

Palladium(II)-Catalyzed C–H Activation/ C–C Cross Coupling Reactions

Chunrui Sun
Lee Group

Definition

General

“bond activation” refers to any process which increase *the* reactivity of a bond.

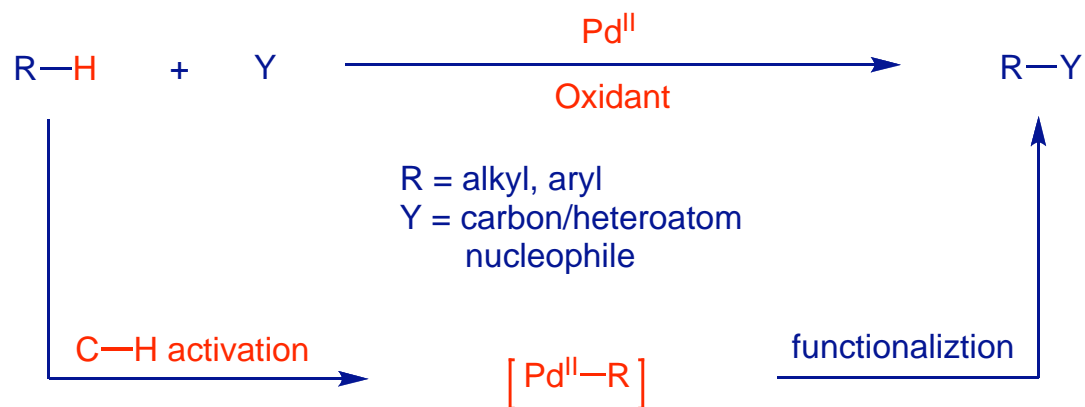
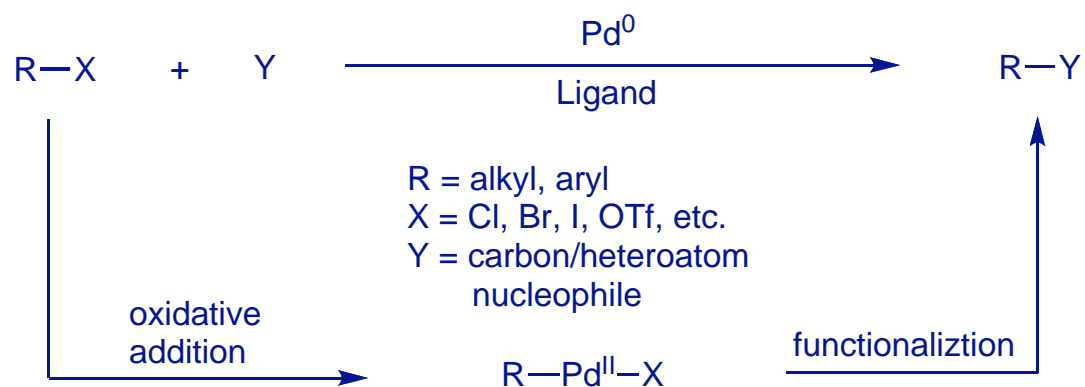
Organometallic

“C–H bond activation” refers to the formation of a complex wherein the C–H bond interacts directly with the metal to afford a C–M intermediate in the absence of a free radical or an ionic Intermediate.

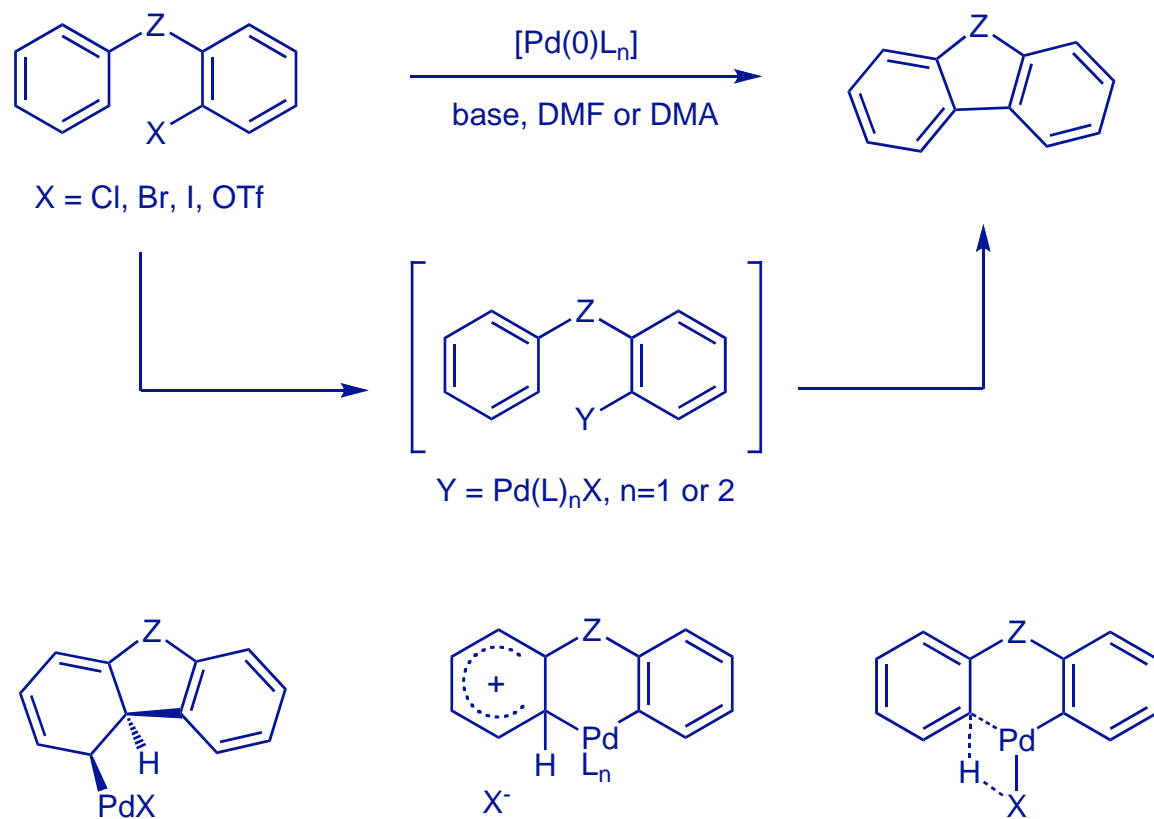
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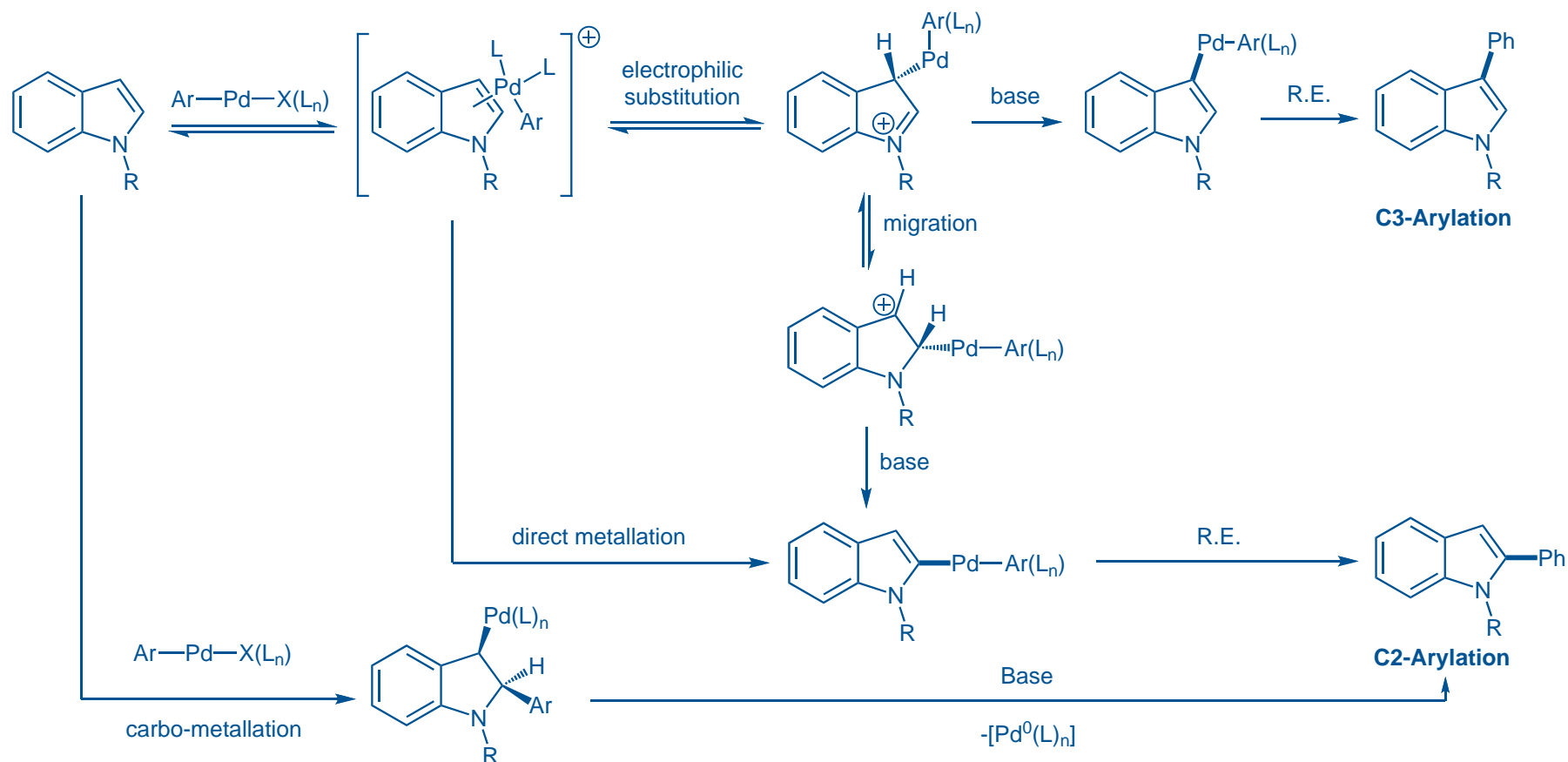
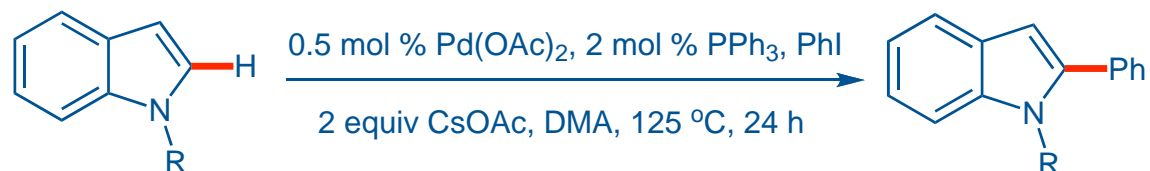
Introduction



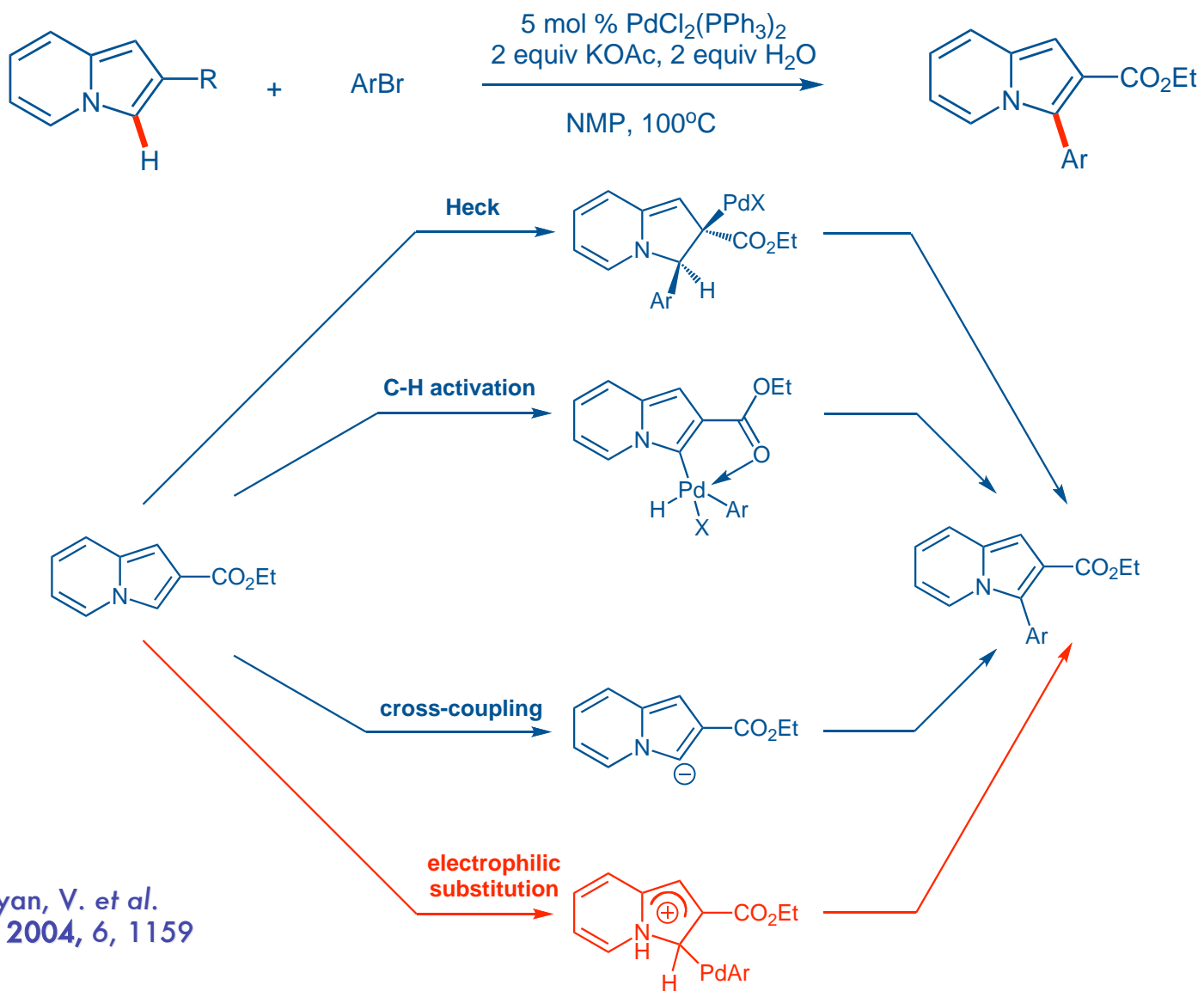
Mechanisms



Electrophilic Aromatic Substitution

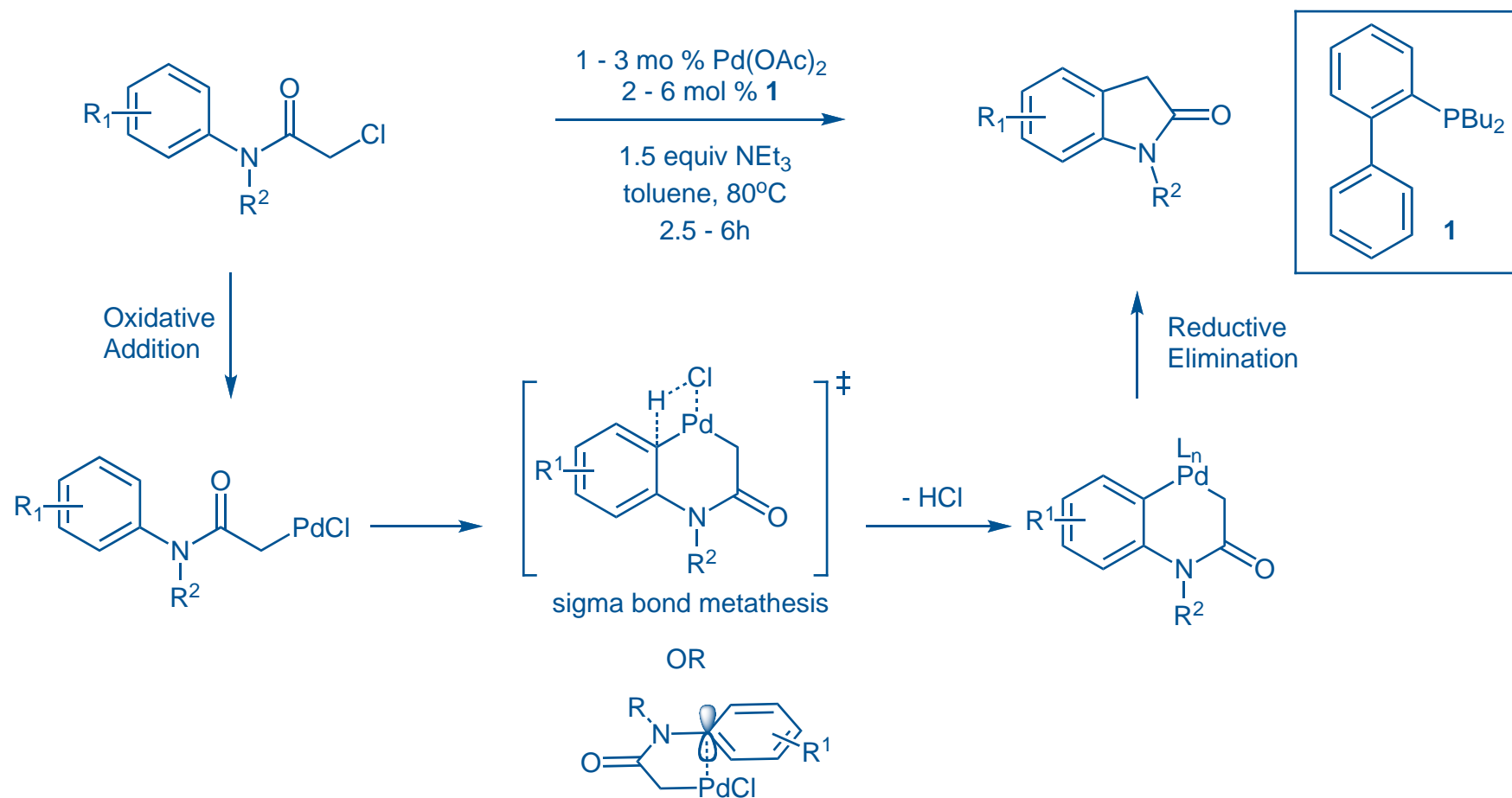


Electrophilic Aromatic Substitution

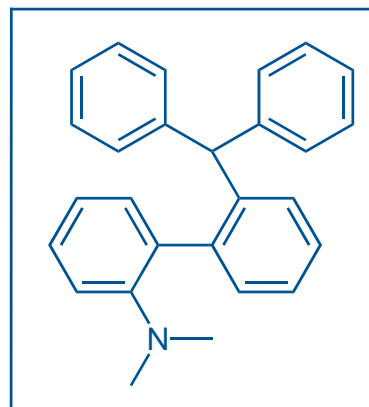
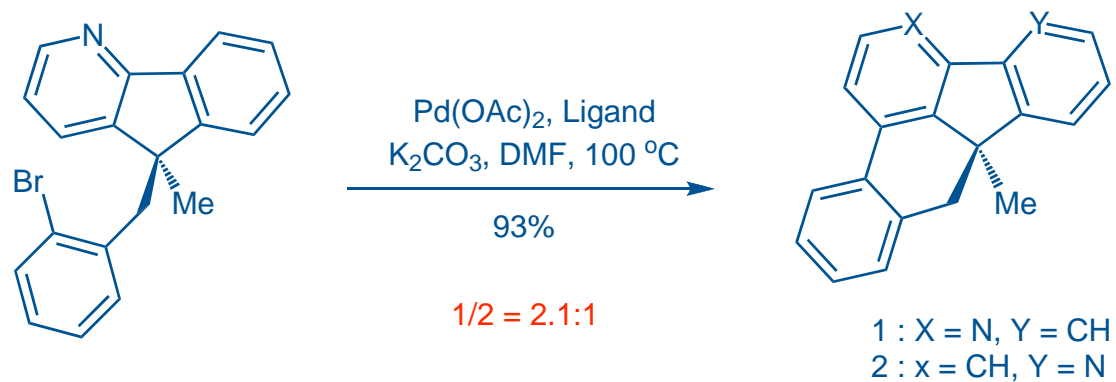


Gevorgyan, V. et al.
Org. Lett. 2004, 6, 1159

σ -Bond Metathesis

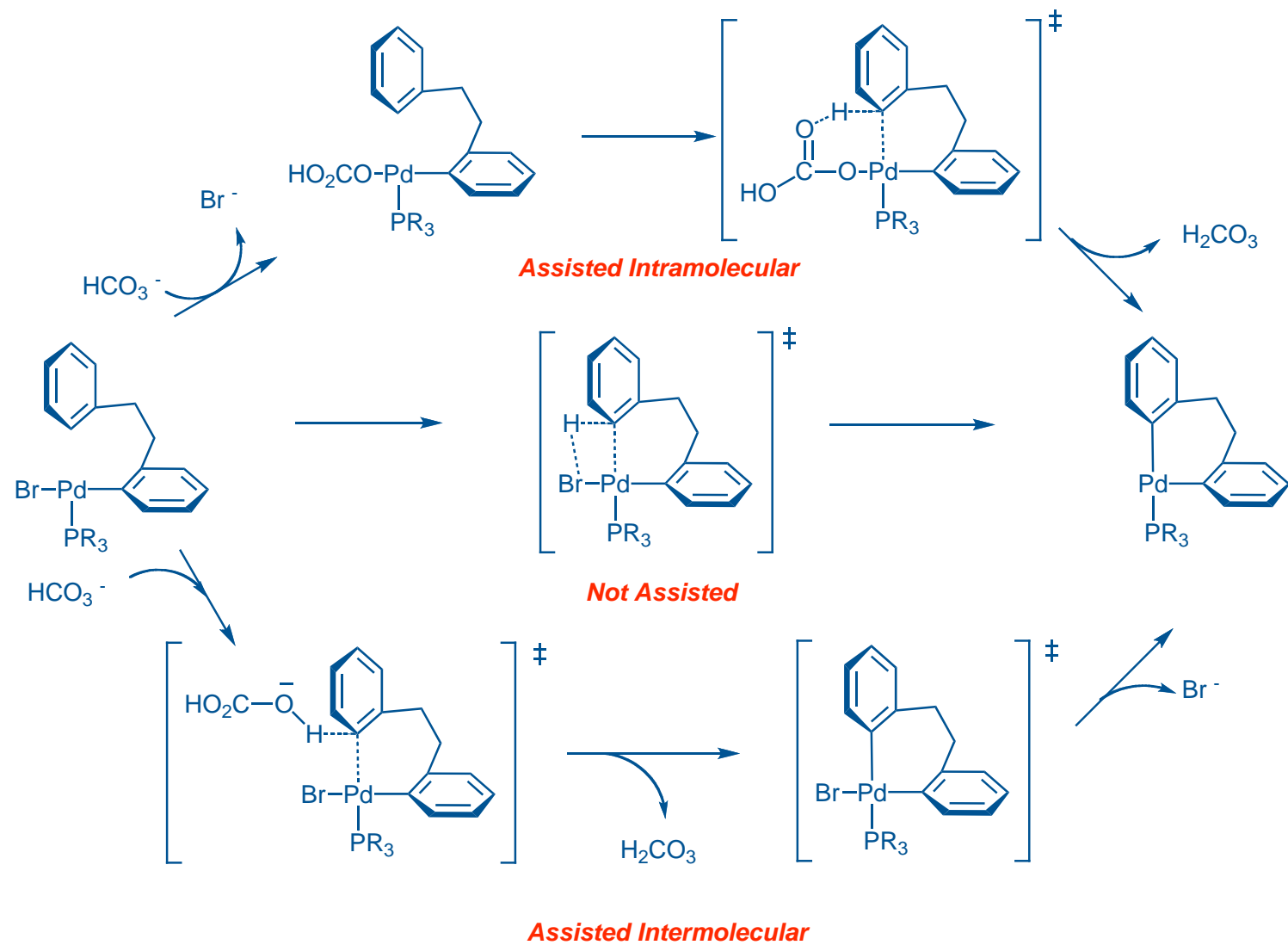


Proton Abstraction Mechanism

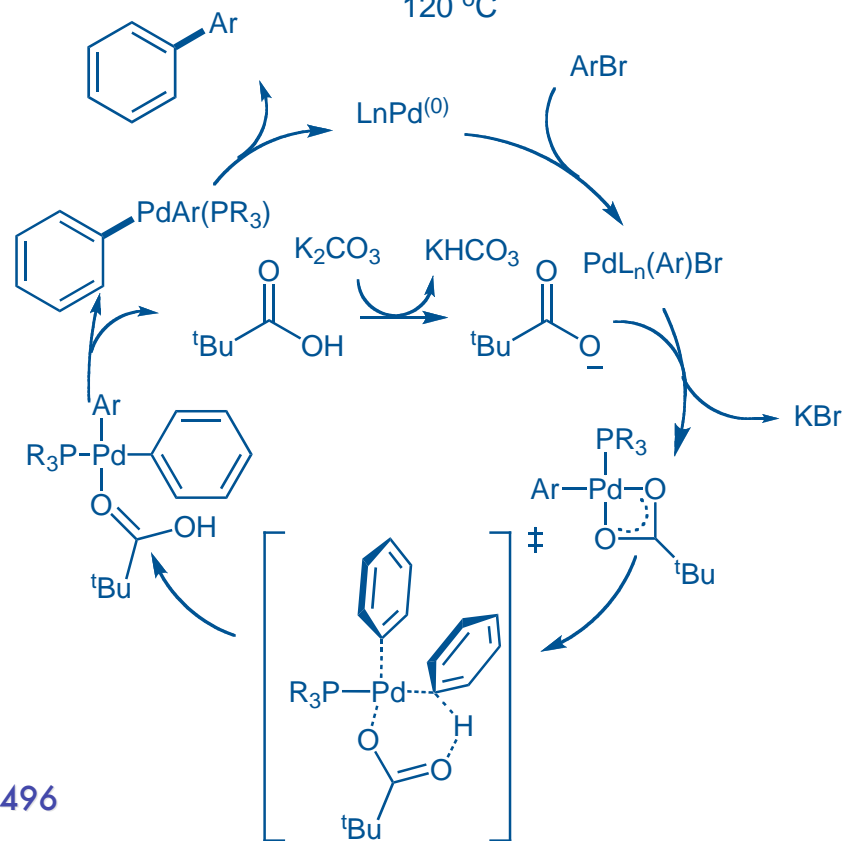
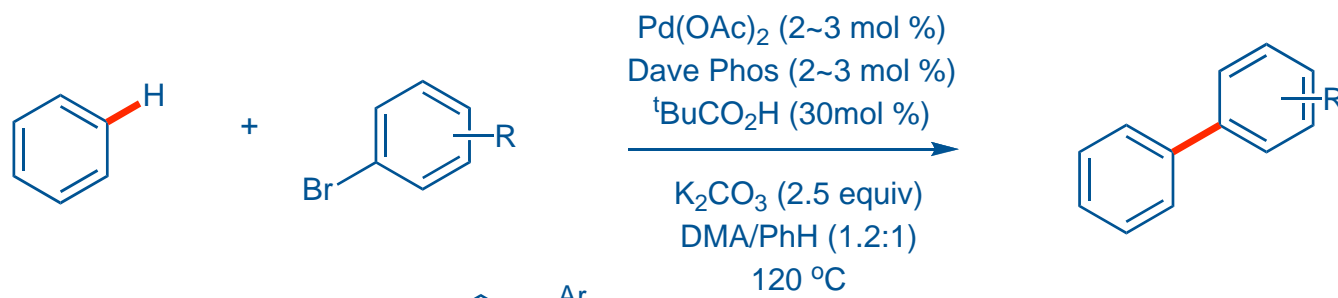


Ligand

Proton Abstraction Mechanism



Proton Abstraction Mechanism

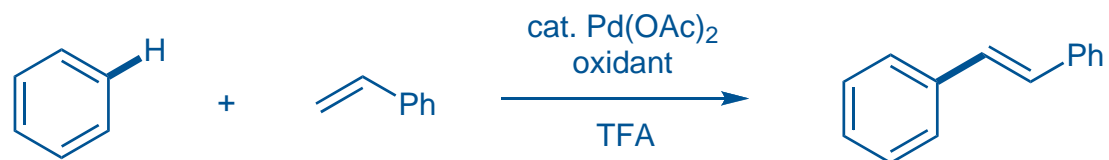


Fagnou, K. *et al.*
J. Am. Chem. Soc. **2006**, *128*, 16496

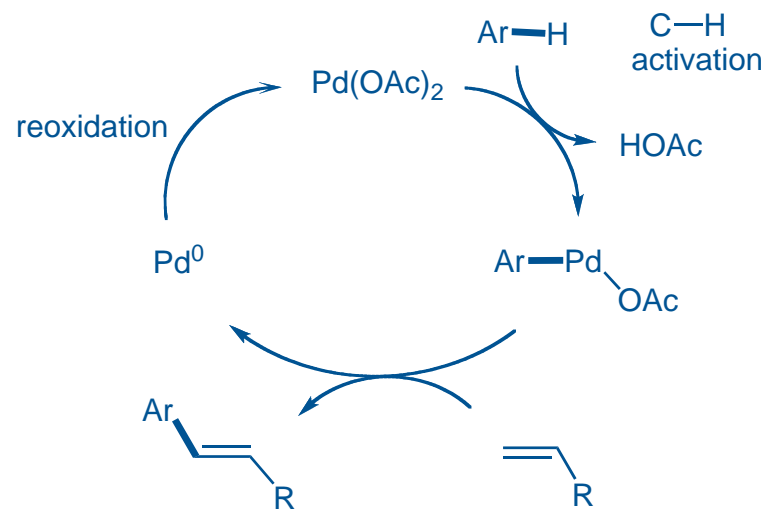
Olefination of C(sp²)–H Bonds: Pd^{II}/Pd⁰ Catalysis

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with Organometallic Reagents: Pd^{II}/Pd⁰ Catalysis*
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Early Report



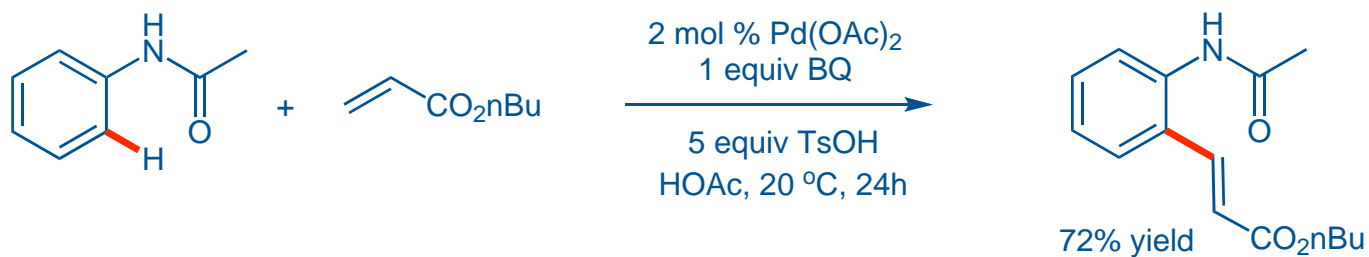
$\text{Pd}^{\text{II}}/\text{Pd}^0$ Catalytic cycle



ortho-Selective Olefination of Arene

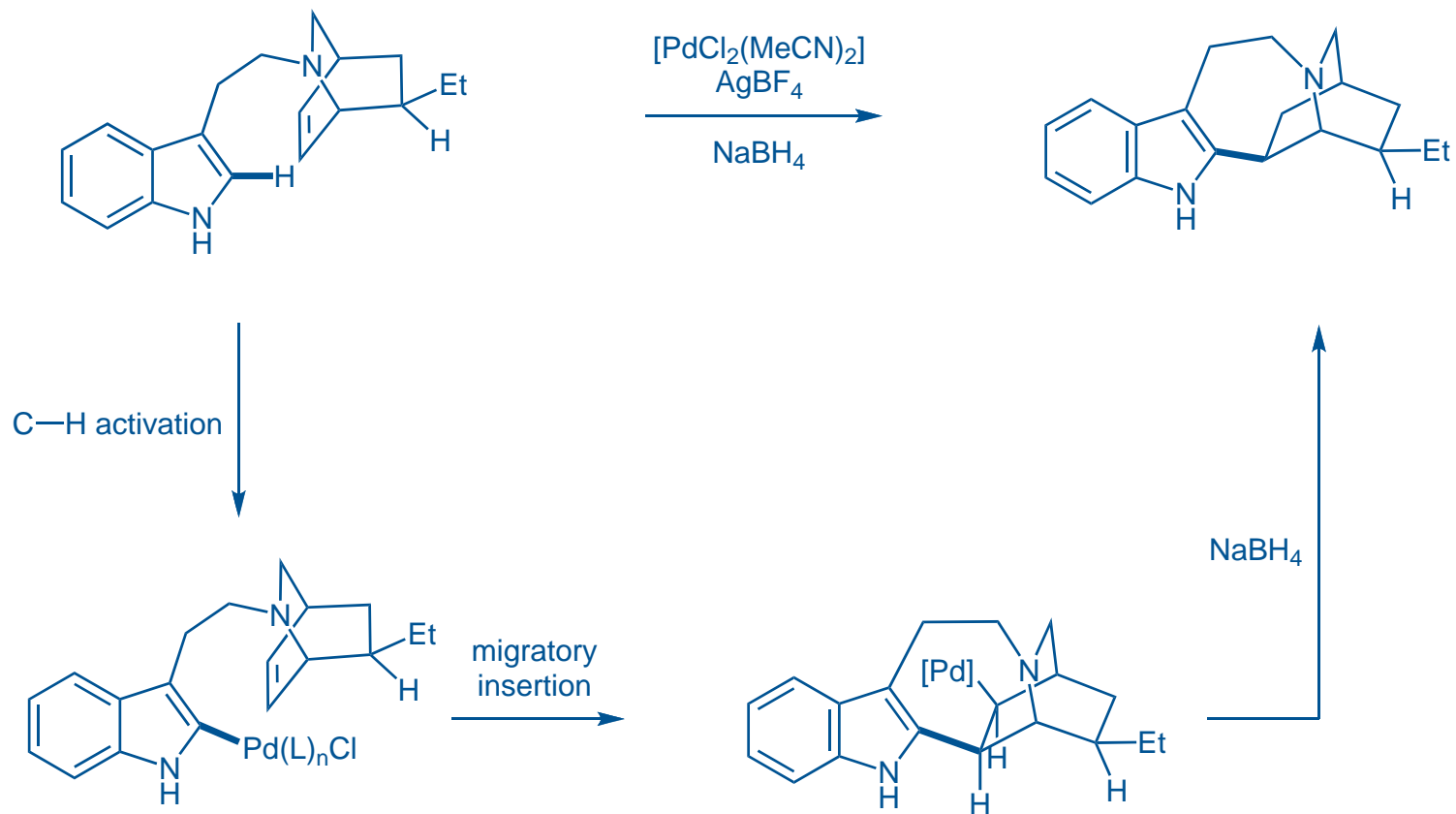


Miura, M. *et al.* *J. Org. Chem.* **1998**, *63*, 5221

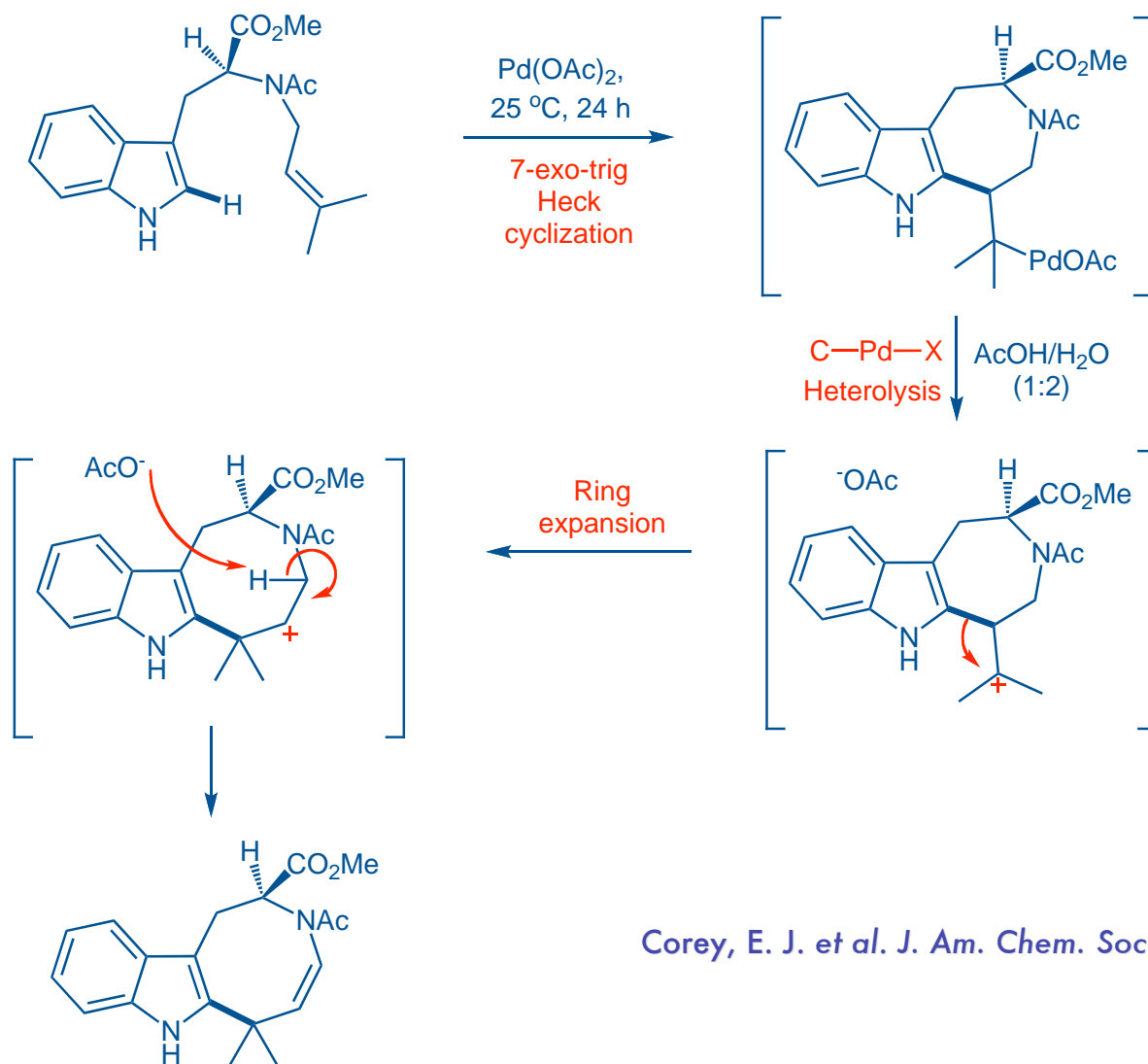


de Vries. *et al.* *J. Am. Chem. Soc.* **2002**, *124*, 1586

Indole Olefination

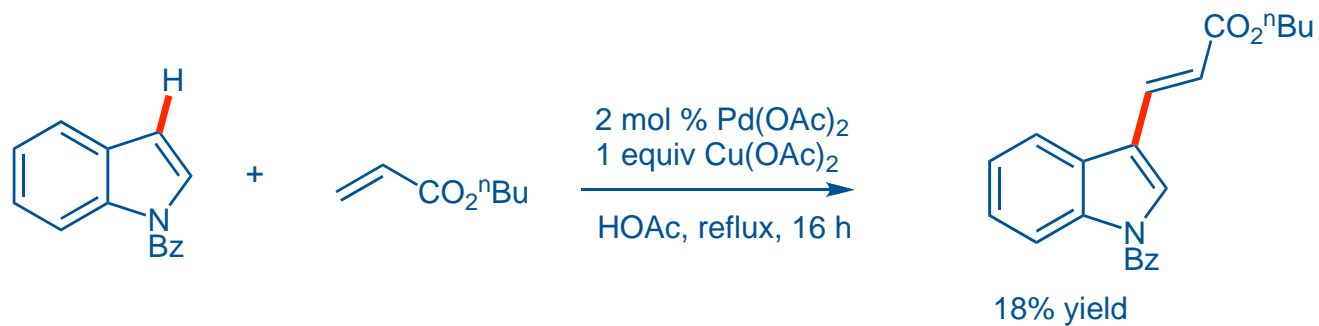


Indole Olefination

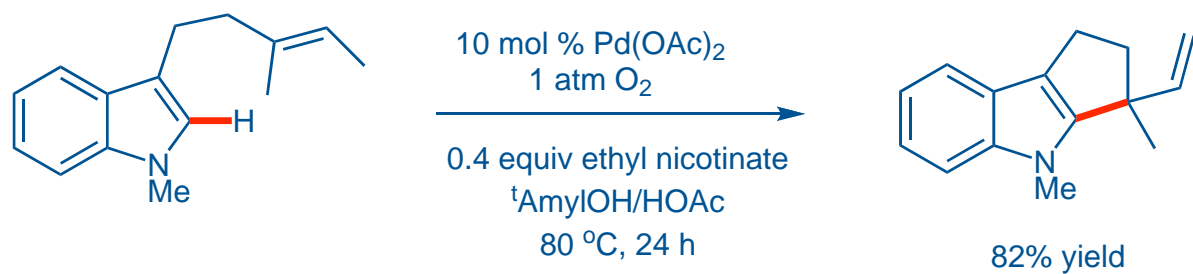


Corey, E. J. et al. *J. Am. Chem. Soc.* 2002, 124, 7904

Different Oxidant

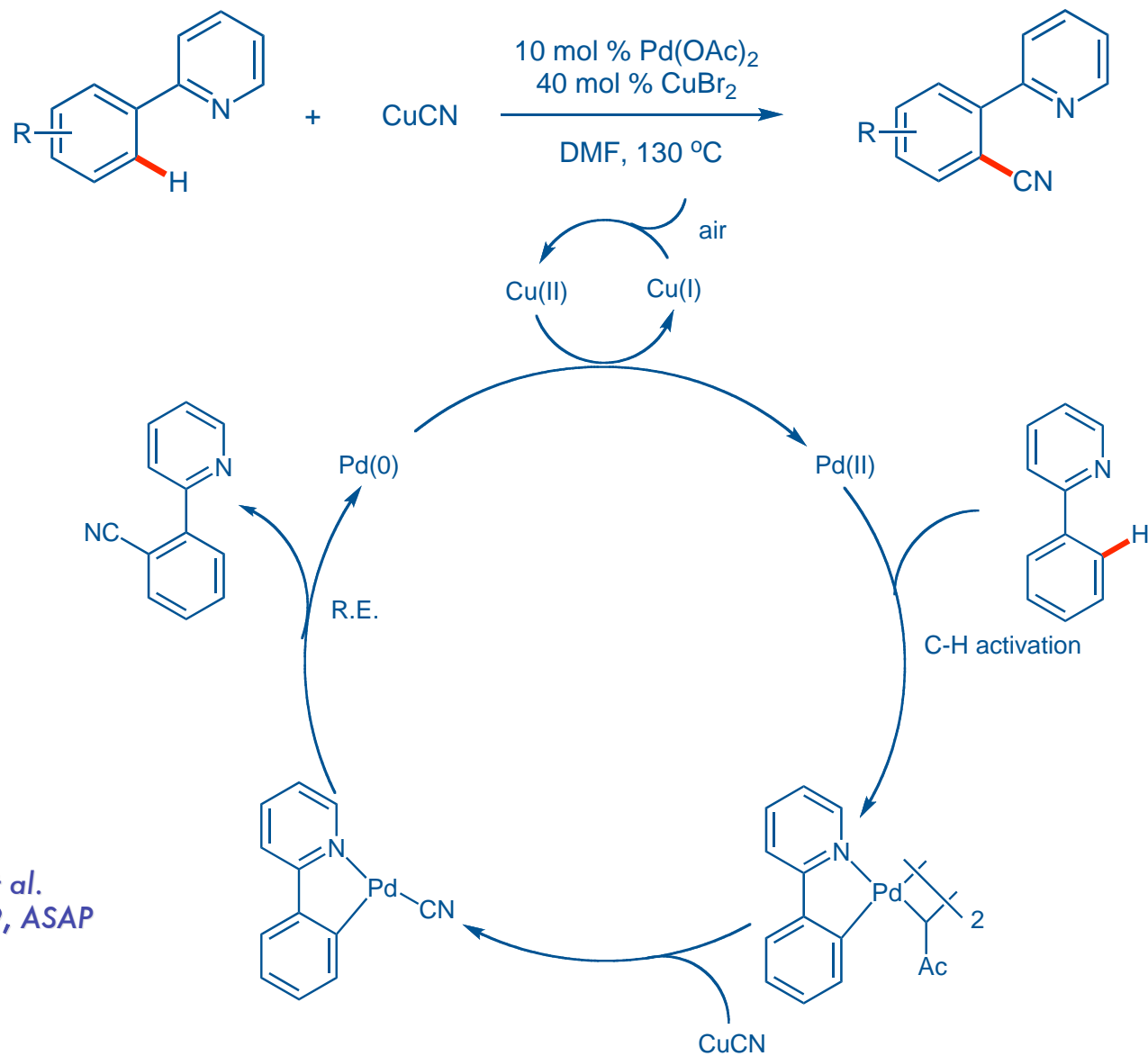


Itahara, T. et al. *J. Chem.Soc. Perkin Trans. 1* **1983**, 1361



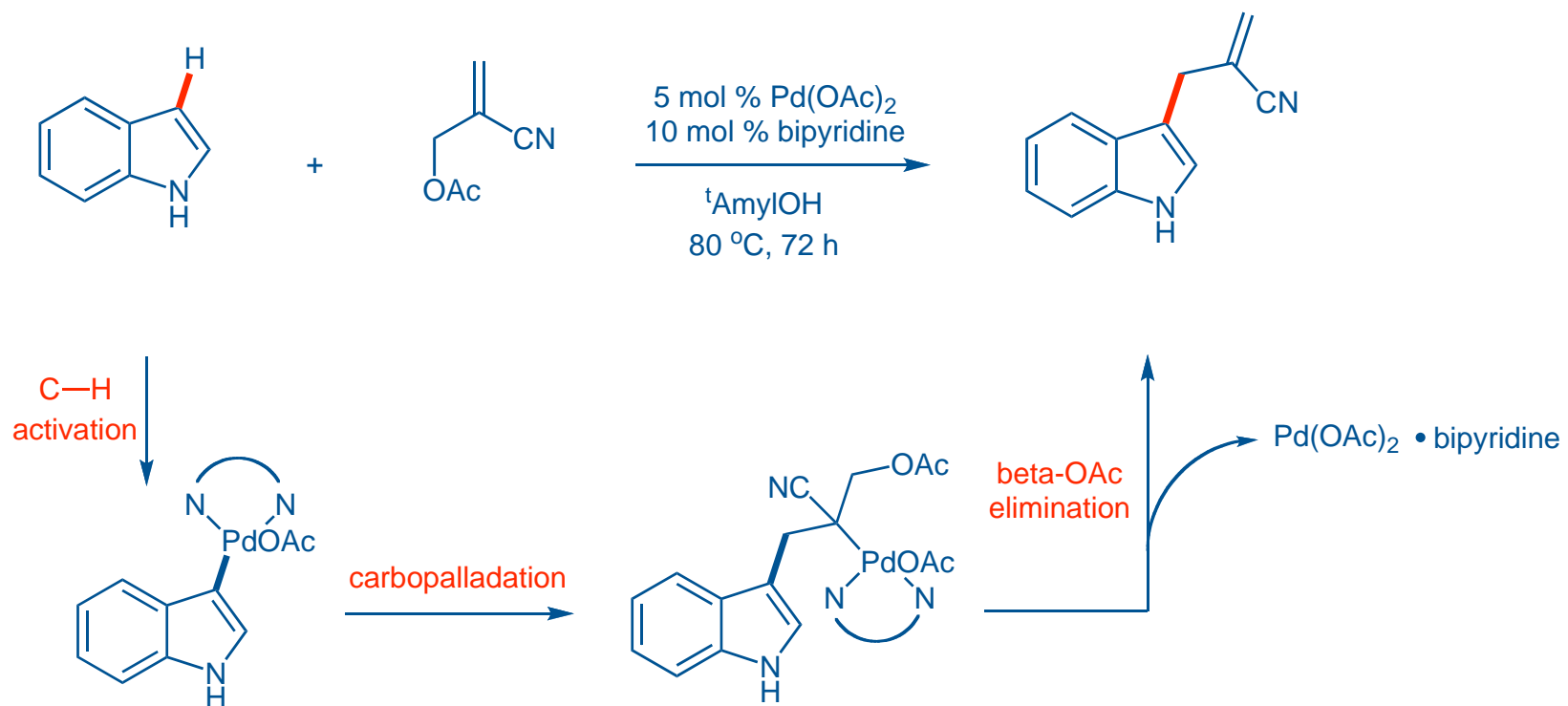
Stoltz, B.M. et al. *J. Am. Chem. Soc.* **2003**, 125, 9578

Different Oxidant



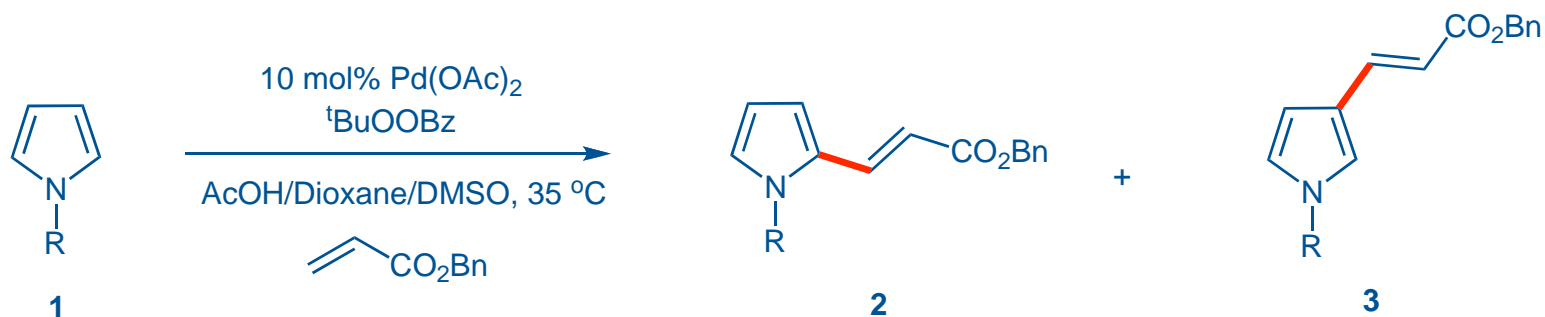
Cheng, J. et al.
Org. Lett. 2009, ASAP

Oxidant-free



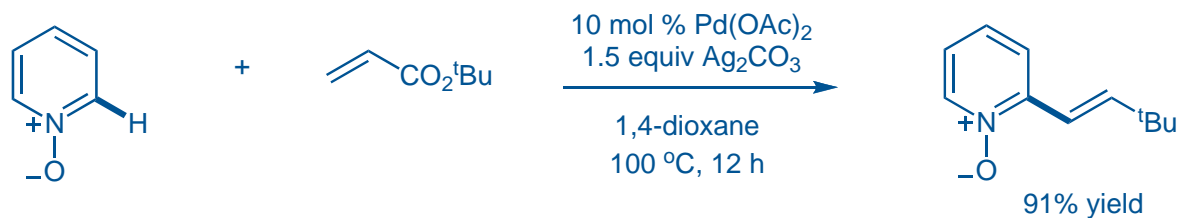
Ma, S. et al. *Tetrahedron Lett.* 2004, 45, 8419

Regioselective Olefination of Pyrroles

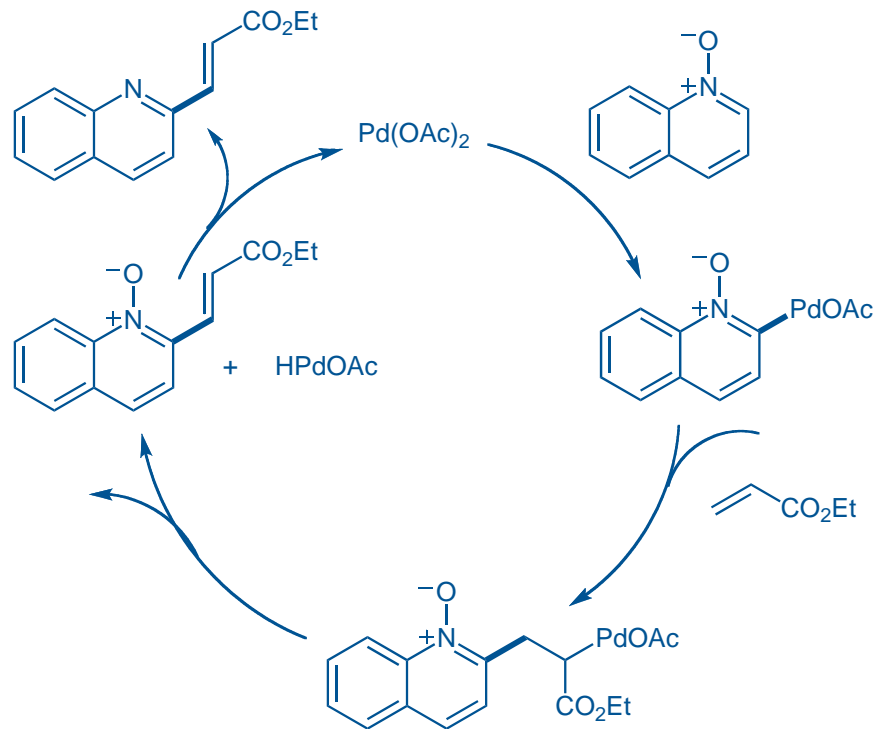
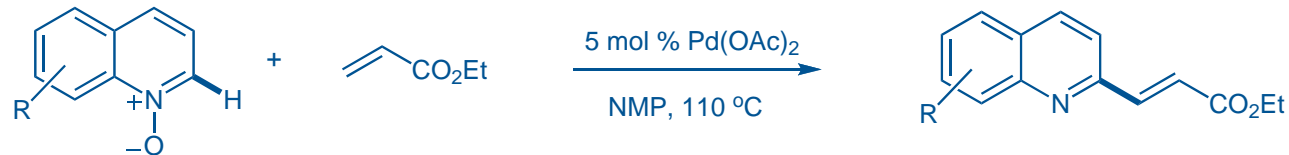


entry	catalyst loading	R	yield of C2	yield of C3	ratio 2:3
1	10	Bn	48	23	2.1:1
2	10	SEM	48	21	2.3:1
3	10	Ac	65	-	>95:5
4	10	Boc	73	-	>95:5
5	10	Ts	70	-	>95:5
6	10	TIPS	-	78	<5:95

Olefination of Pyridine *N*-oxide

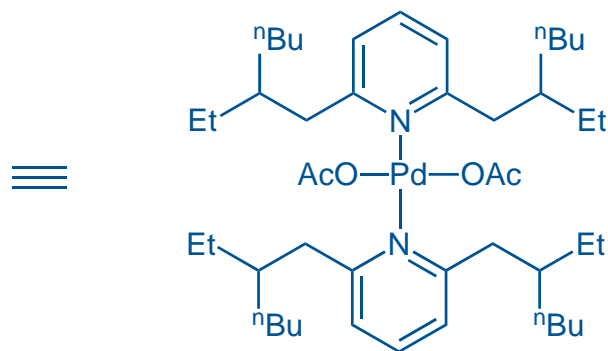
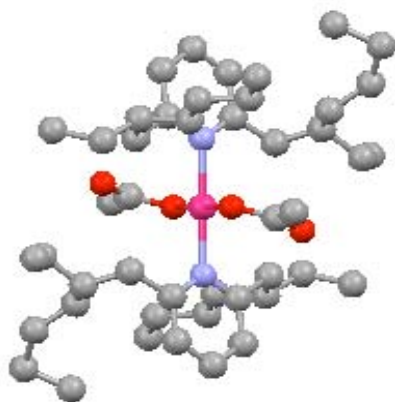
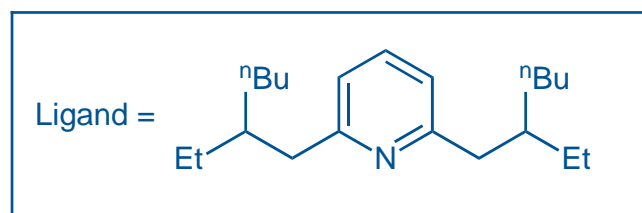
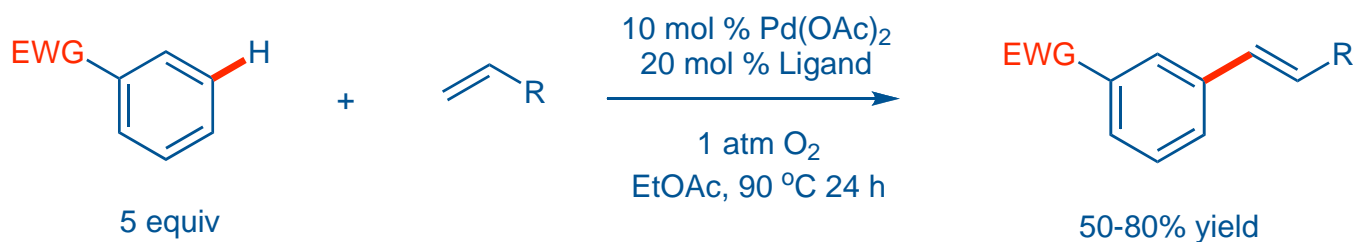


Chang, S. et al.
J. Am. Chem. Soc. **2008**, *130*, 9254



Wu, Y. et al.
J. Am. Chem. Soc. **2009**, ASAP

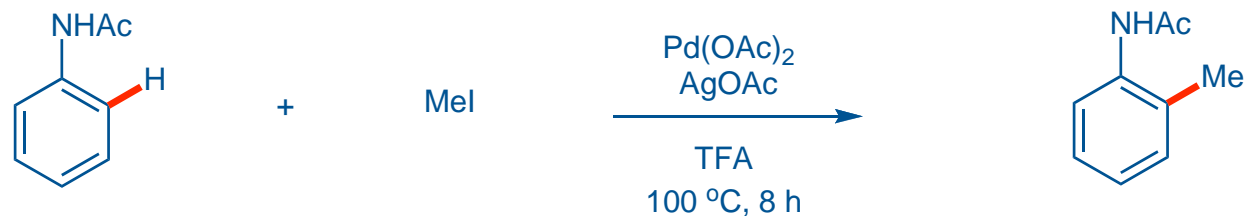
meta C-H Activation/Olefination



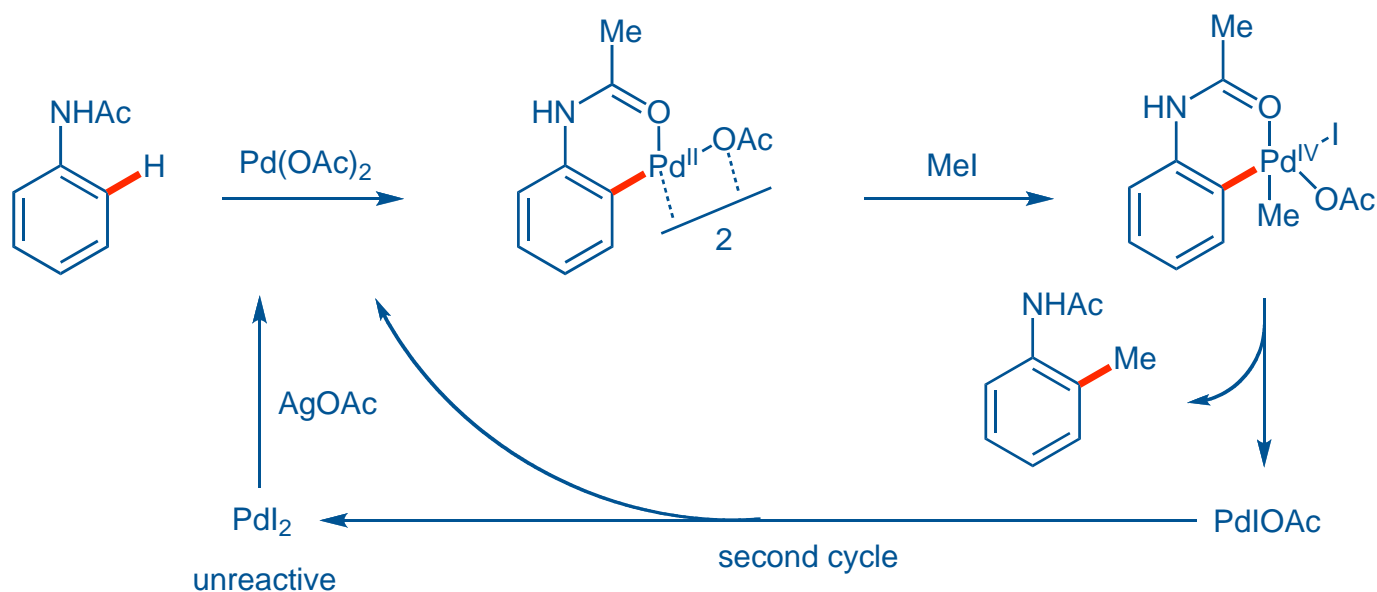
Arylation of C(sp²)-H and C(sp³)-H Bonds: Pd^{II}/Pd^{IV} Catalysis

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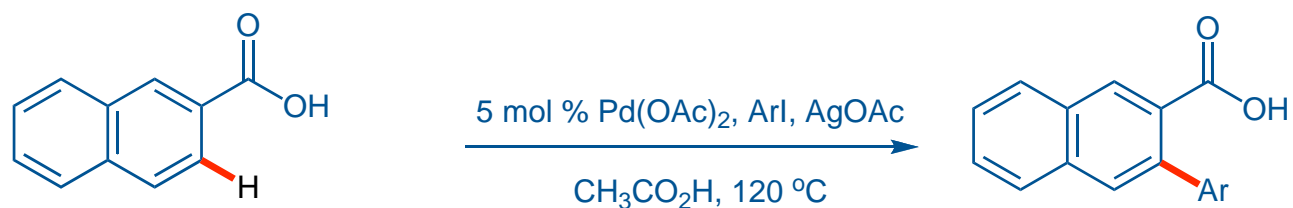
ortho-Methylation of anilides



without AgOAc : 1.5 turnovers
with excess AgOAc : 10 turnovers



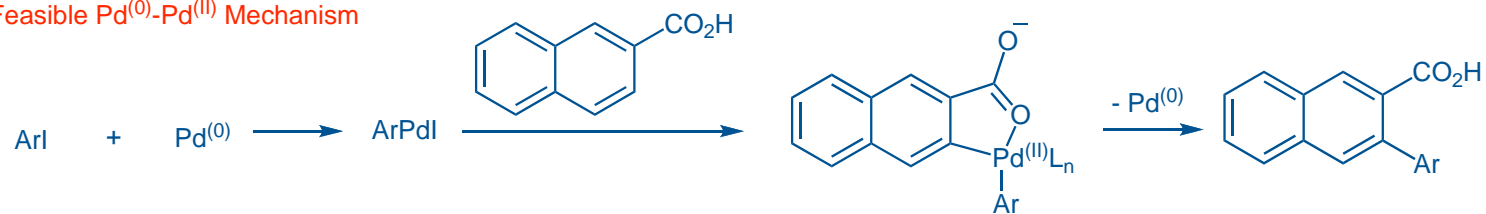
Direct *ortho*-Arylation of Naphthoic acids



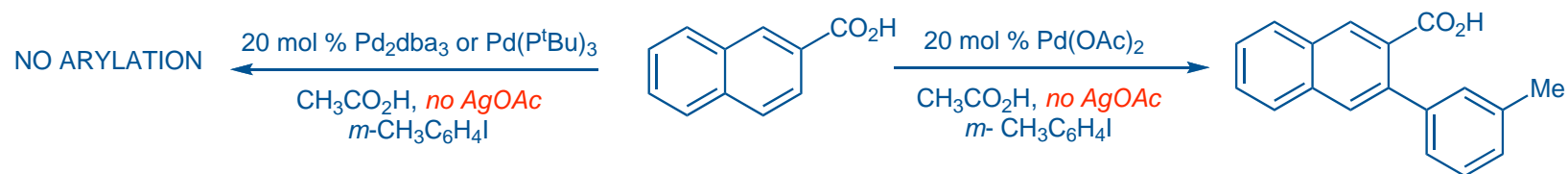
A Feasible Pd^(II)-Pd^(IV) Mechanism



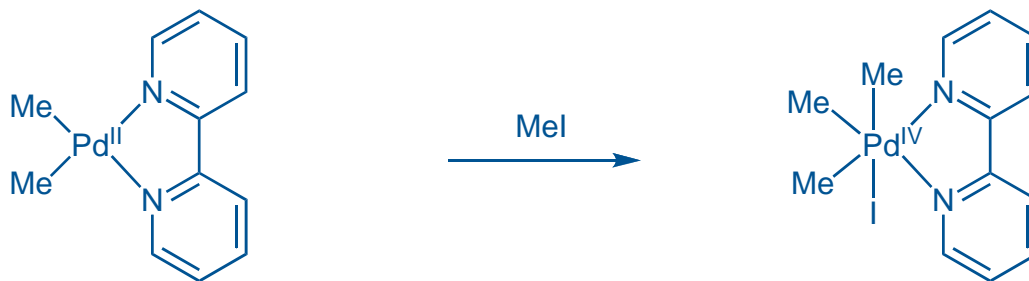
A Feasible Pd⁽⁰⁾-Pd^(II) Mechanism



Experimental Results Support Pd^(II)-Pd^(IV) Catalytic cycle

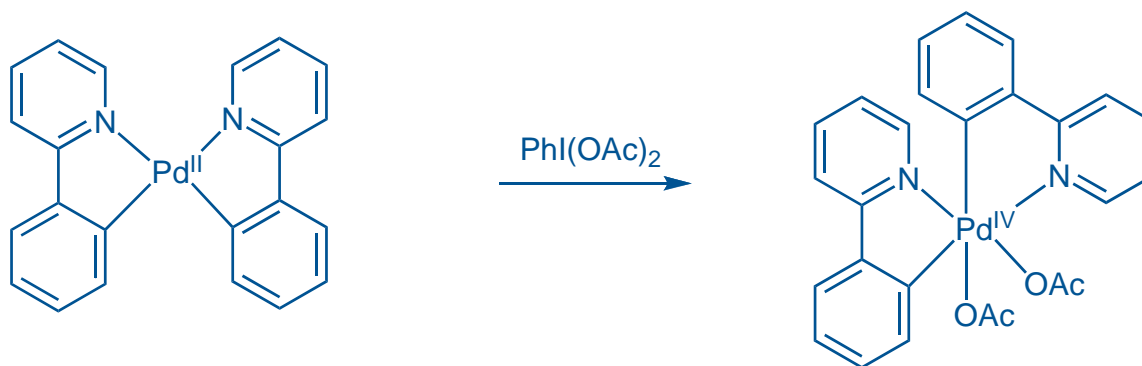


X-ray crystallographic Structure of Pd^{IV} Complexes



x-ray crystal structure

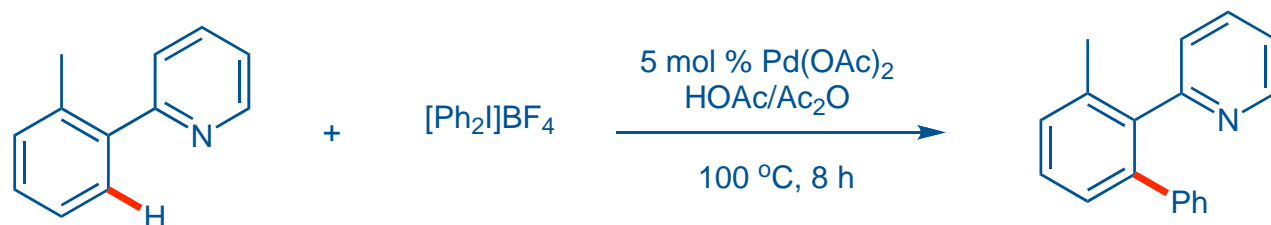
Canty, A. et al. *J. Chem. Soc. Chem. Commun.* **1986**, 1722



x-ray crystal structure

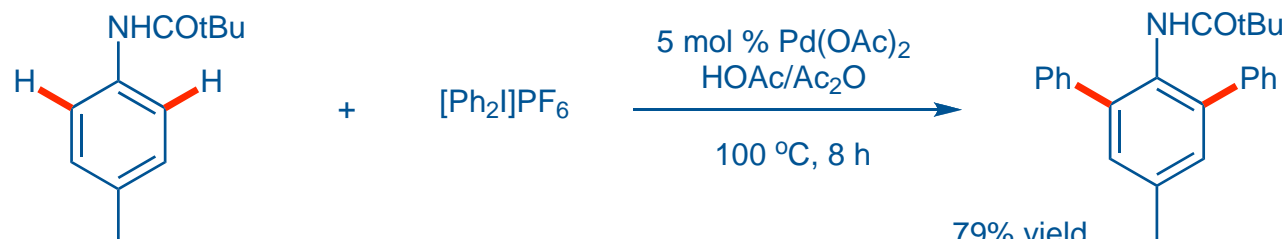
Sanford, M. et al. *J. Am. Chem. Soc.* **2005**, 127, 12790

Arylation of C–H bonds by Pd^{II}/Pd^{IV} catalysis



88% yield

Sanford, M. S. *et al.*
J. Am. Chem. Soc. **2005**, *127*, 7330



79% yield

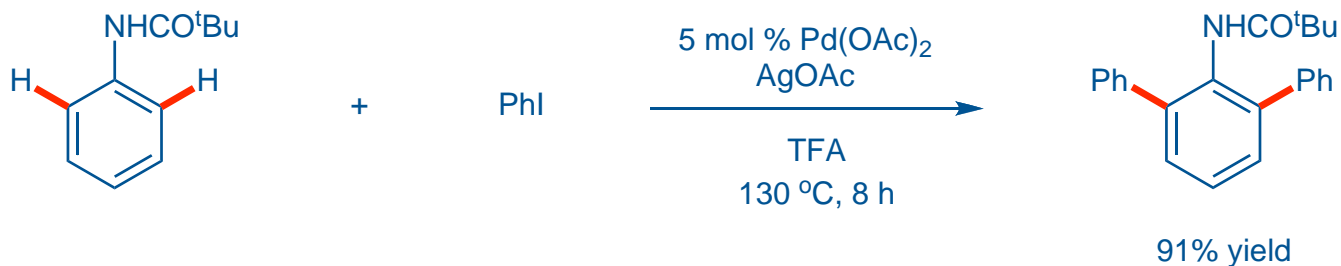
Daugulis, O. *et al.*
Angew. Chem. Int. Ed. **2005**, *44*, 4046



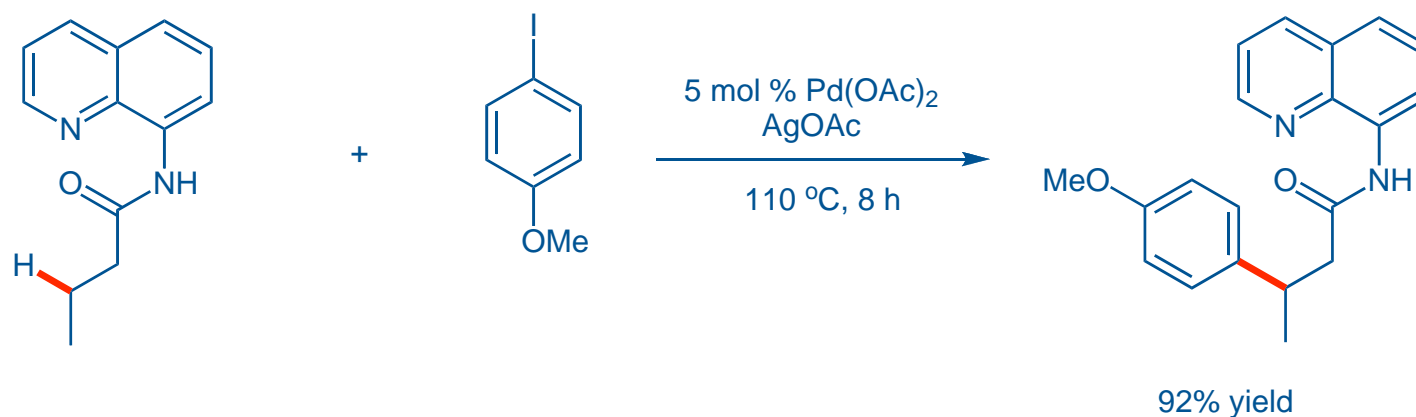
Sanford, M. S. *et al.*
J. Am. Chem. Soc. **2006**, *128*, 4972

Pd(OAc) ₂	49%, 5 min
IMesPd(OAc) ₂	86%, 18 h

Arylation of C–H bonds using ArI



Daugulis, O. et al.
Angew. Chem. Int. Ed. **2005**, *44*, 4046

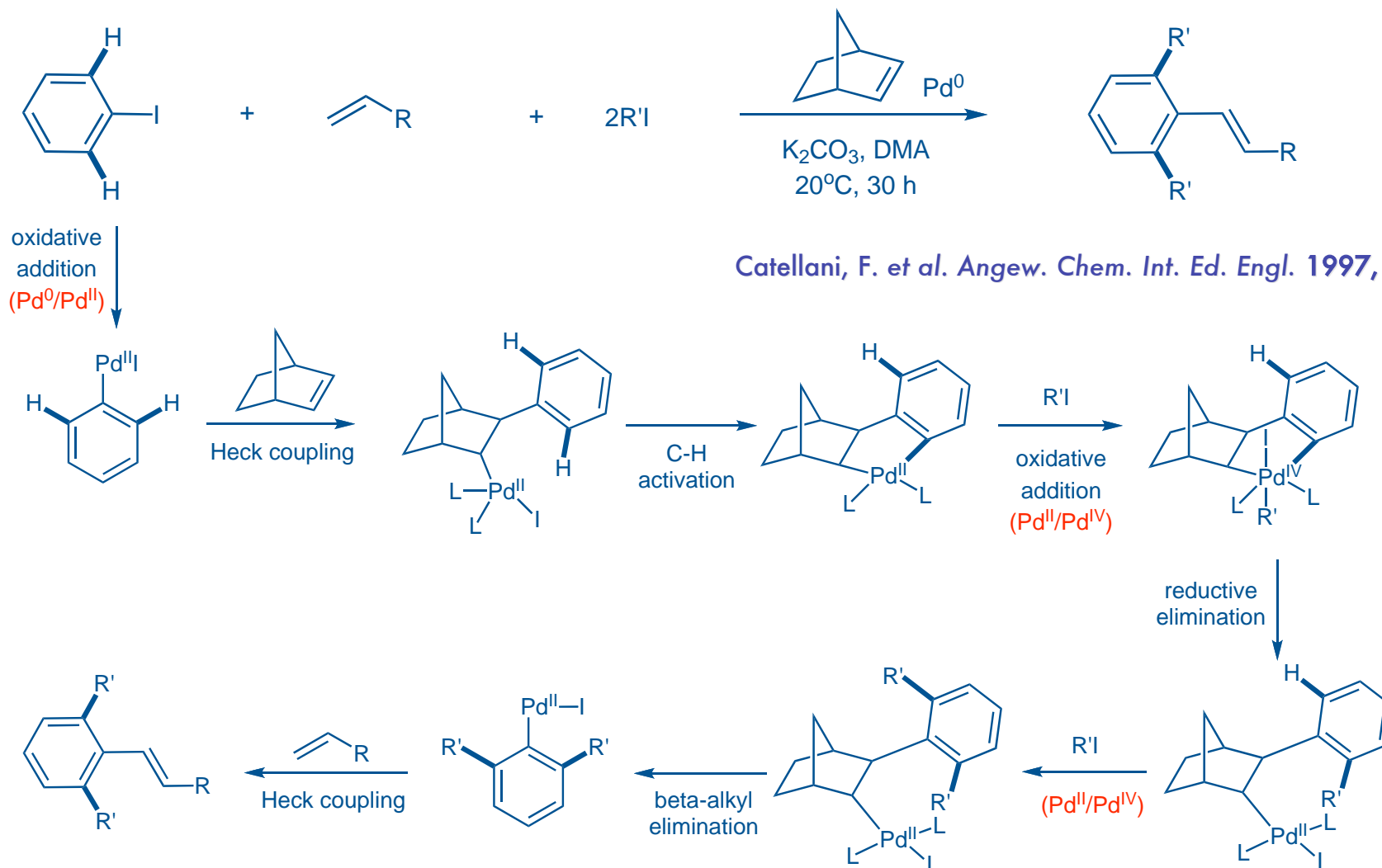


Daugulis, O. et al.
J. Am. Chem. Soc. **2005**, *127*, 13154

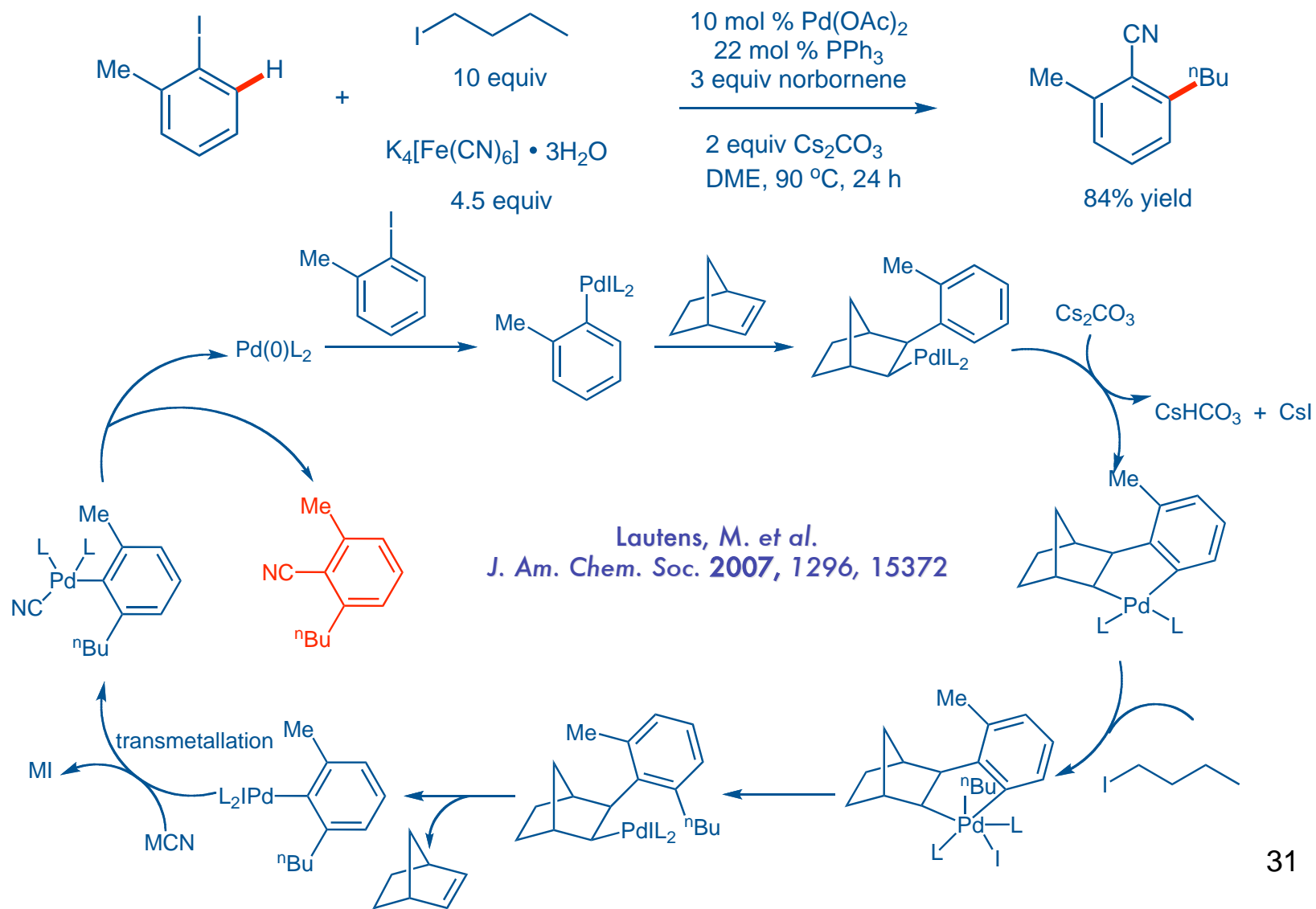
Sequential ortho-Alkylation and Olefination of Aryl Iodides: Pd⁰/Pd^{II}/Pd^{IV} Catalysis

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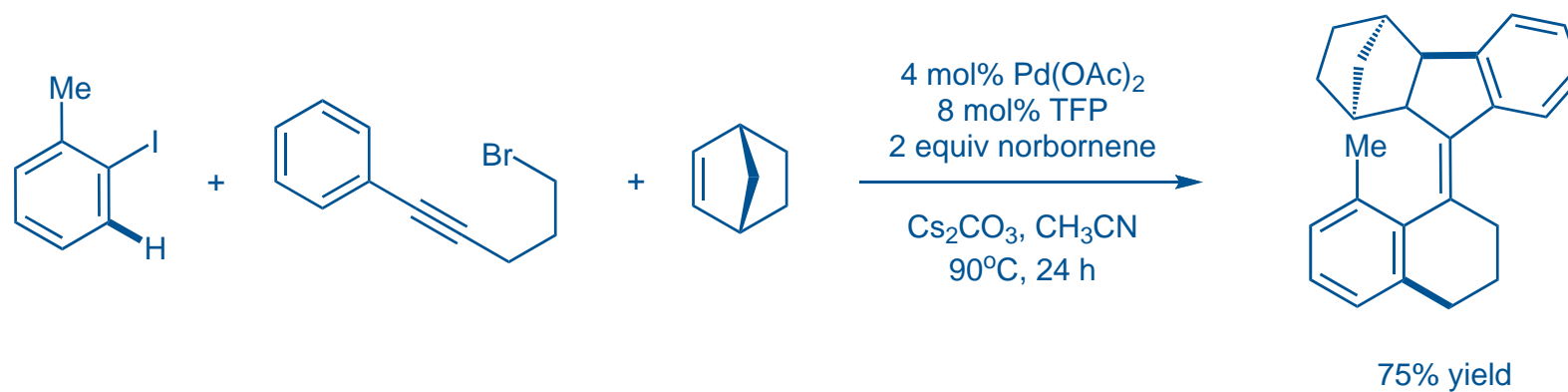
ortho-Alkylation of C-H bonds by Pd⁰/Pd^{II}/Pd^{IV}



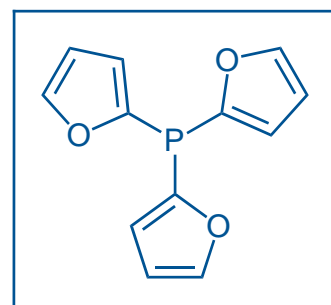
ortho Alkylation and Cyanation of Arenes



Tetrasubstituted Helical Alkenes



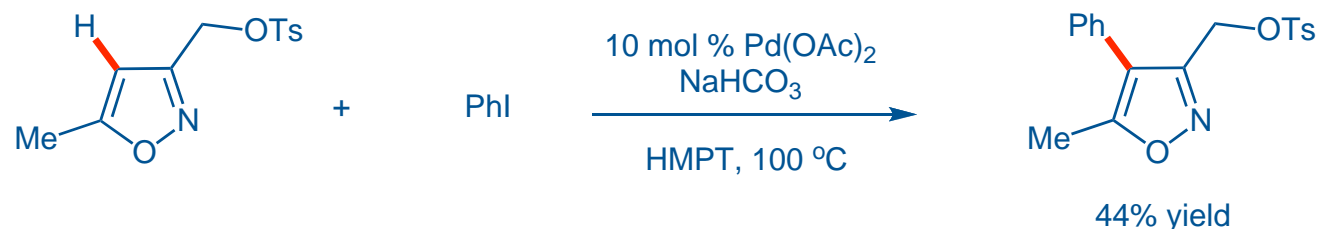
TFP



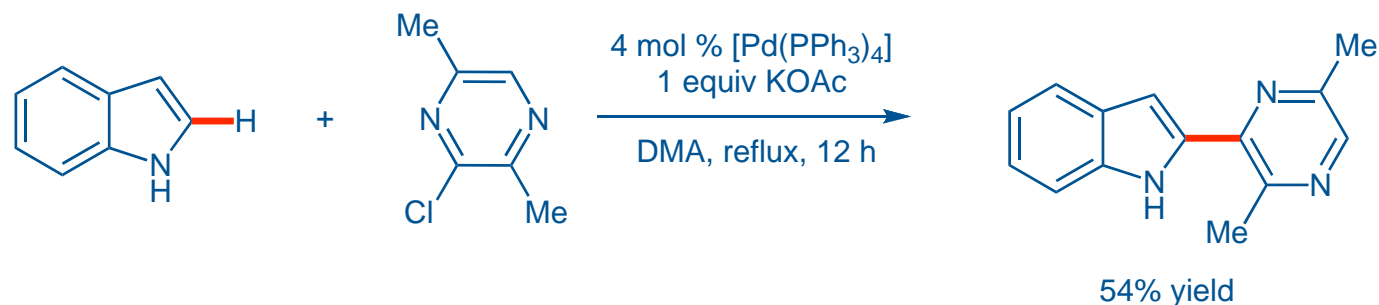
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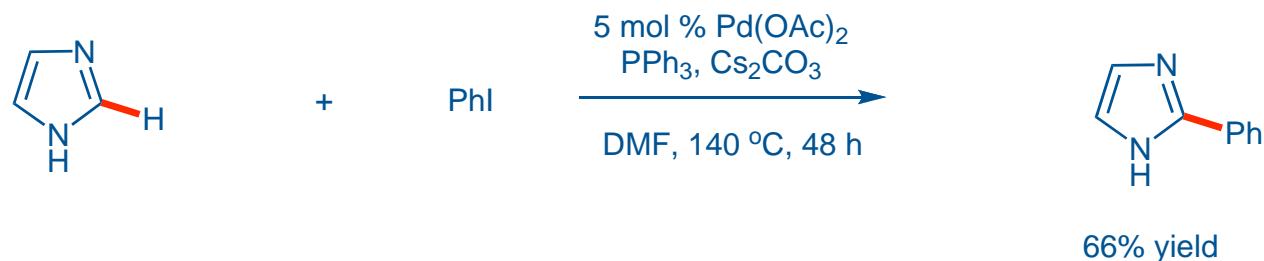
Arylation of Electron Rich Heterocycles



Sakai, K. et al. *Heterocycles*. 1982, 17, 235

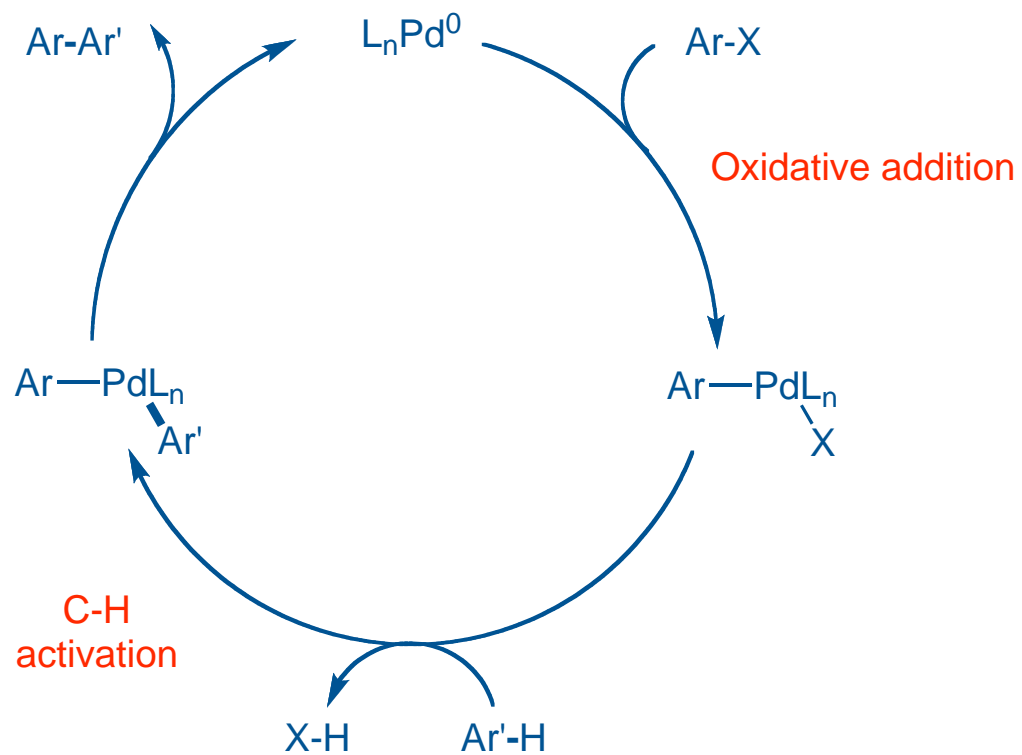


Ohta, A. et al. *Heterocycles*. 1982, 19, 329

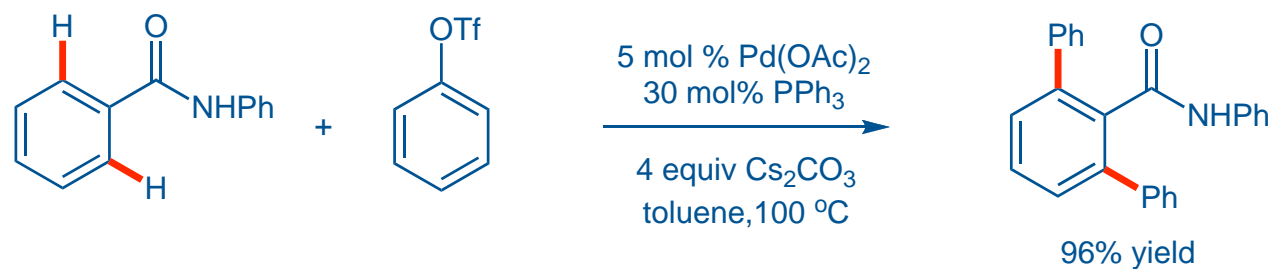


Nomura, M. et al. *Bull. Chem. Soc. Jpn.* 1998, 71, 467

Pd⁰/Pd^{II} Catalytic cycle

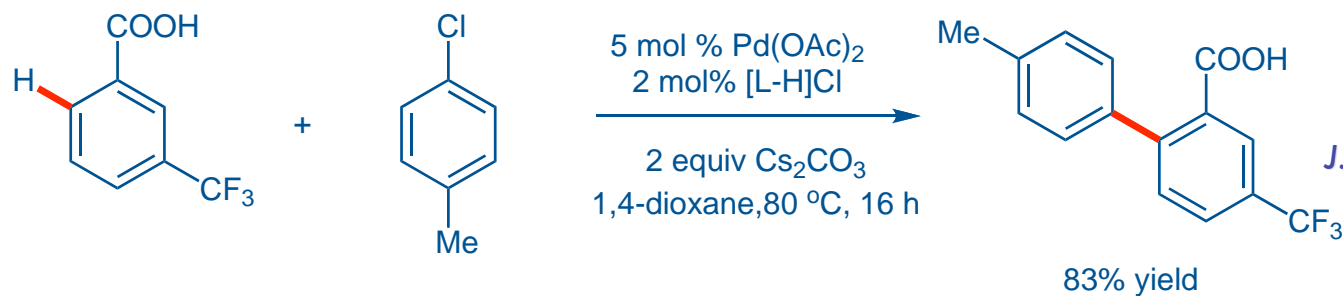
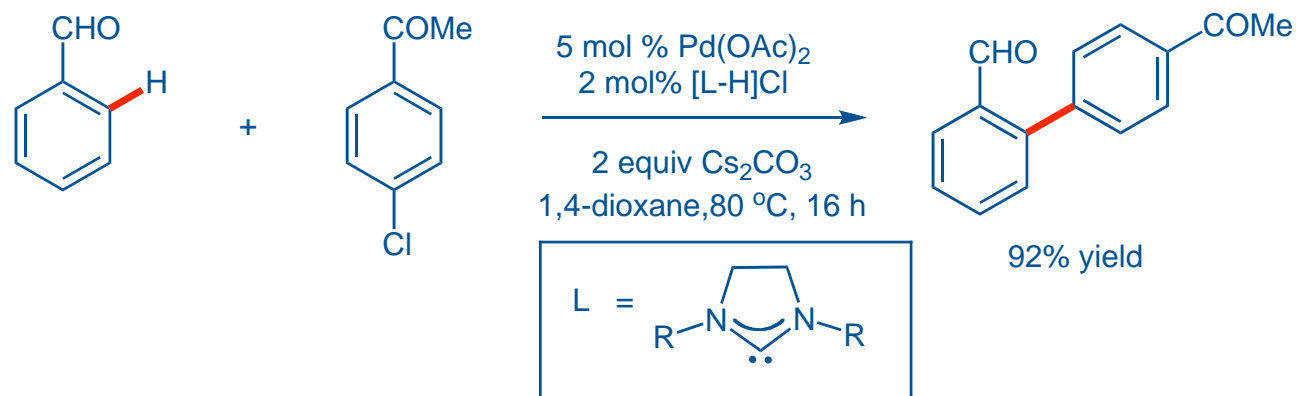


ortho-Coupling of broad substrates



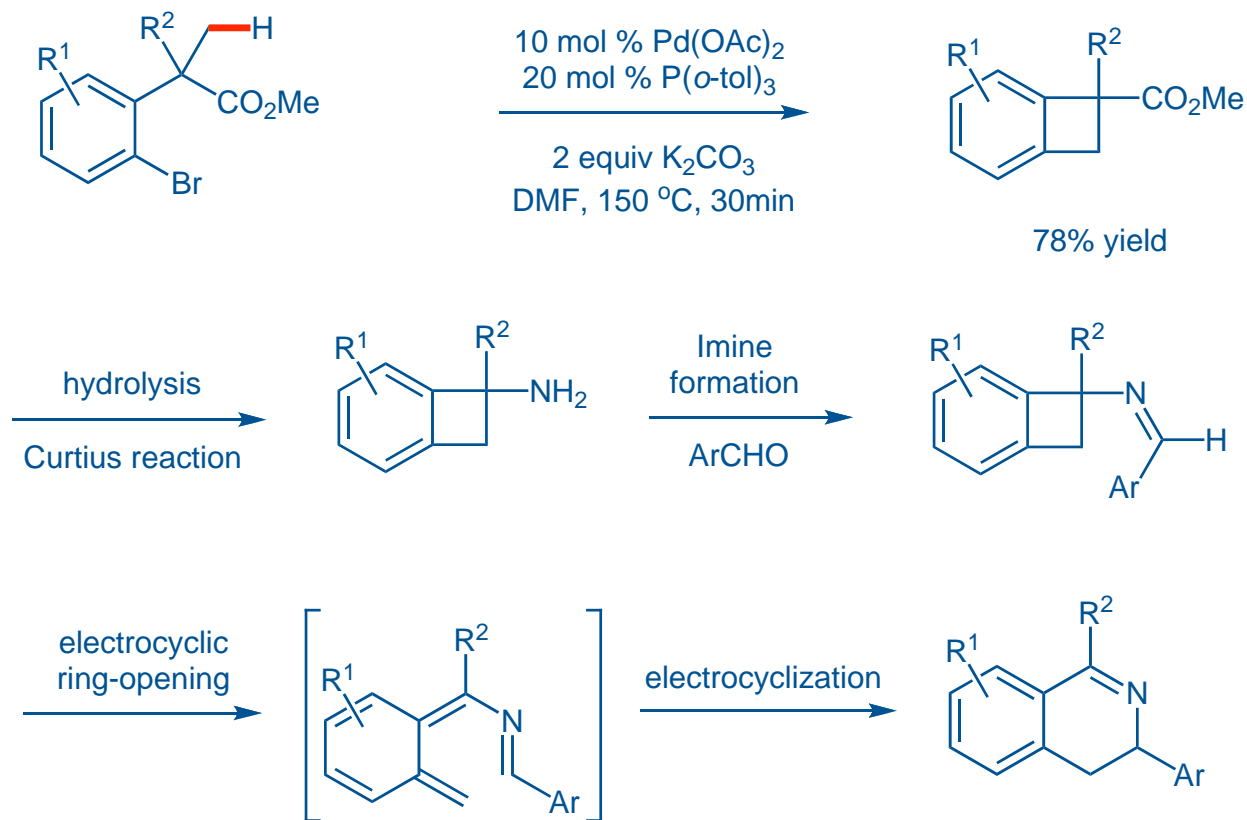
Miura, M. et al.
Tetrahedron Lett. **2000**, *41*, 2665

Cetinkaya. et al.
Tetrahedron Lett. **2005**, *46*, 2273



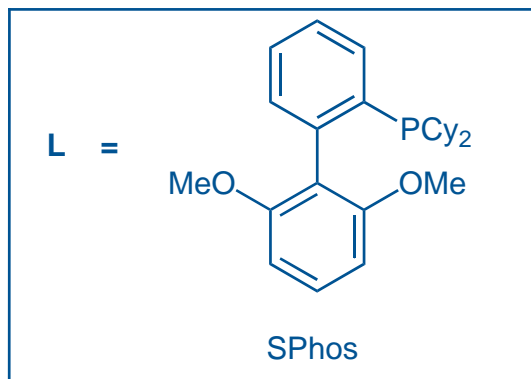
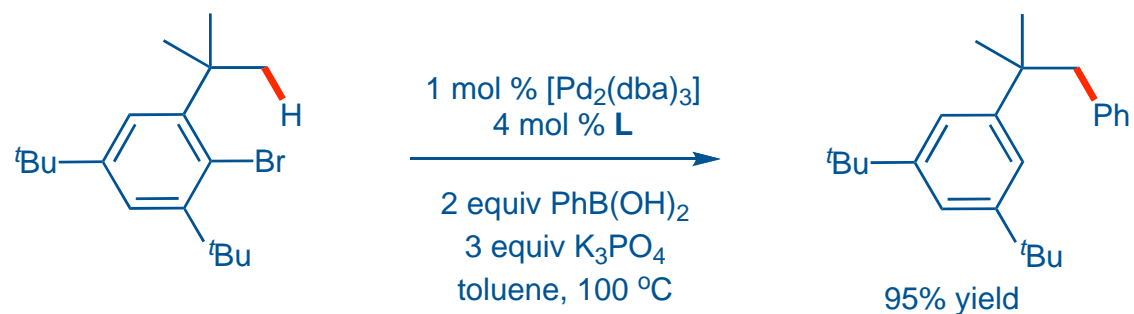
Daugulis, O. et al.
J. Am. Chem. Soc. **2007**, *129*, 9879

Intramolecular Arylation of C(sp³)–H bonds

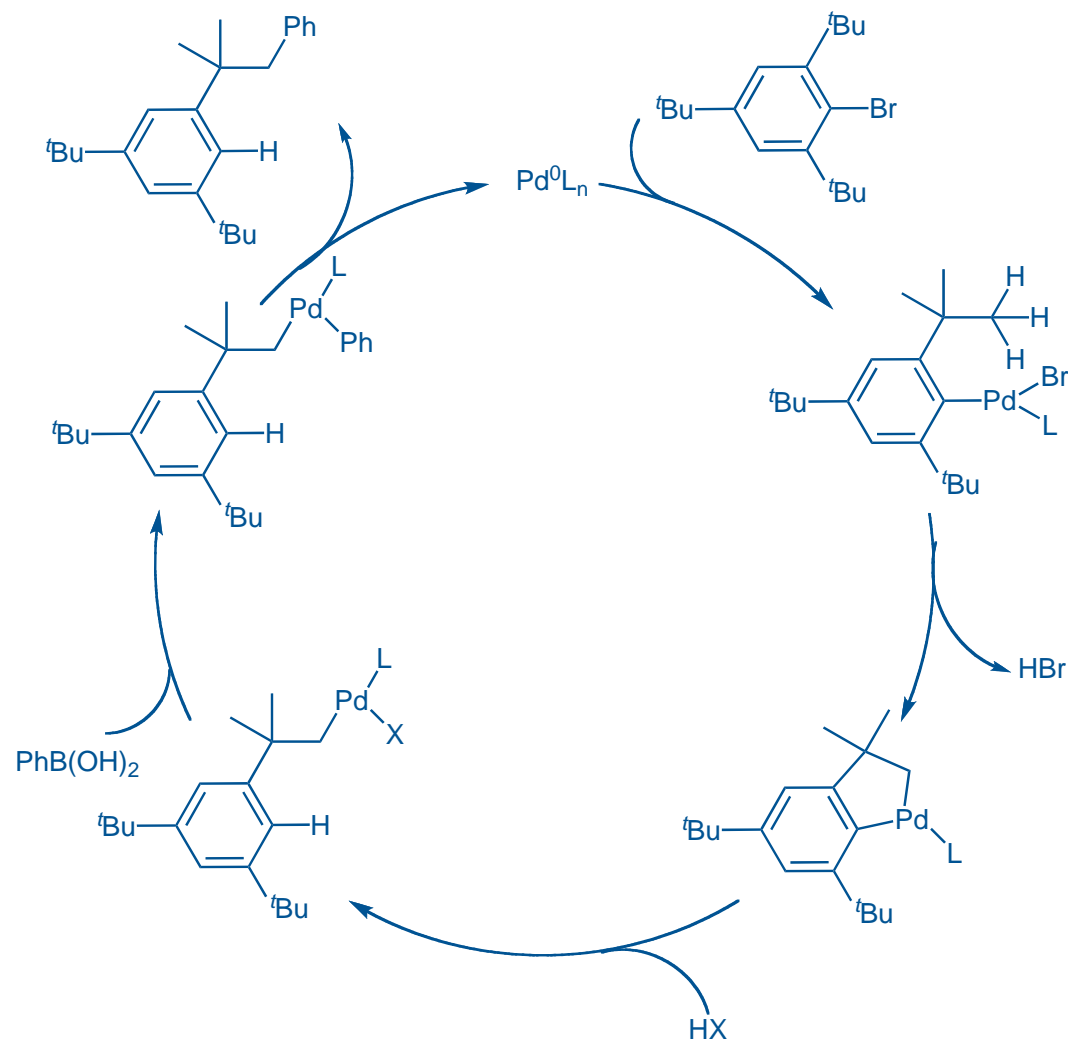


Baudoin, O. et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 179
Baudoin, O. et al. *J. Am. Chem. Soc.* **2008**, *130*, 15157

Arylation of C(sp³)–H Bonds with External ArB(OH)₂

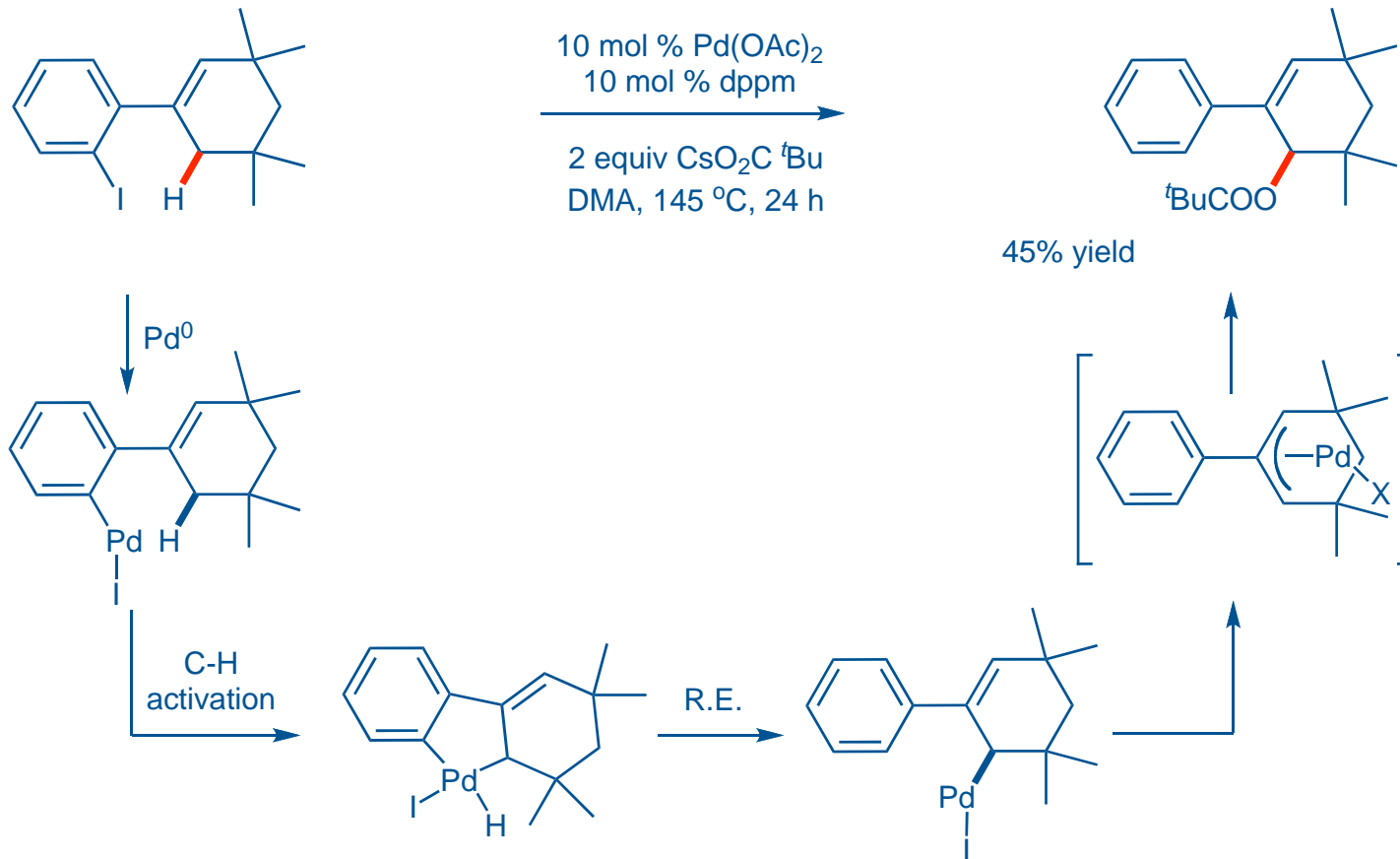


Arylation of C(sp³)–H Bonds with External ArB(OH)₂



Bulchwald, S. *et al.*
J. Am. Chem. Soc. **2005**, *127*, 4685

Pd-Migration

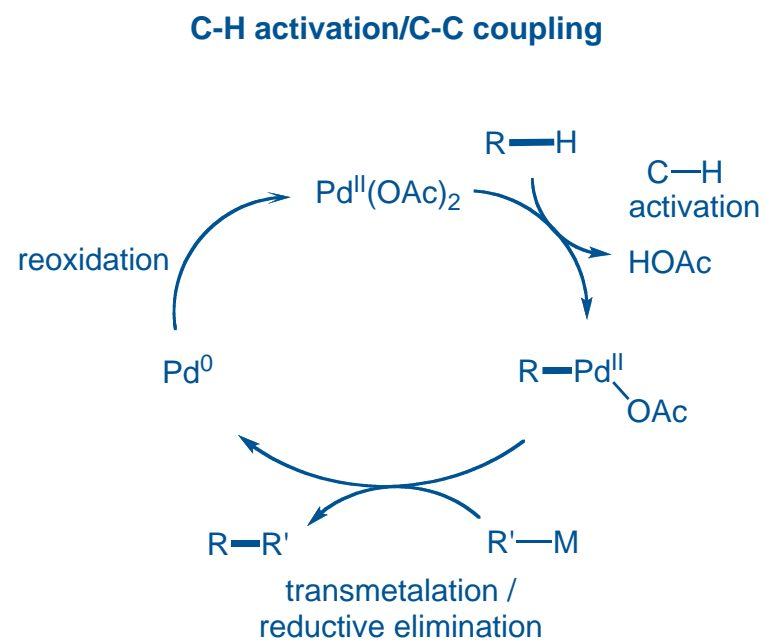
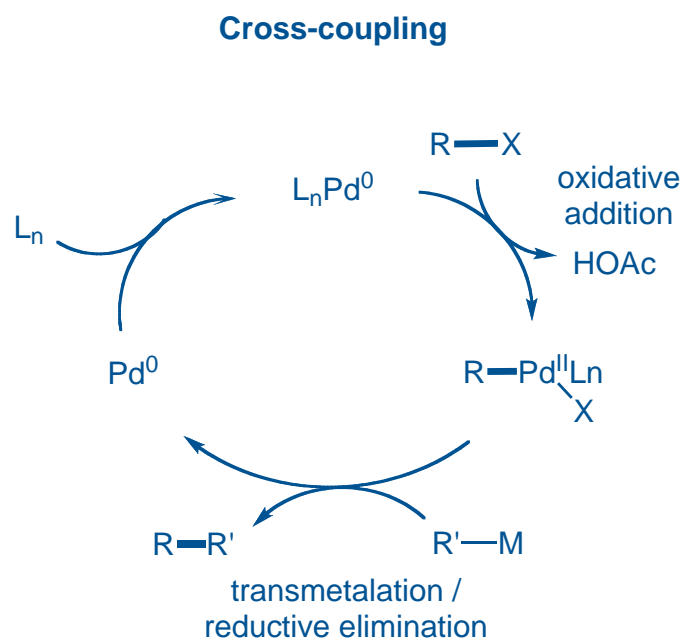


Larock, R. et al. *Angew. Chem. Int. Ed.* 2005, 44, 1873

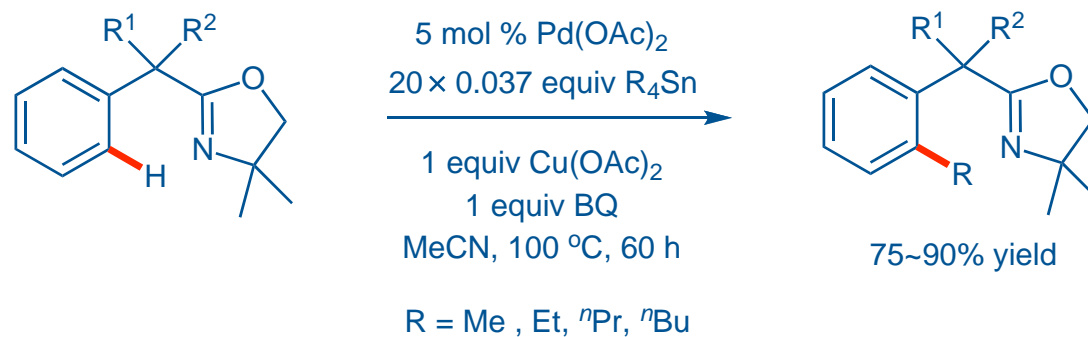
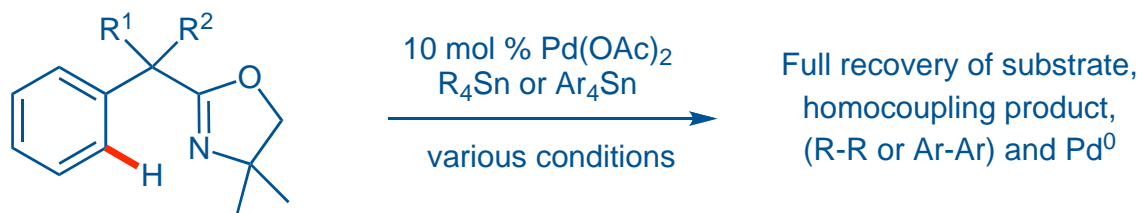
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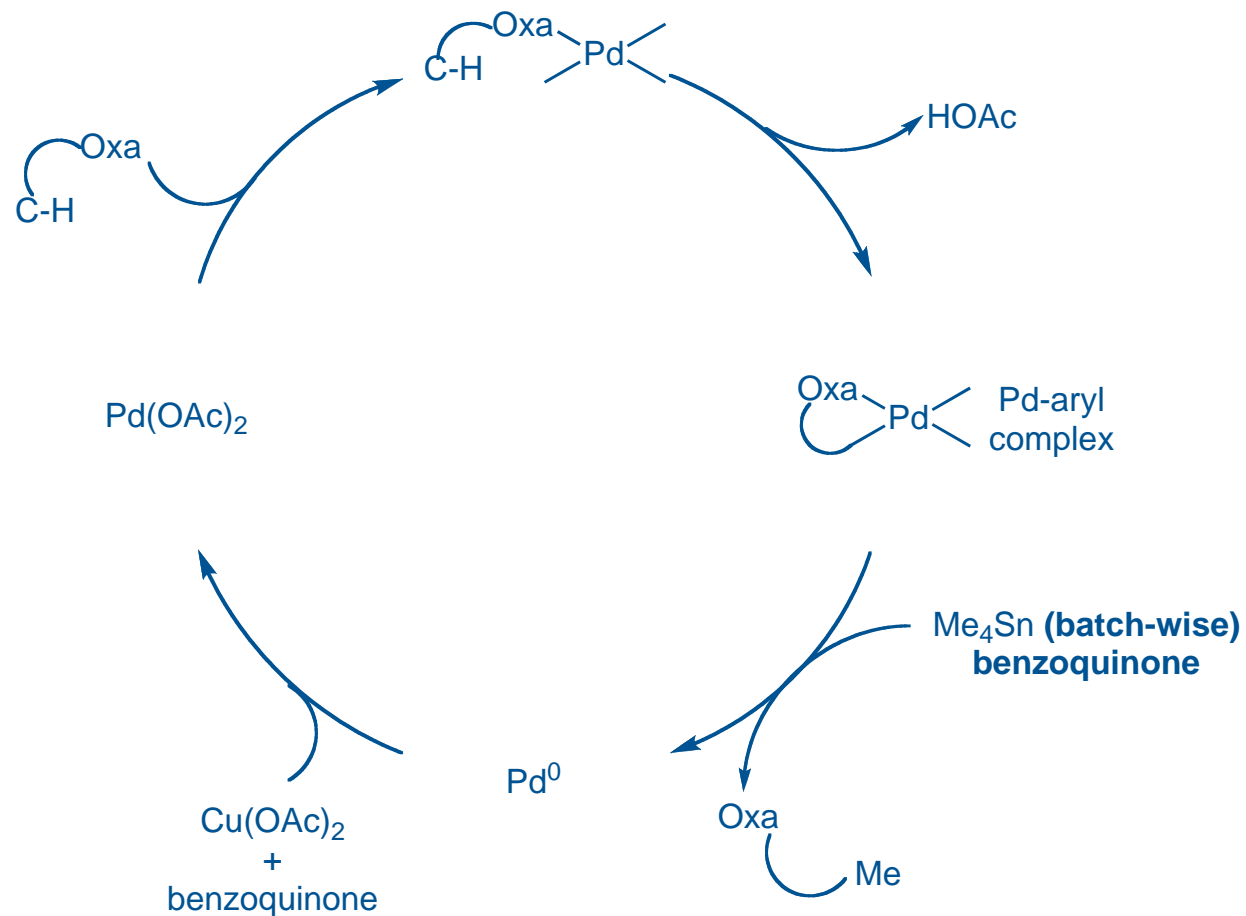
Comparison of Conventional Cross-coupling With C–H Activation/C–C Coupling



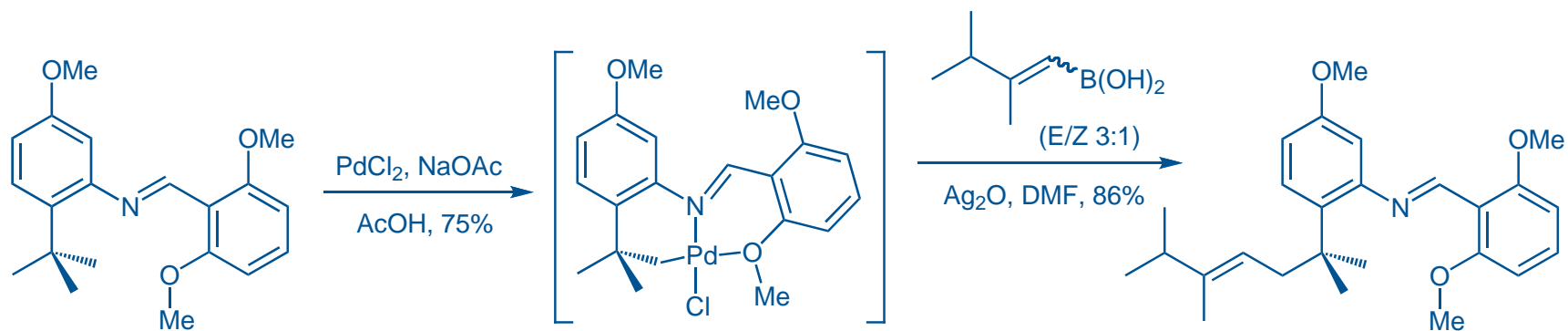
C–H Coupling with Organotin Reagents



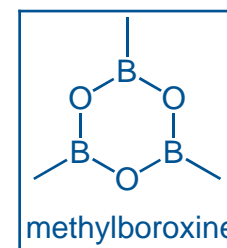
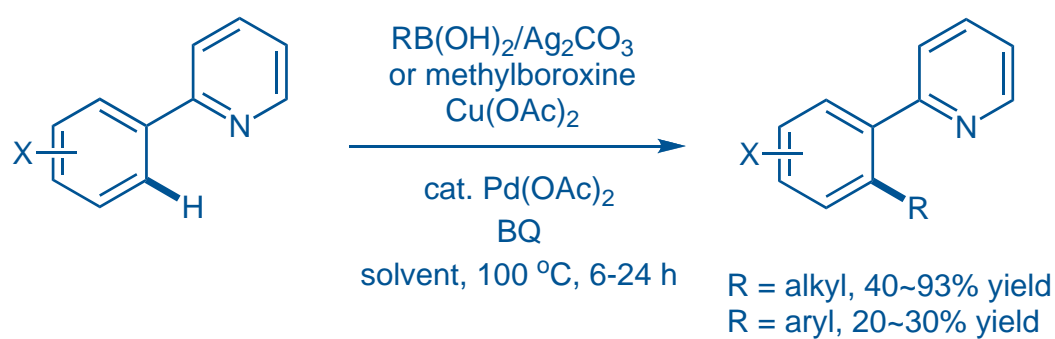
C–H Coupling with Organotin Reagents



Scope of Coupling Partner



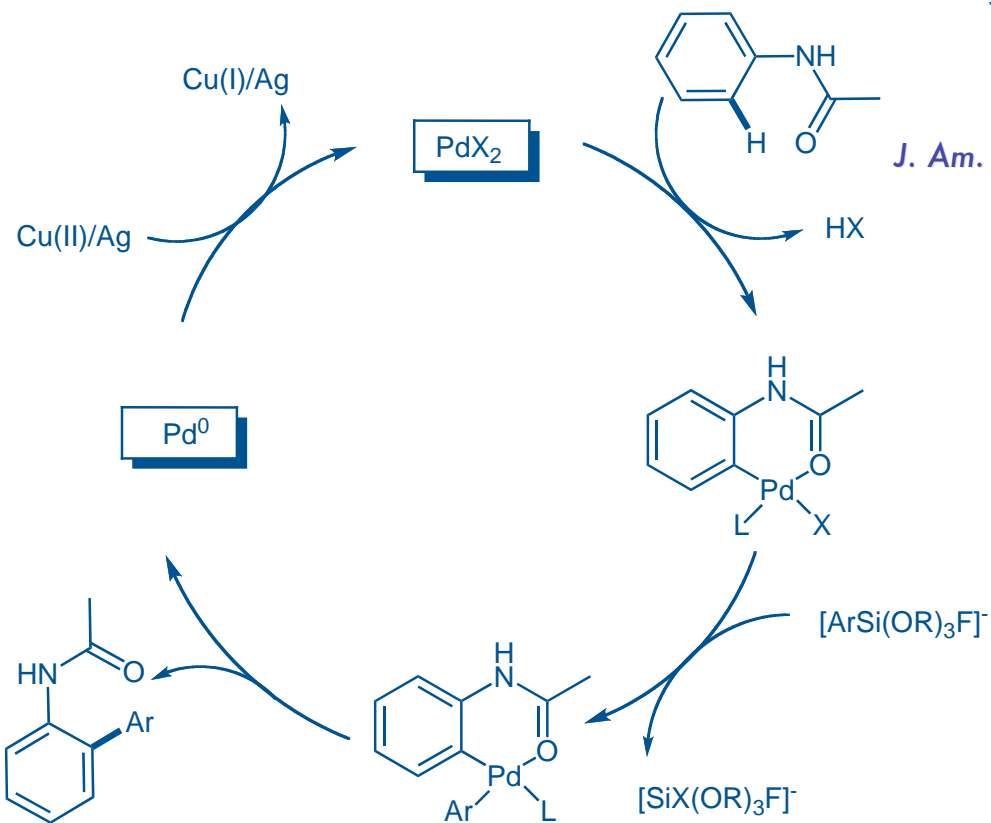
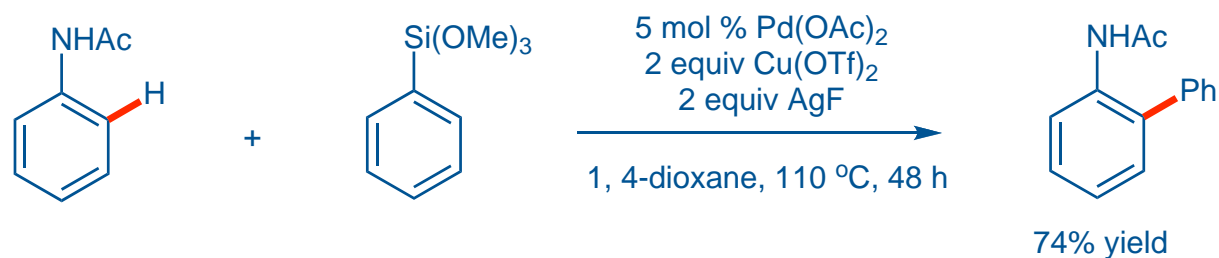
Sames, D. et al. *J. Am. Chem. Soc.* 2002, 124, 11856



R = Me, Et, ⁿBu, ⁿHex, $\text{Ph(CH}_2)_2$, cyclopropyl, aryl

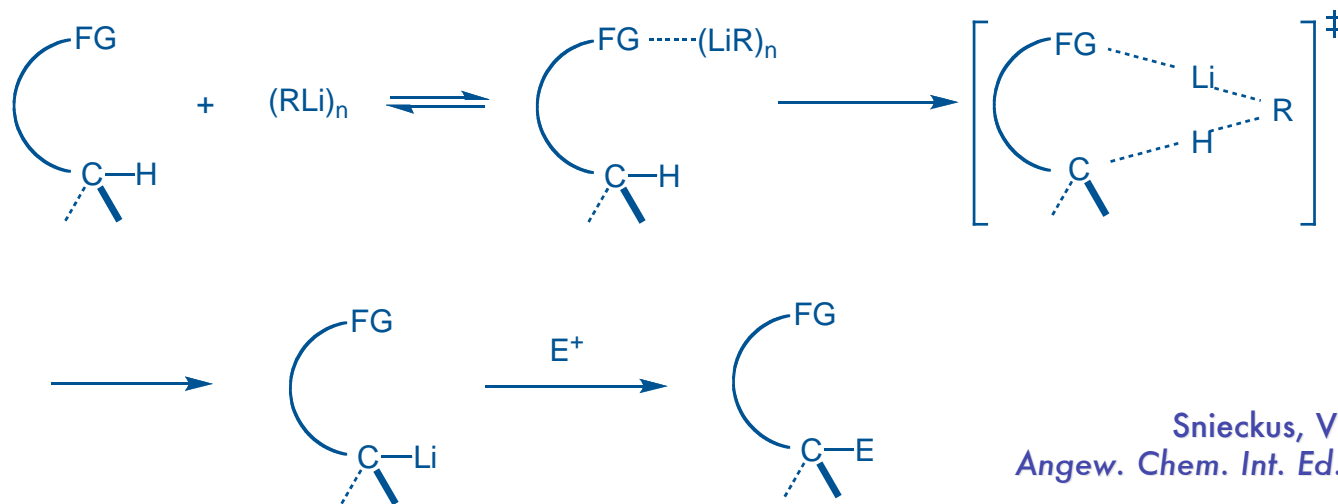
Yu, J-Q. et al. *J. Am. Chem. Soc.* 2006, 128, 12634

Scope of Coupling Partner

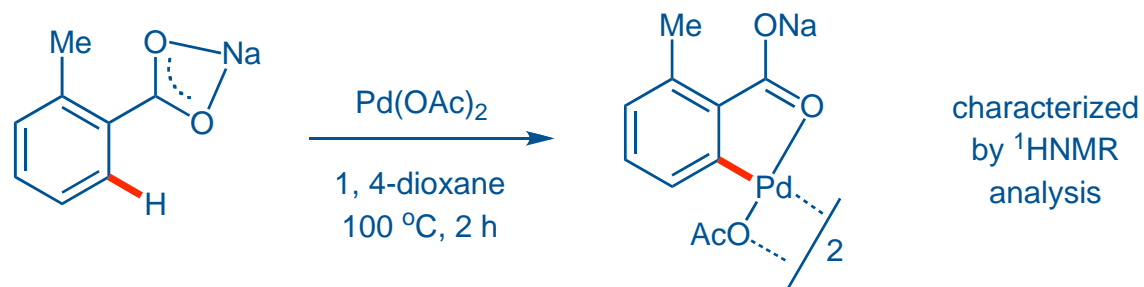


Shi, Z. et al.
J. Am. Chem. Soc. **2007**, *129*, 6066

Expanding the Substrate Scope

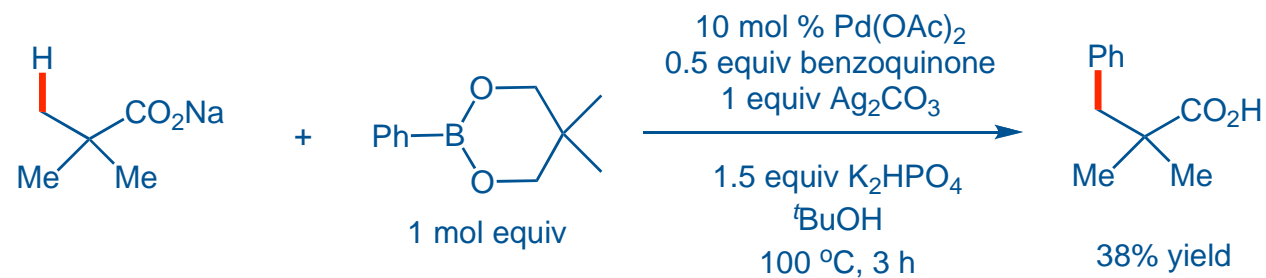
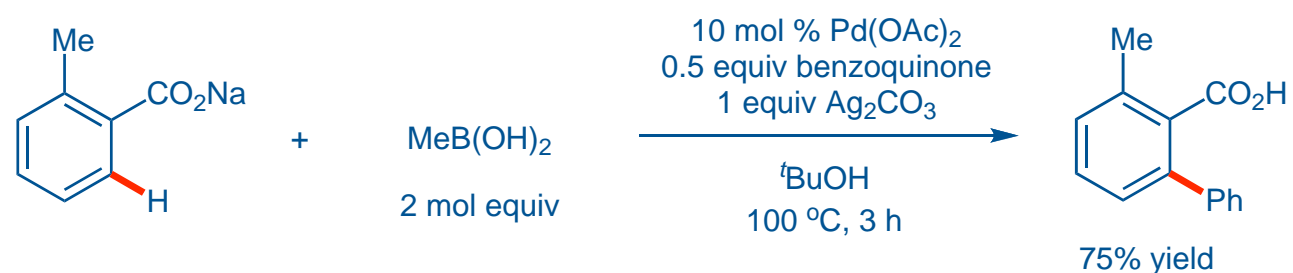
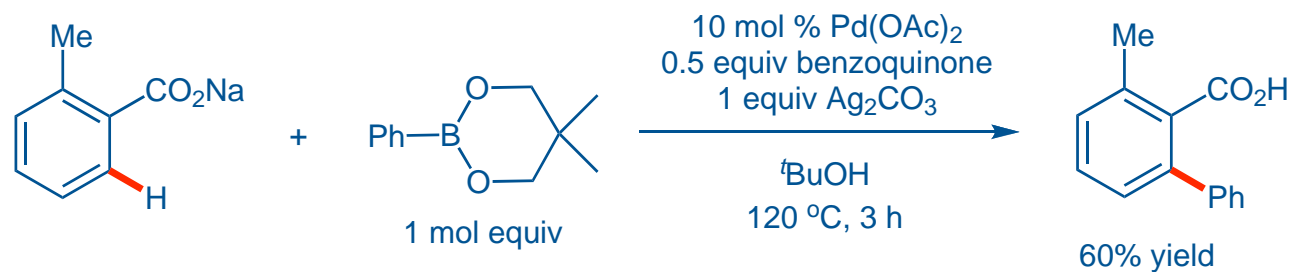


Snieckus, V. *et al.*
Angew. Chem. Int. Ed. **2004**, *43*, 2206

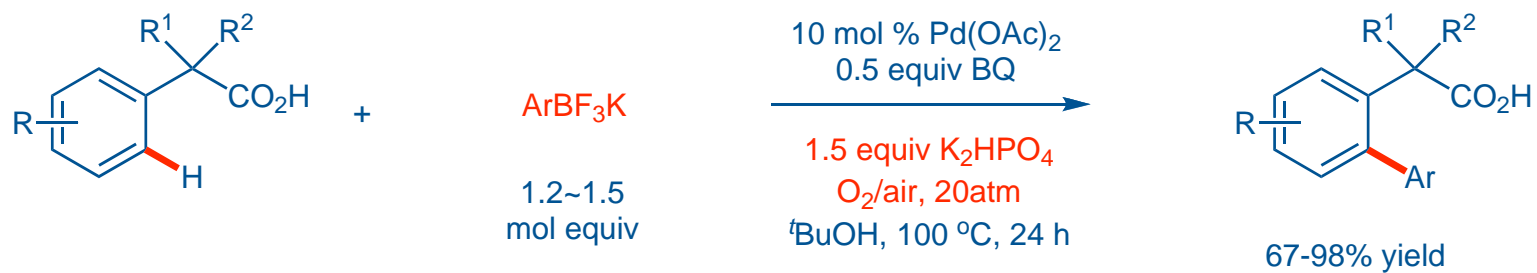
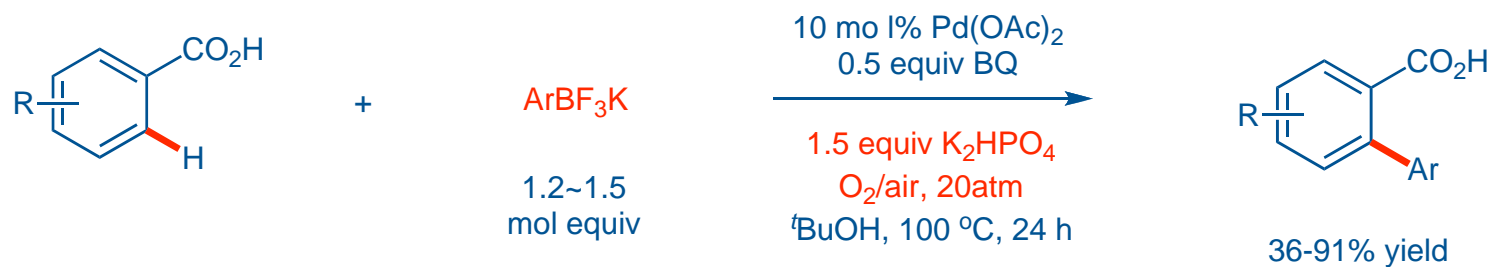


Yu, J-Q. *et al.* *J. Am. Chem. Soc.* **2008**, *130*, 14082

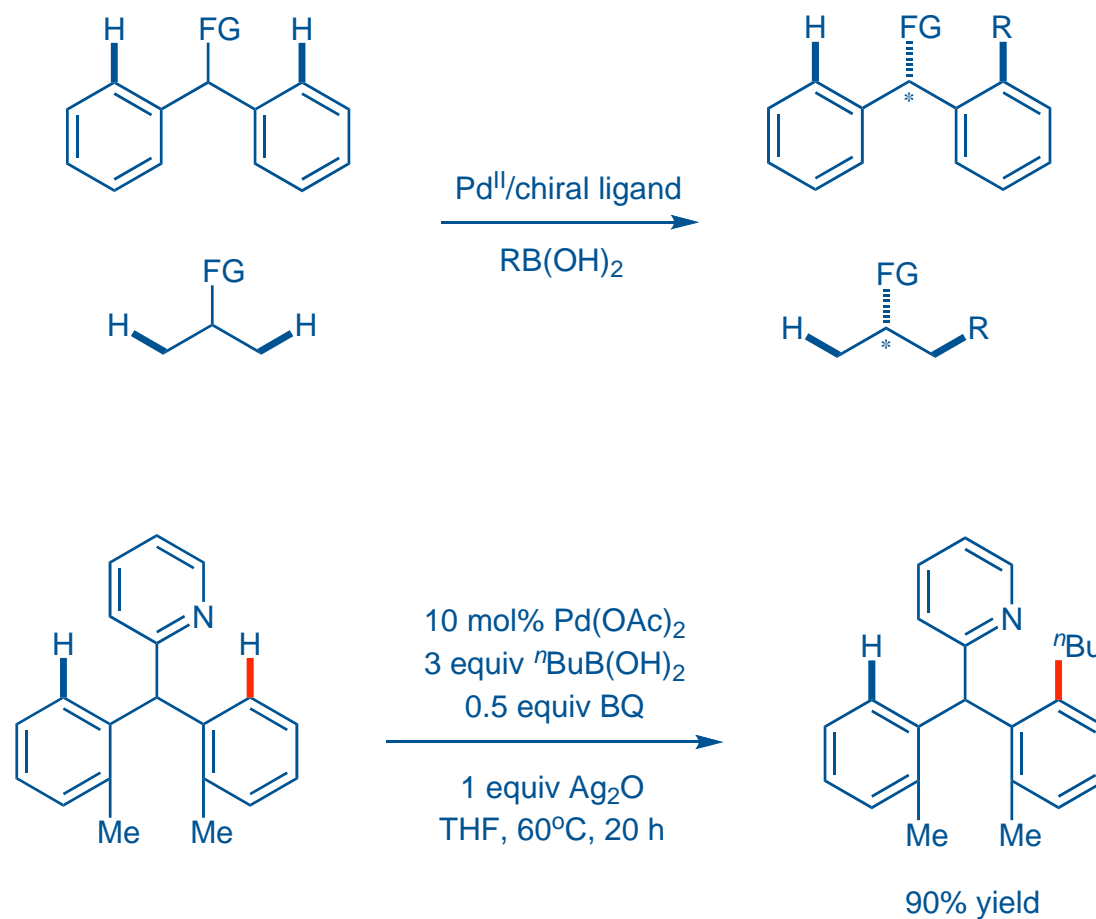
Expanding the Substrate Scope



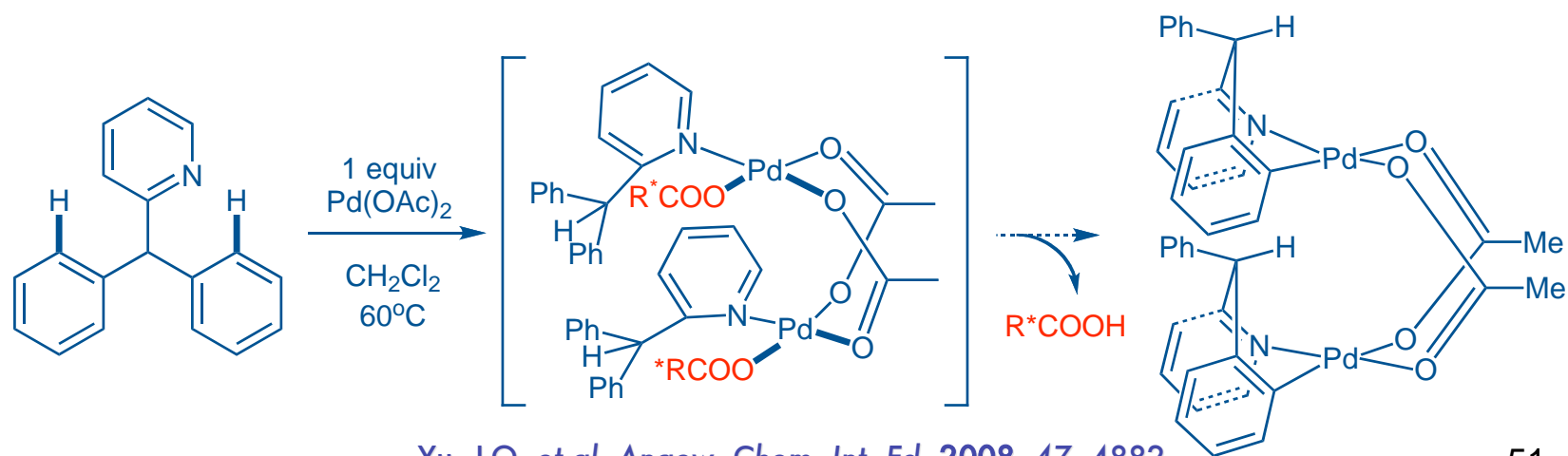
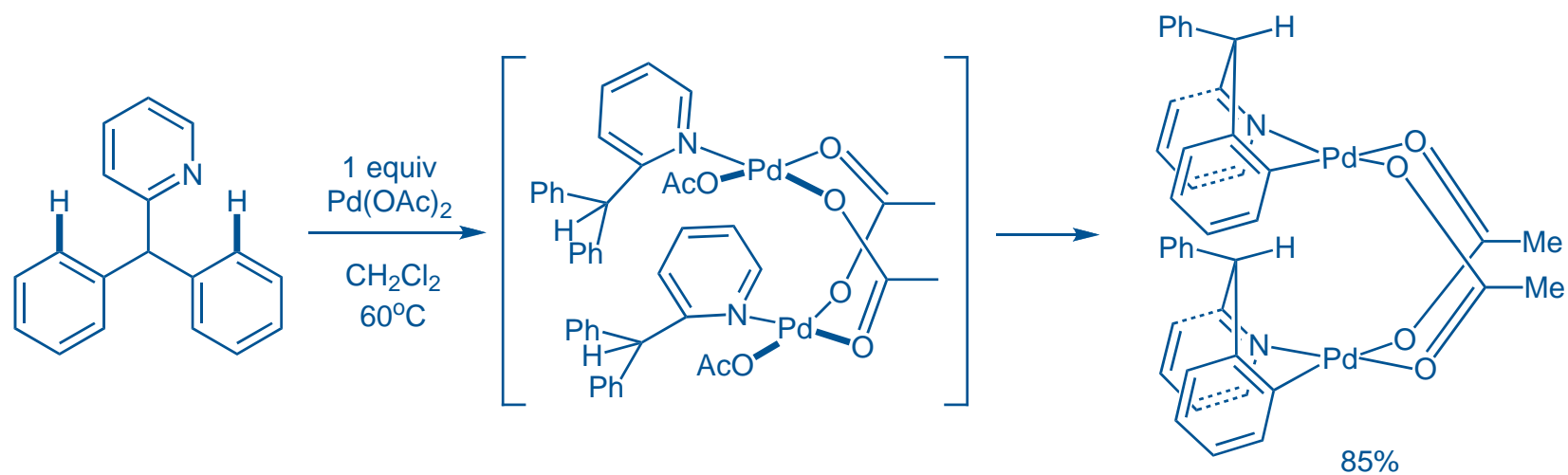
Expanding the Substrate Scope



Enantioselective C–H Activation/C–C Coupling

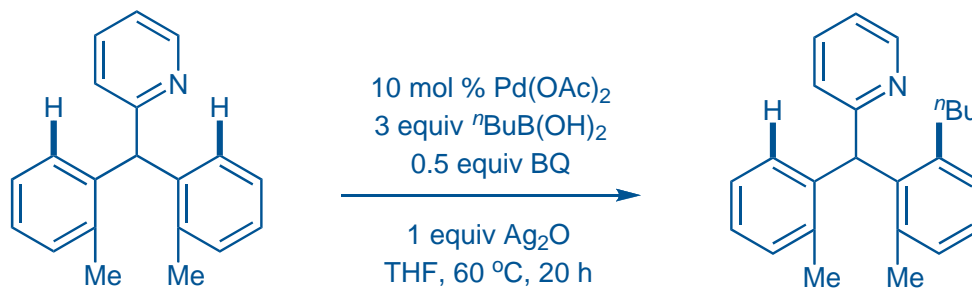


Proposed Working Model



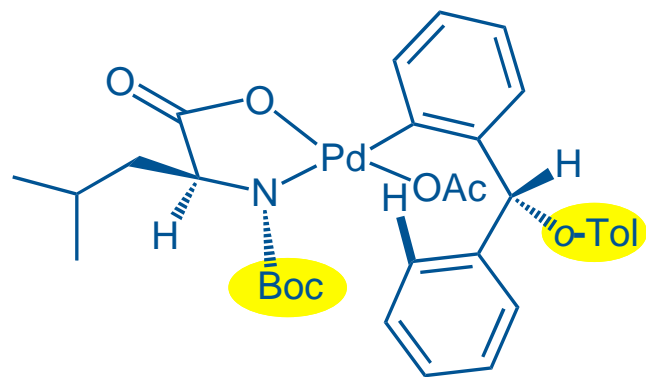
Yu, J.-Q. *et al.* *Angew. Chem. Int. Ed.* 2008, 47, 4882

Influence of the Ligand

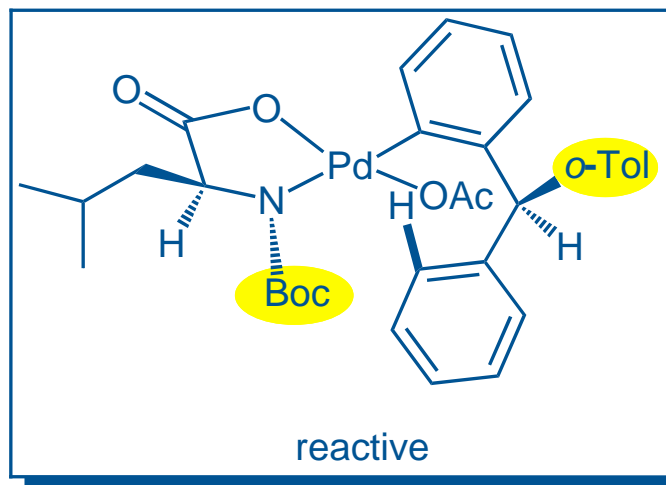


Ligand	Yield	ee	Ligand	Yield	ee	Ligand	Yield	ee
	63	90		83	83		53	6
	47	85		n. r.			74	80
	69	70		n. r.			88	79
	69	80		86	0		87	85
	66	81		58	7		91	87

Simplified Stereomodel



unreactive or disfavored



reactive

Conclusions and Outlook



Air as the Oxidant



Reduced catalyst loading



Regioselective arene C–H activation



Enantioselective C–H activation of C(sp³)–H bonds

Thank you

