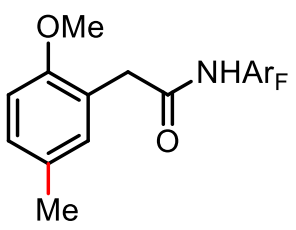


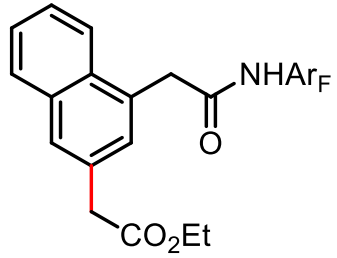


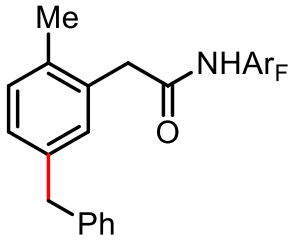
Angew. Chem. Int. Ed. **2015**, *54*, 12664; *Angew. Chem. Int. Ed.* **2015**, *54*, 12669.

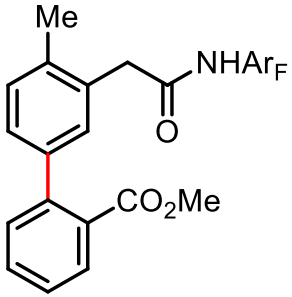
Meta-Selective C–H Activation *via* Pd/NBE Catalysis

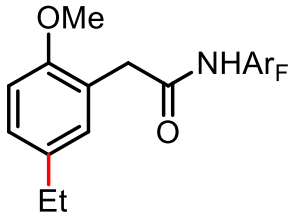


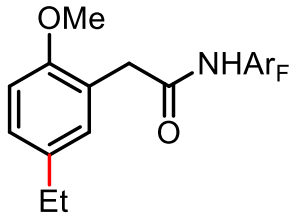

91% yield

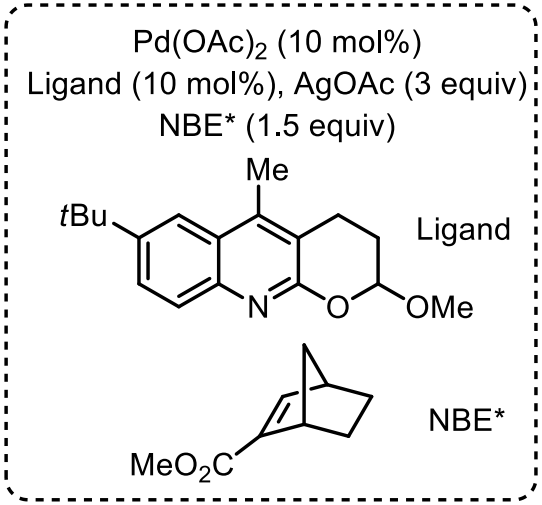

91% yield

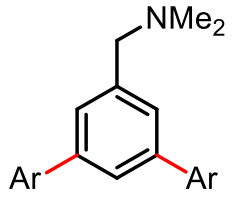

66% yield


64% yield

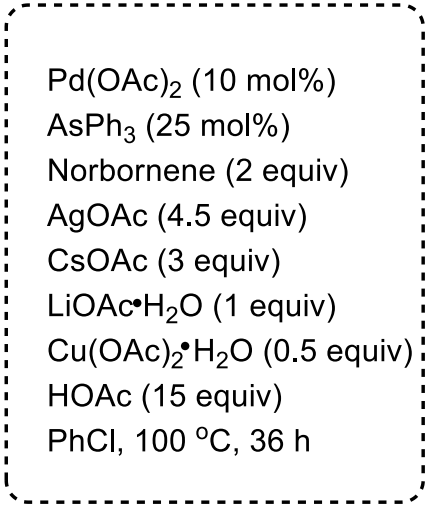

21% yield


93% yield



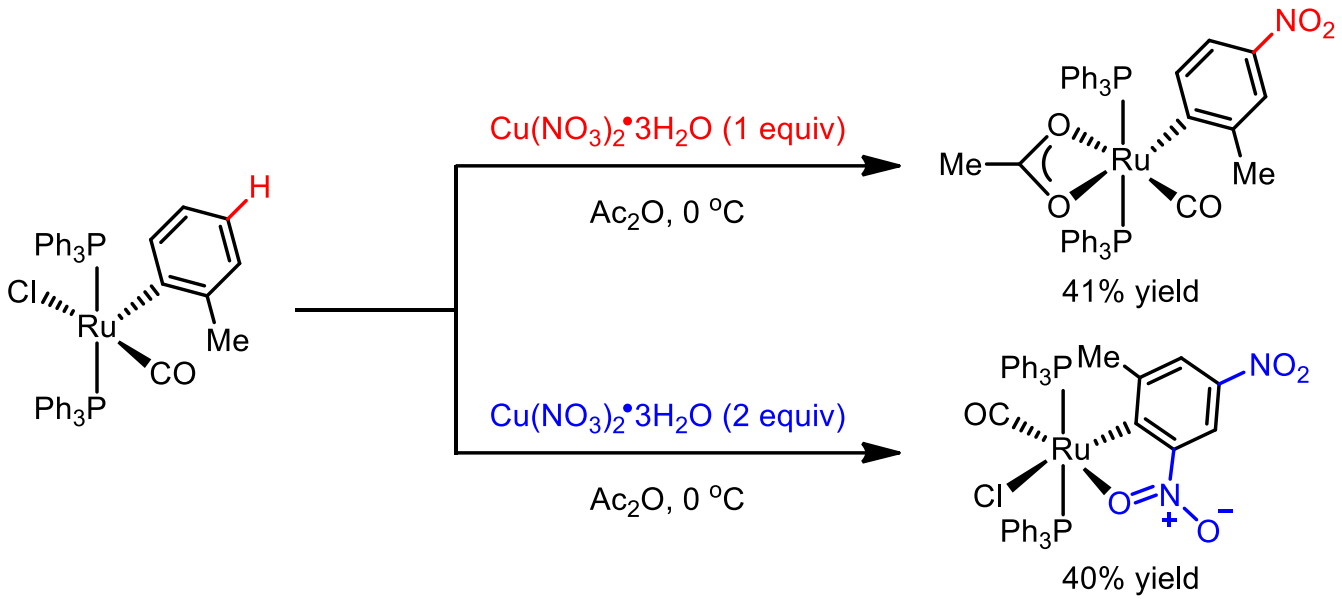

Ar = *o*-CO_2MePh

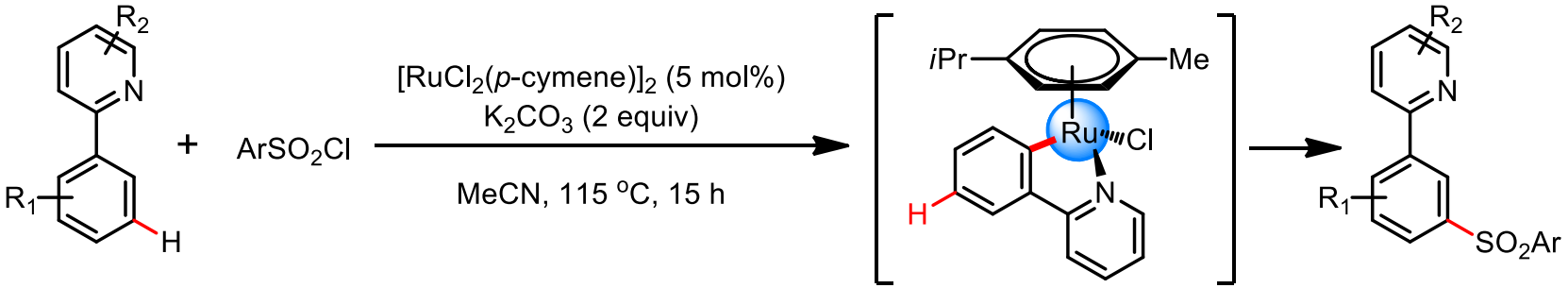
72% yield



Nature **2015**, *519*, 334; *J. Am. Chem. Soc.* **2015**, *137*, 5887; *J. Am. Chem. Soc.* **2015**, *137*, 11574.

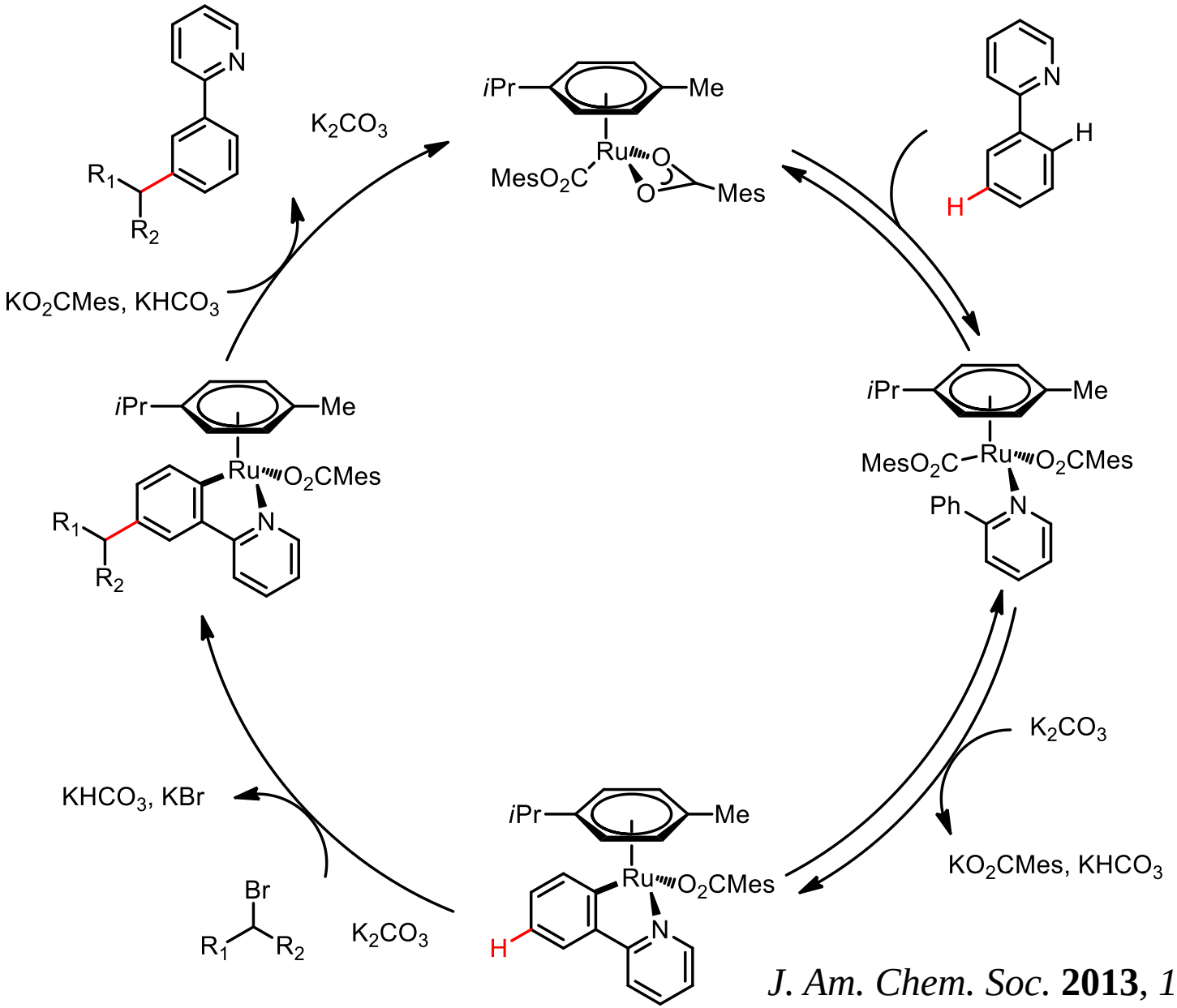
Ortho-Metalation-Triggered S_EAr Reaction





Roper, W. R. *et al*, *Inorg. Chim. Acta*. **1994**, *220*, 261; *J. Am. Chem. Soc*. **2011**, *133*, 19298.

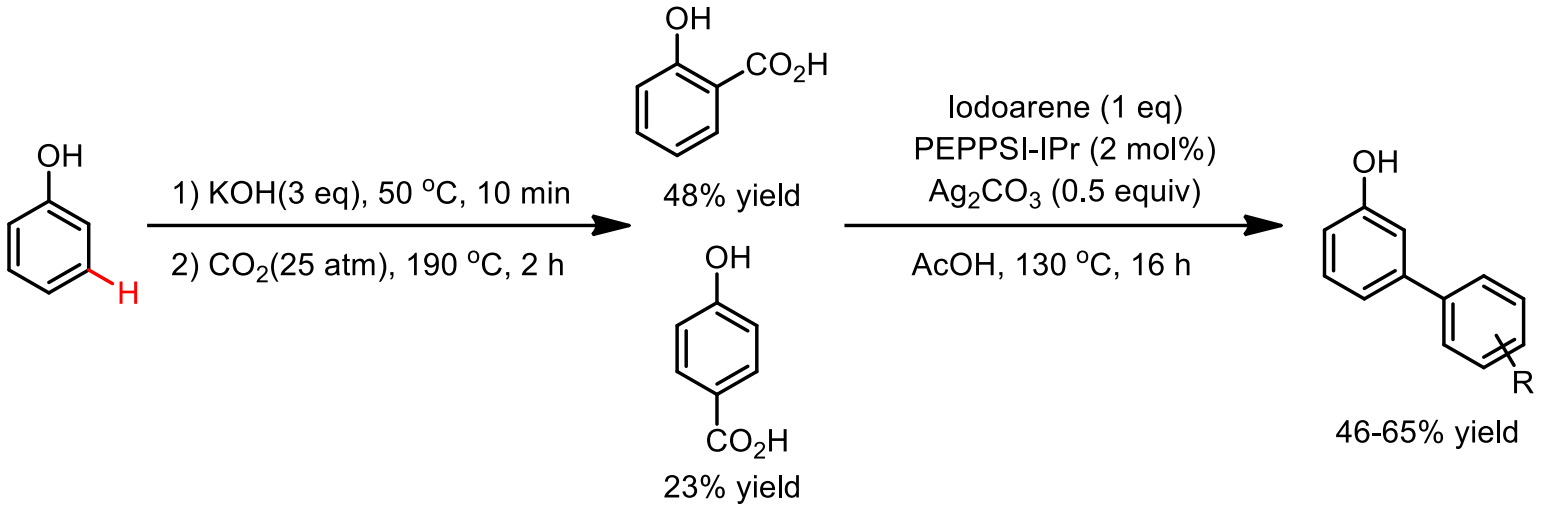
Ortho-Metalation-Triggered S_EAr Reaction



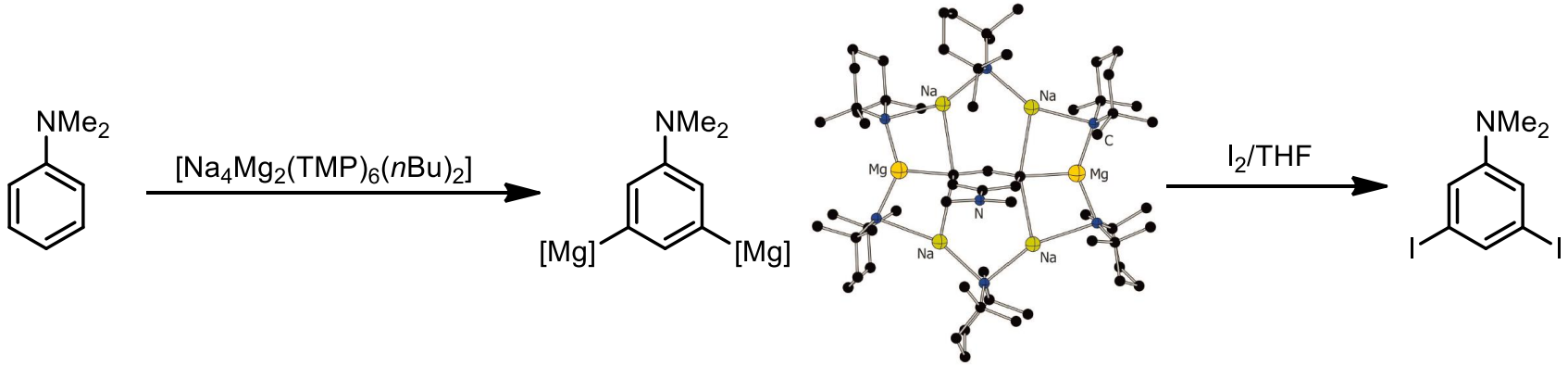
J. Am. Chem. Soc. **2013**, *135*, 5877.

Others

- Use of a traceless directing group.

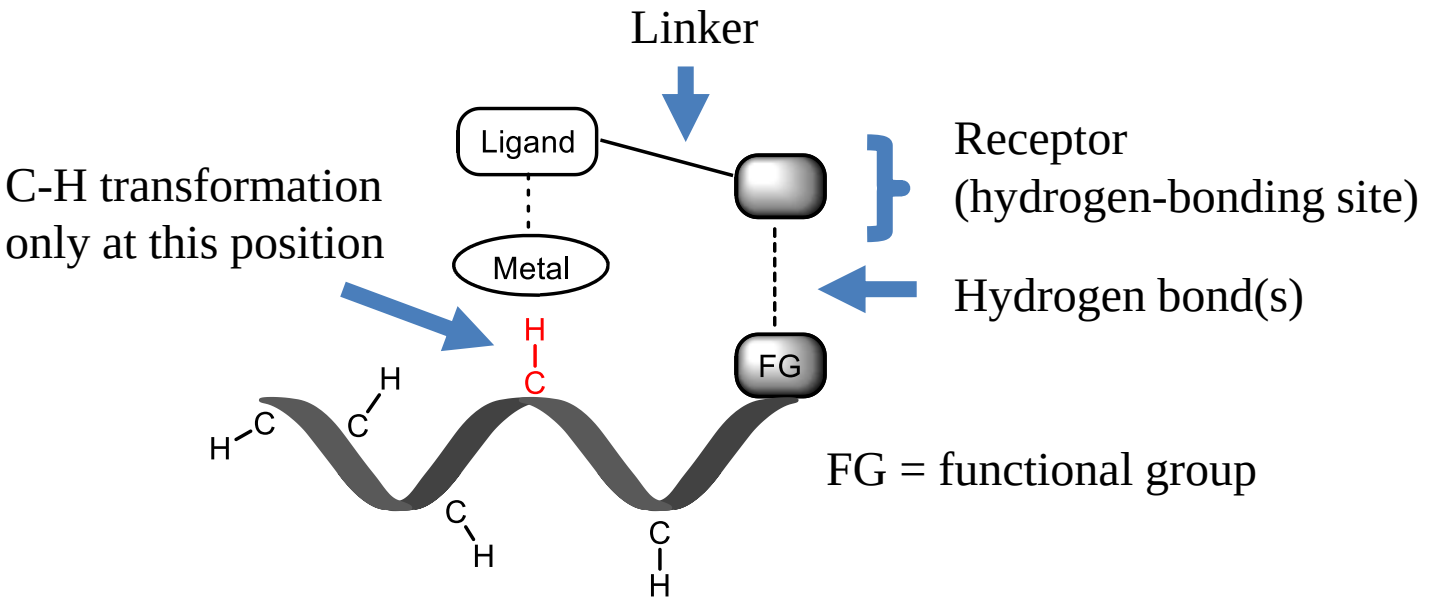


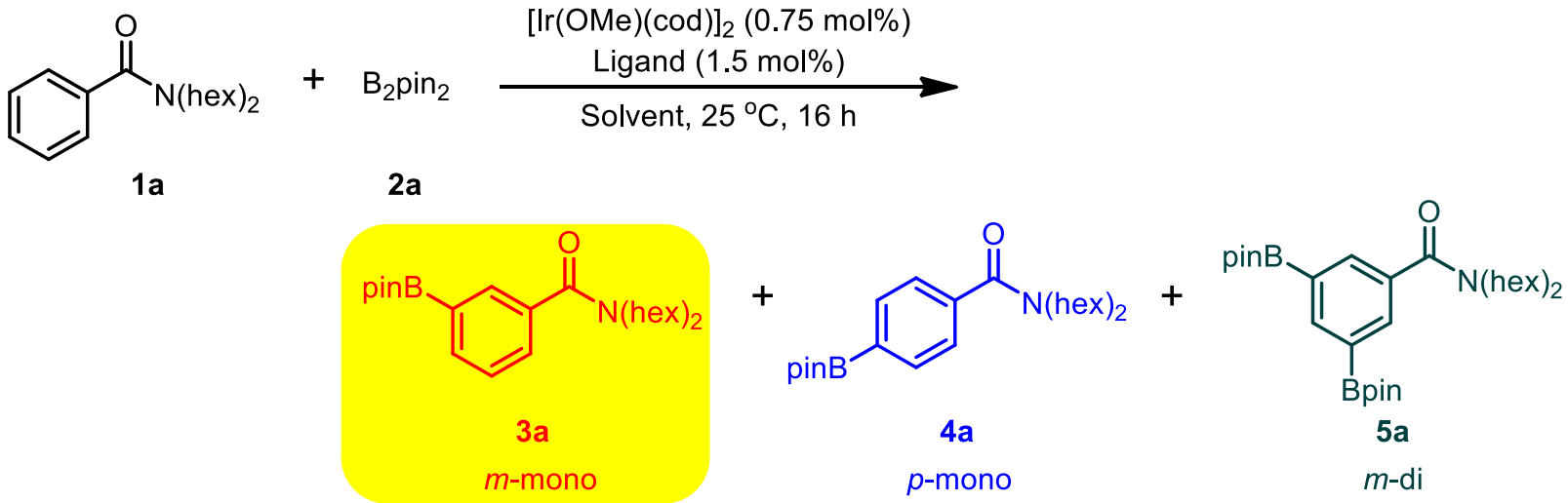
- Cluster-templated metalation.



J. Am. Chem. Soc. **2014**, *136*, 4109; *Science* **2014**, *346*, 834.

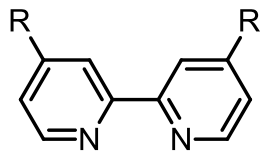
Catalyst Design





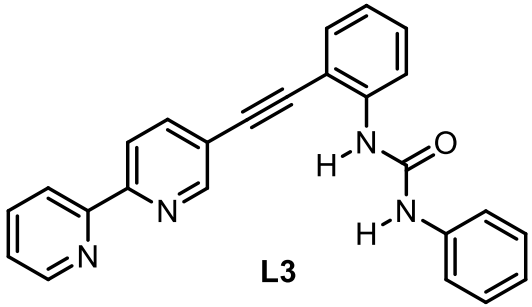
Kanai, M. *et al*, *Nature Chem.* **2015**, *7*, 712.

Optimization

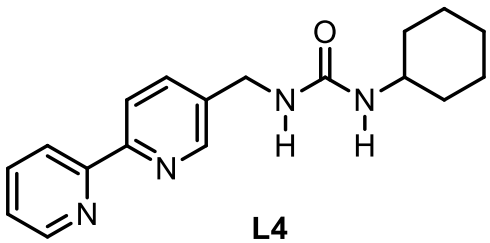


L1: R = *t*Bu

L2: R = OMe



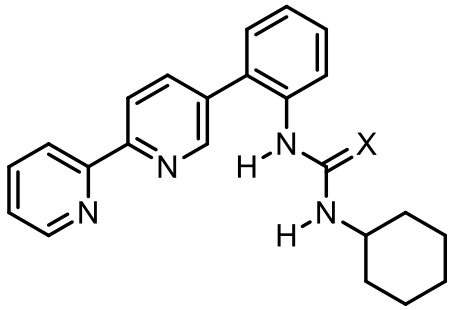
L3



L4

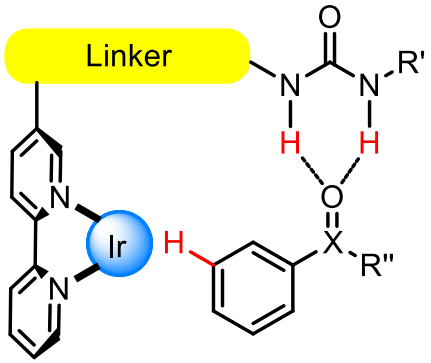
Entry	Ligand	Yield[a,b]		
		mono: **3a** + **4a** (**3a**/**4a**)	di: **5a**	Recovery of **1a**
1	**L1**	67% (1.9)	3%	30%
2	**L2**	52% (1.4)	4%	44%
3	**L3**	0	0	99%
4	**L4**	47% (2.0)	3%	50%
5	**L5**	50% (8.3)	3%	47%
6	**L6**	0	0	99%

[a] **2a** (0.75 equiv). [b] *p*-Xylene was used as a solvent.



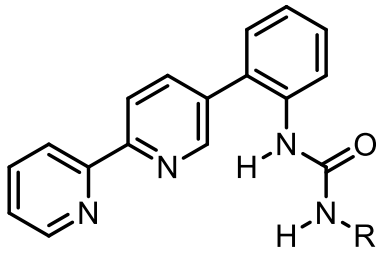
L5: X = O

L6: X = S



Optimization

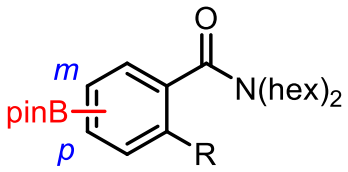
Entry	Ligand	Yield[a,b]		
		mono: **3a** + **4a** (**3a**/**4a**)	di: **5a**	Recovery of **1a**
1	**L5**	44% (27)	10%	45%
2[c]	**L5**	50% (8.3)	3%	47%
3	**L7**	31% (7.4)	0%	69%
4	**L8**	22% (1.4)	1%	77%
5	**L9**	31% (7.2)	1%	66%
6	**L10**	40% (3.9)	4%	56%
7	**L11**	32% (3.6)	0%	68%
8[c,d]	**L5**	51% (17)	22%	27%
		48% (19)[e]	17%[e]	



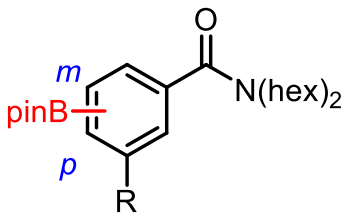
L5: R = Cy
L7: R = Hex
L8: R = 4-(MeO)-C_6H_4
L9: R = 4-CF_3-C_6H_4
L10: R = 4-(*n*Bu)-C_6H_4
L11: R = 2,6-2Me-C_6H_3

[a] **2a** (0.75 equiv). [b] Hexane was used as a solvent. [c] *p*-Xylene was used as a solvent. [d] $[lr(OMe)(cod)]_2$ (1.5 mol%), **L5** (3.0 mol%), **2a** (1.0 equiv). [e] Isolated yield.

Substrate Scope



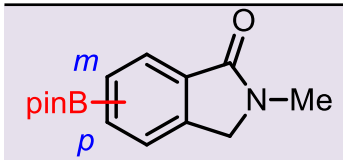
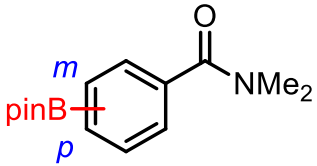
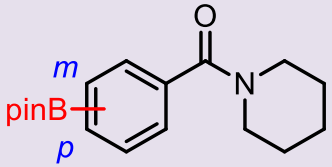
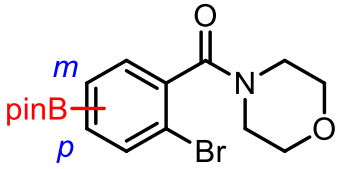
	Yield[a]	
	L5	**L1**
R = OMe	59% (7.8)	40% (0.46)
R = Me	35% (12)	39% (0.72)
R = Br	96% (7.5)	97% (0.46)
R = Cl	>99% (13)	>99% (0.61)
R = CF_3	>99% (>30)	>99% (0.86)
R = OCF_3	>99% (6.9)	>99% (0.25)
R = CO_2Me	>99% (>30)	>99% (2.1)
R = Ph	26% (>30)	32% (3.9)

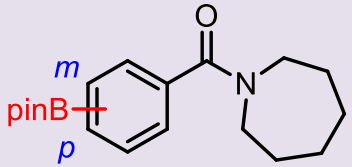
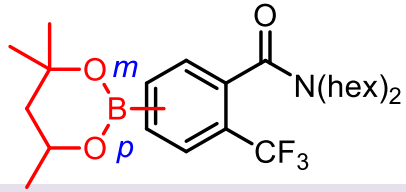
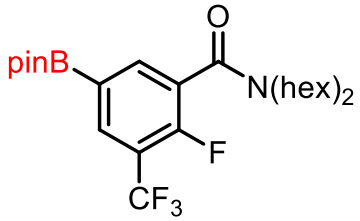


	Yield[a]	
	L5	**L1**
R = F	>99% (9.1)	>99% (1.0)
R = Br	85%	>99%
R = Ph	>99%	>99%
R = CN	92% (20)	75% (12)

[a] ^{1}H NMR yield of mono-borylated products (as a mixture of *meta*-and *para*-products) with the *meta*/*para* ratio described in parentheses.

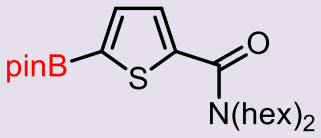
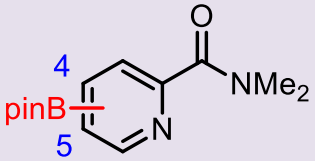
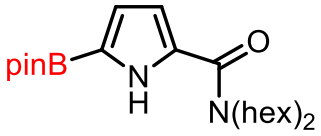
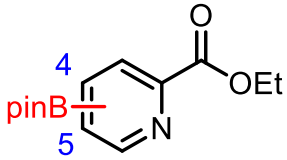
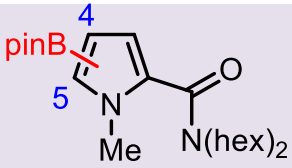
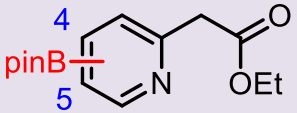
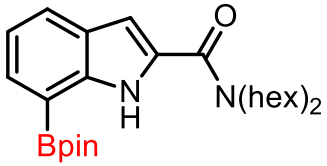
Substrate Scope

	Yield[a]	
	L5	**L1**
	51% (3.3)	54% (1.1)
	44% (27)	49% (1.5)
	46% (>30)	40% (1.5)
	95% (3.3)	5% (0.67)

	Yield[a]	
	L5	**L1**
	51% (3.3)	54% (1.1)
	44% (27)	49% (1.5)
	46% (>30)	40% (1.5)
	95% (3.3)	5% (0.67)

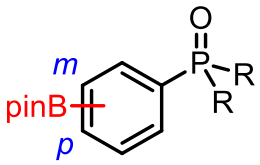
[a] ^{1}H NMR yield of mono-borylated products (as a mixture of *meta*-and *para*-products) with the *meta*/*para* ratio described in parentheses.

Substrate Scope

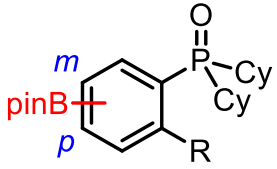
	Yield[a]			Yield[a]	
	L5	**L1**		**L5**	**L1**
	86%	90%		86% (6.4)	88% (1.9)
	94%	96%		>99% (4.3)[b]	92% (1.3)
	84% (6.6)	95% (2.3)		99% (1.5)[b]	89% (0.48)
	86% (>30)	89% (>30)			

[a] ^{1}H NMR yield of mono-borylated products (as a mixture of *meta*-and *para*-products) with the *meta*/*para* ratio described in parentheses. [b] **L9** was used as a ligand

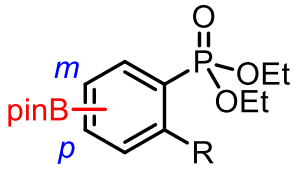
Substrate Scope



	Yield[a]	
	L5	**L1**
R = NEt_2	46% (>30)	61% (1.3)
R = OEt	44% (>30)	99% (0.55)
R = Cy	44% (>30)	53% (1.9)



	Yield[a]	
	L5	**L1**
R = OMe	>99% (>30)	86% (0.42)
R = Cl	>99% (>30)	>99% (0.14)

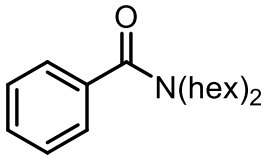


	Yield[a]	
	L5	**L1**
R = OMe	82% (0.52)	>99% (0.28)
R = Me	85% (7.5)	>99% (0.59)
R = Br	99% (13)	>99% (0.32)
R = CF_3	44% (>30)	99% (0.55)

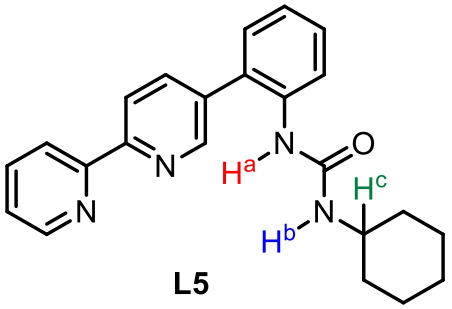
[a] ^{1}H NMR yield of mono-borylated products (as a mixture of *meta*-and *para*-products) with the *meta*/*para* ratio described in parentheses.

Mechanistic Study

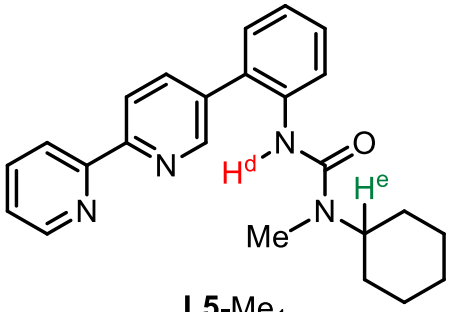
- ^{1}H NMR chemical shift changes caused by interaction between ligand and amide.



1a



L5



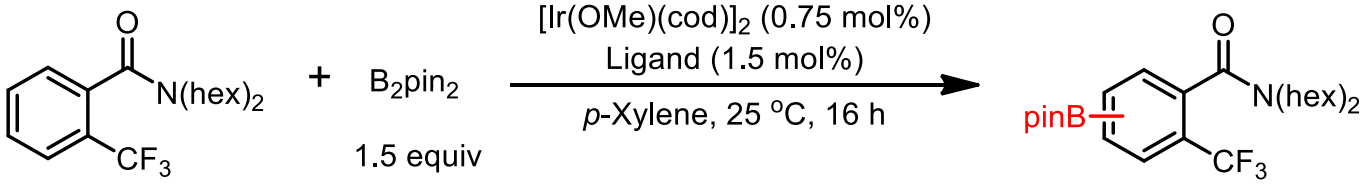
L5-Me$_1$

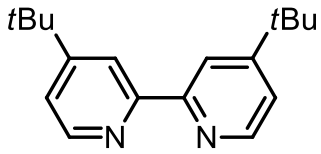
Entry	**L5**/**1a**	H^a (ppm)	H^b (ppm)	H^c (ppm)
1	1/0	5.65	3.60	3.63
2	1/1	5.78	3.74	3.65
3	1/64	7.00-7.50	5.88	3.89

Entry	**L5**-Me$_1$/**1a**	H^d (ppm)	H^e (ppm)
1	1/0	6.26	3.91
2	1/1	6.26	3.91
3	1/64	6.37	3.92

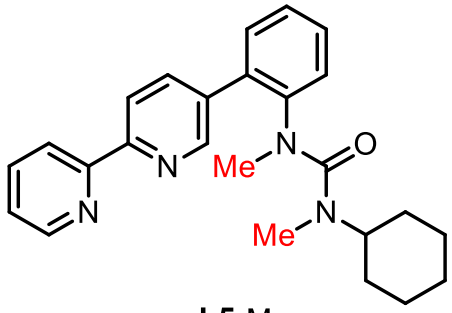
^{1}H NMR spectra were measured using benzene-d_6.

Mechanistic Study

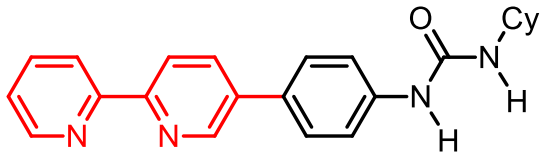




L1

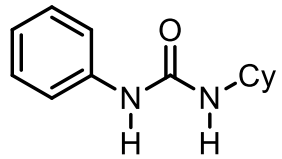


L5-Me_2



L12

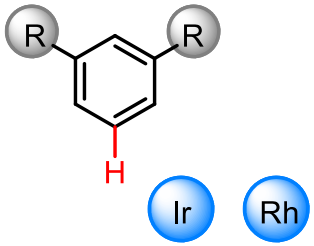
Entry	Ligand	Yield	*meta*/*para*
1	**L5**	95%	18
2	**L5**-Me_1	90%	1.6
3	**L5**-Me_2	90%	0.84
4	**L12**	99%	1.0
5	**L1**	98%	0.96
6	bpy + *N*-Ph-*N*'-Cy-urea	99%	1.1



N-Ph-*N*'-Cy-urea

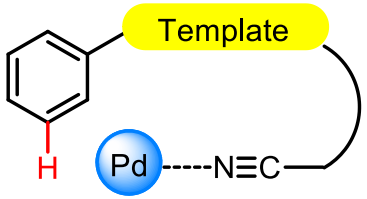
Summary and Perspective

Steric control: Ir, Rh



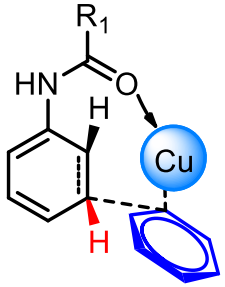
- No directing group
- Inherent reactivity

Template approach: Pd



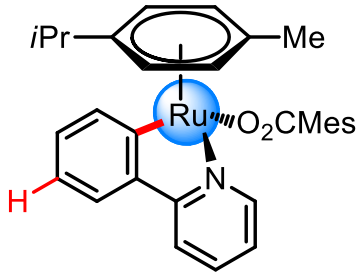
- Stoichiometric auxiliary
- Subsequent removal

Electronic effects: Cu



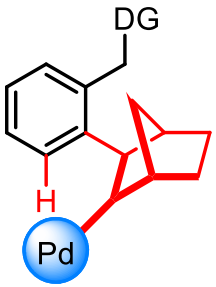
- Excellent selectivity
- Limited substrate scope

Remote σ-activation: Ru



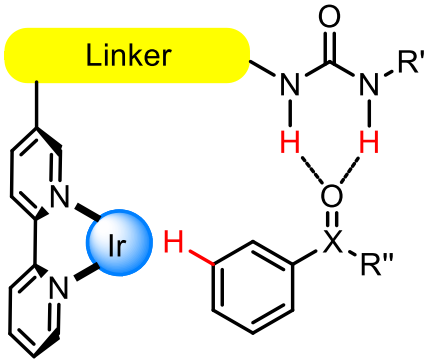
- Hetarene-based directing group
- Excellent selectivity

Transient mediator: Pd



- Step-economical
- Excellent selectivity

Secondary hydrogen-bond interaction: Ir



- Rational design
- Step-economical

Regioselective transformations are important for efficient syntheses. Regioselectivity can be achieved by introducing activated functional groups such as halogens and triflates, but bypassing this step would be attractive. For this reason, C–H transformations have recently received increasing attention as efficient and ideal alternative reactions. C–H transformations require fewer reaction steps to attain the target molecule and generate less waste than conventional methods involving preactivation processes. However, it is usually difficult to realize regioselective C–H transformations except with special substrates bearing only one possible reaction site and/or a directing group. In the case of C(sp^2)–H transformations of aromatic rings, the use of directing groups generally produces only *ortho*-selective reactions. The development of *meta*-selective transformations is very difficult, but synthetically useful. Several pioneering examples of *meta*-selective transformations have been reported recently.

In summary, we have successfully developed a regioselective aromatic C–H borylation using a designed iridium catalyst comprising a bipyridine moiety, with a pendant hydrogen-bond donor. This is the first reported catalyst-controlled regioselective C–H borylation of aromatic compounds. The important aspect of this reaction is that hydrogen bonding between the substrates and the catalyst controls the regioselectivity of a C–H bond transformation. The present catalytic system has the following merits: (1) it has a wide substrate scope; (2) common functional groups are used for catalyst direction; and (3) the ligands are easily accessed. We believe that the present concept will give a general solution for controlling the regioselectivity of C–H bond transformations and other reactions, without the need for directing groups.