Palladium-catalyzed sp^3 C–H activation

,

Yan Xu

Dong Group Meeting

Apr. 2, 2014

Content

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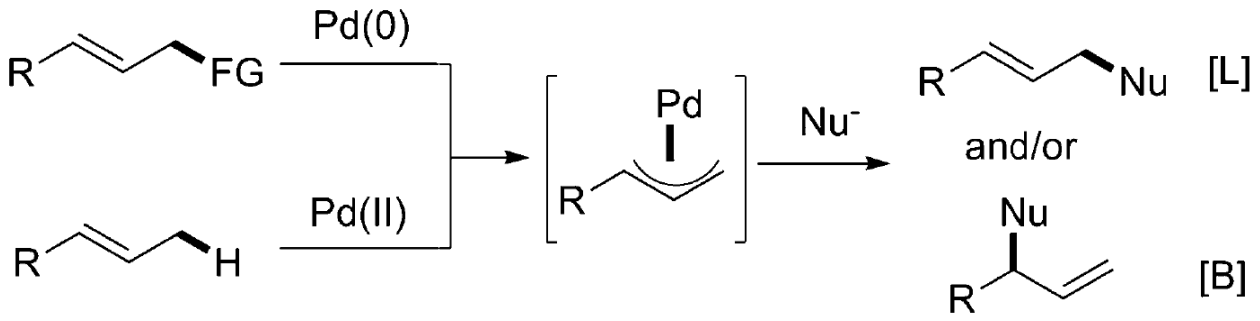
Allylic C–H activation: direct carboxylation

- **Easiest C-H bond to activate**
- allylic C–H oxidation using stoichiometric palladium(II): ***1960s***



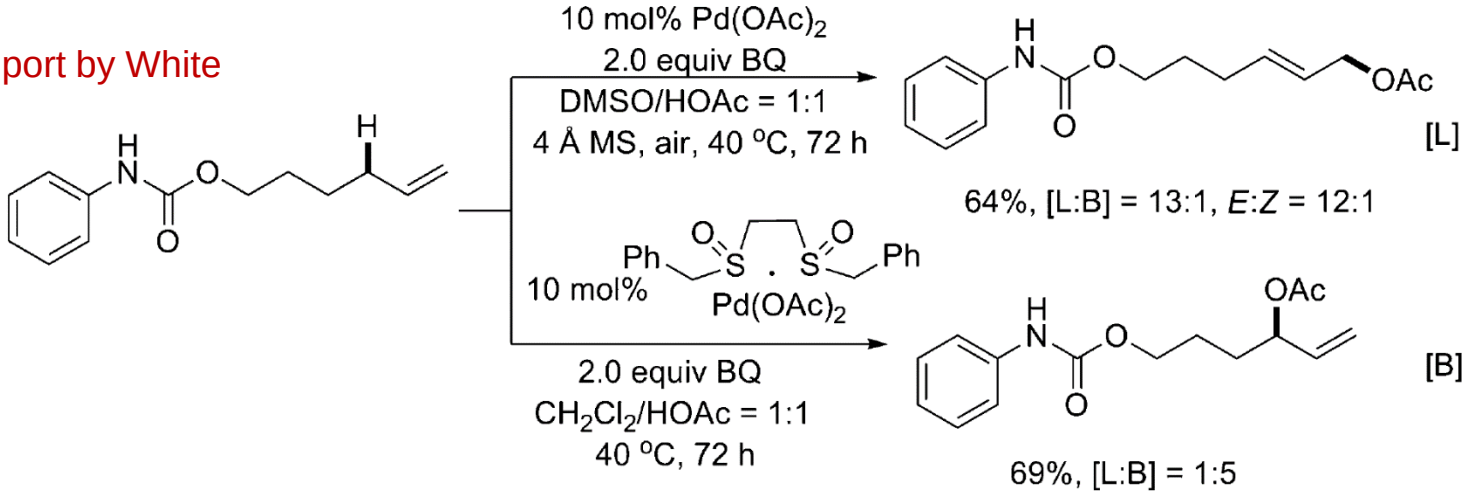
FG = OCOR, OCO_2R, NR_2, SR, $P(OR)_2$, $B(OR)_2$, etc.

- allylic alkylation from prepared allyl–Pd complexes reported by Trost: ***1970s***

W. G. Young, *J. Am. Chem. Soc.,* **1966**, *88*, 2054
P. G. C. Campbell, *J. Am. Chem. Soc.*, **1971**, *93*, 1497
P. G. C. Campbell, *J. Am. Chem. Soc.*, **1971**, *93*, 1499
B. M. Trost and T. J. Fullerton, *J. Am. Chem.* ***Soc***., 1973, *95*, 1780

Allylic C–H activation: direct carboxylation

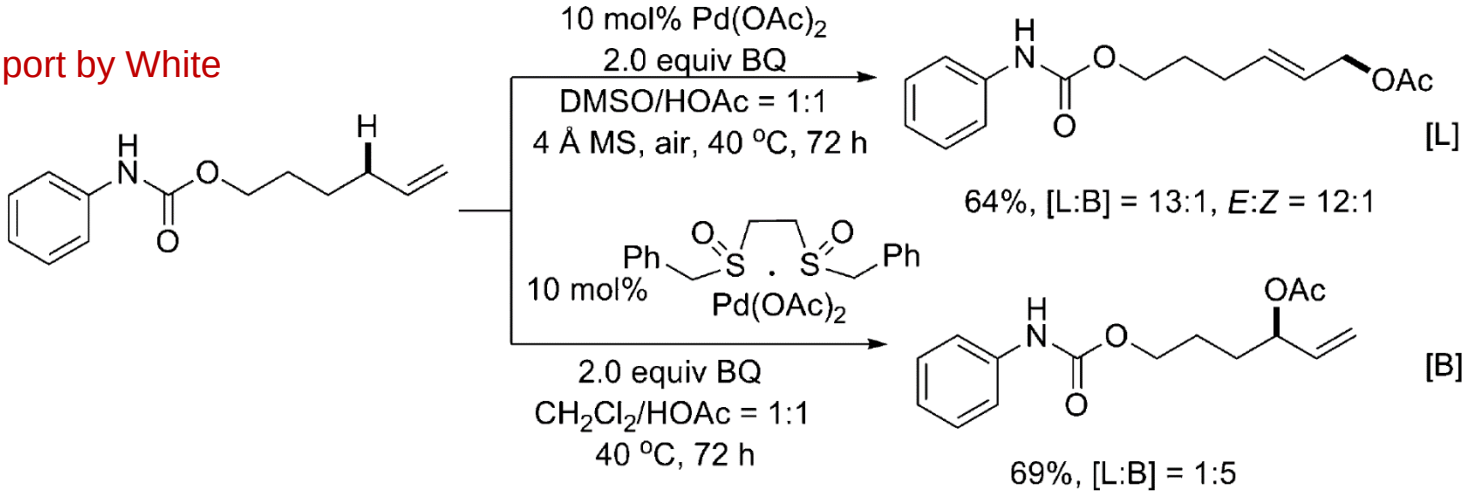
- First report by White



M. C. White, *J. Am. Chem. Soc.*, **2004**, *126*, 1346.

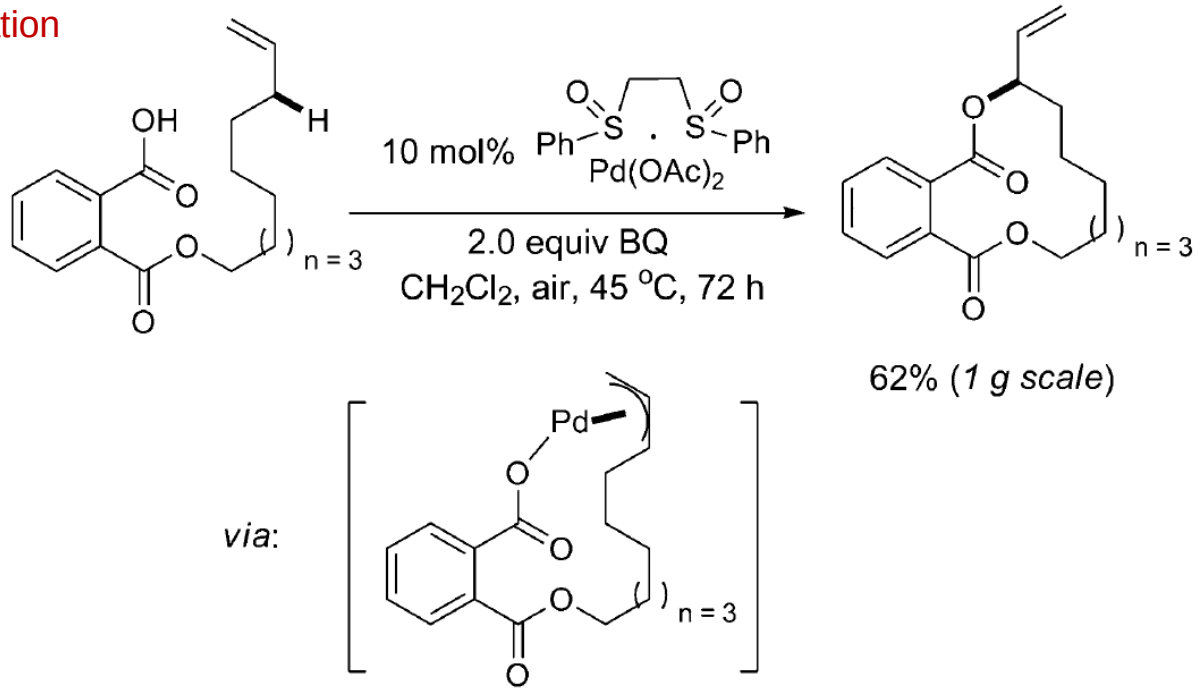
Allylic C–H activation: direct carboxylation

- First report by White



M. C. White, *J. Am. Chem. Soc.*, **2004**, *126*, 1346.

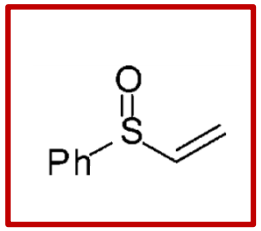
- Macrolactonization



M. C. White, J. *Am. Chem. Soc.*, **2006**, *128*, 9032.

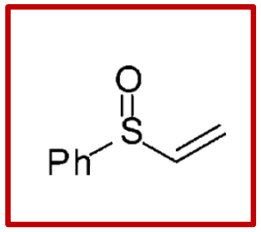
Allylic C–H activation: direct carboxylation

- Real ligand

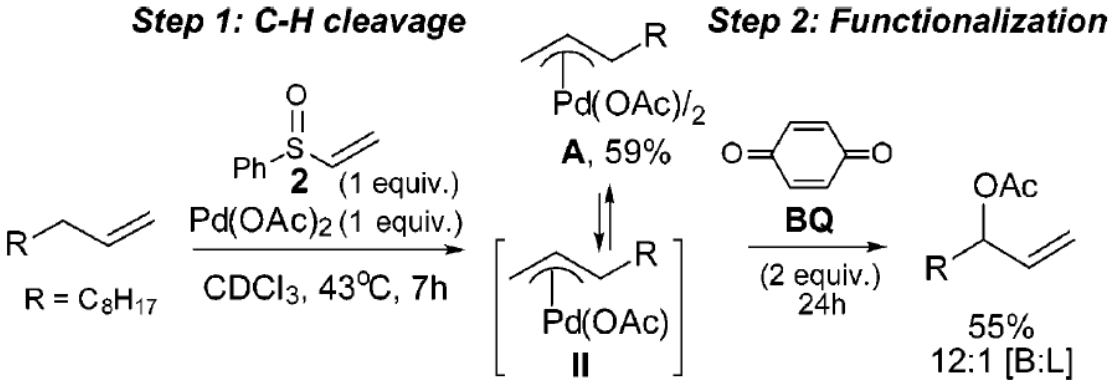


Allylic C–H activation: direct carboxylation

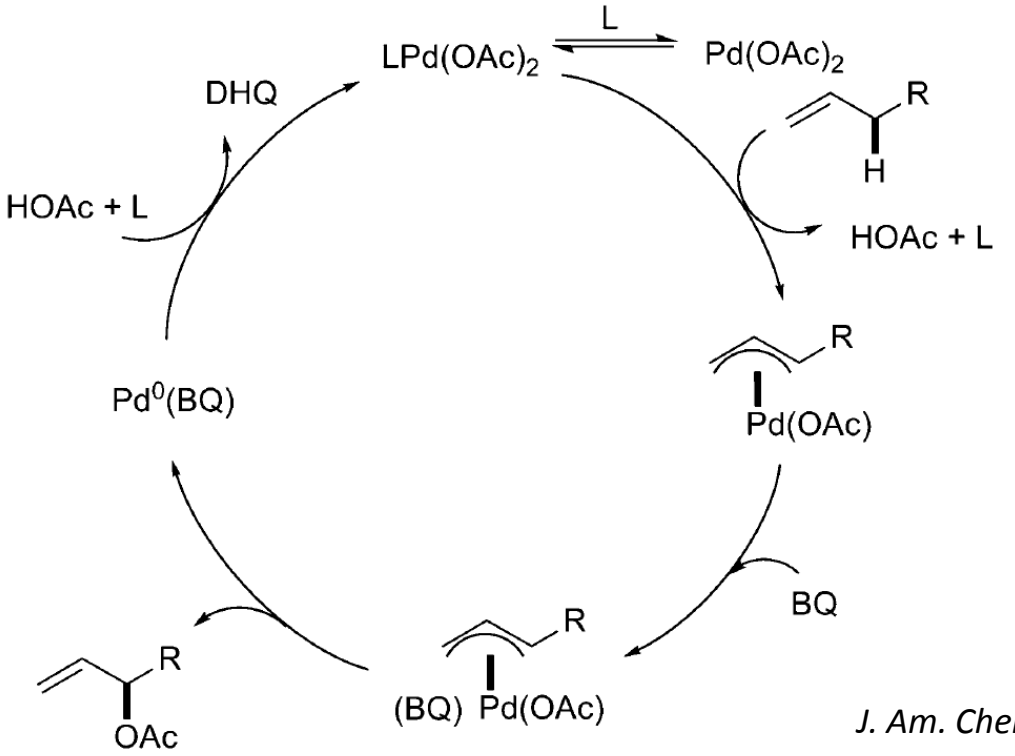
- Real ligand



- Stoichiometric experiment



- Mechanism

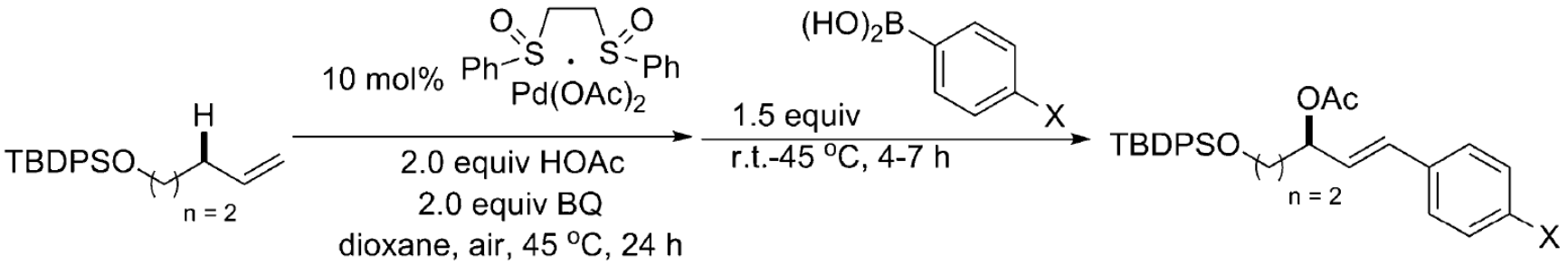


J. Am. Chem. Soc., **2005**, *127*, 6970.

For other RCOOH as substrates, see: *J. Am. Chem. Soc.*, **2010**, *132*, 11323.

Allylic C–H activation: direct carboxylation

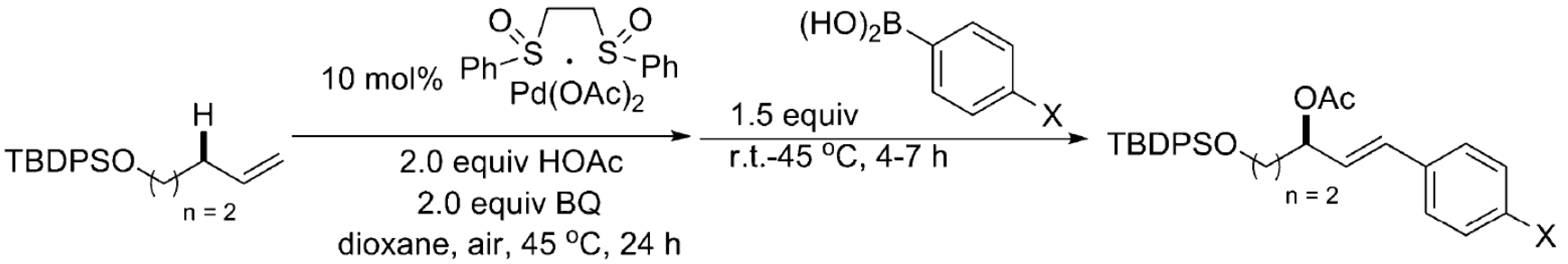
- allylic C–H oxidation/vinylic C–H arylation



M. C. White, *J. Am. Chem. Soc.*, **2006**, *128*, 15076.

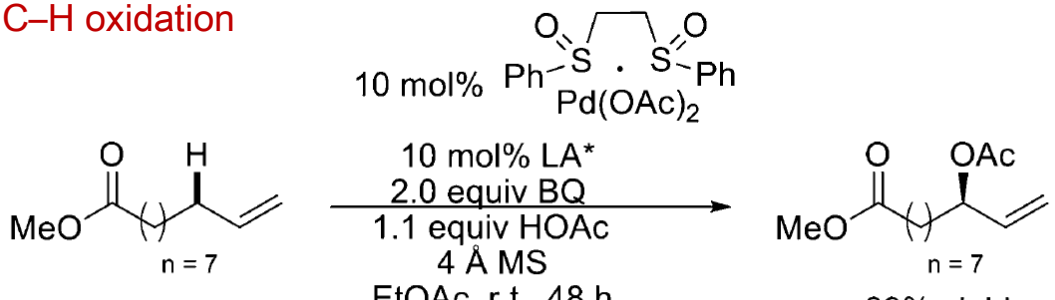
Allylic C–H activation: direct carboxylation

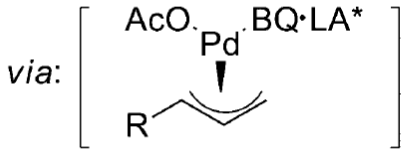
- allylic C–H oxidation/vinylic C–H arylation

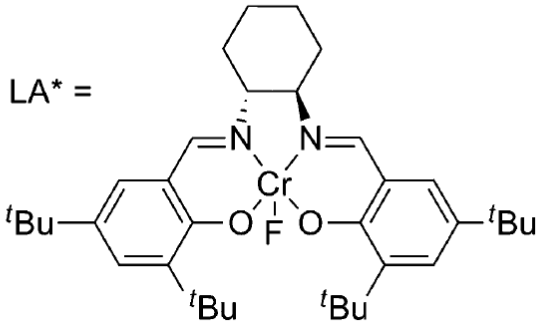


M. C. White, *J. Am. Chem. Soc.*, **2006**, *128*, 15076.

- asymmetric allylic C–H oxidation



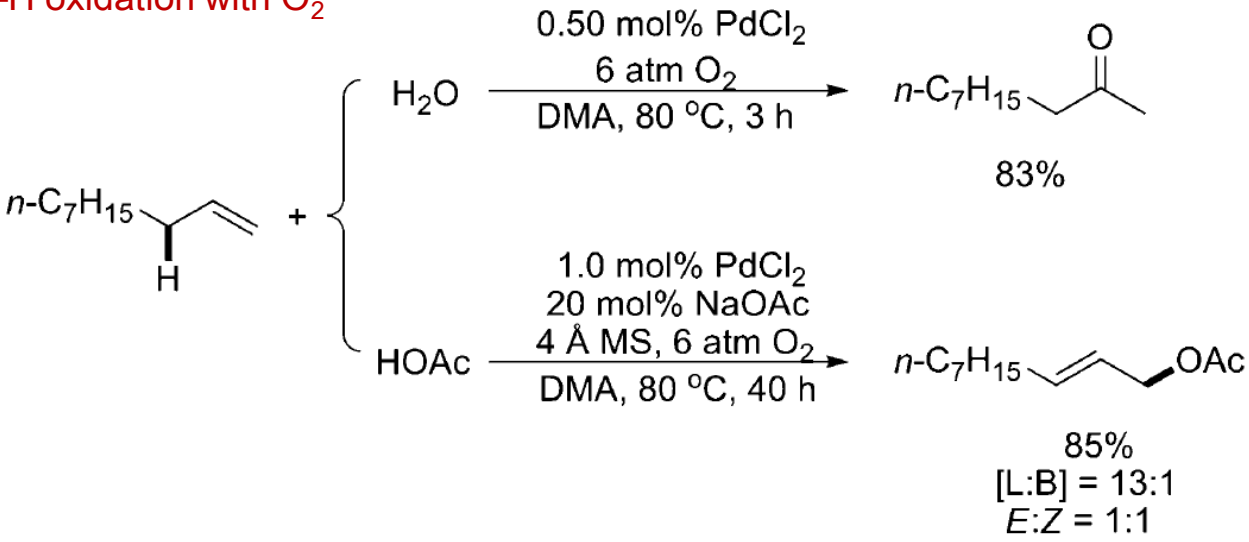




M. C. White, *Angew. Chem., Int. Ed.*, **2008**, *47*, 6448.

Allylic C–H activation: direct carboxylation

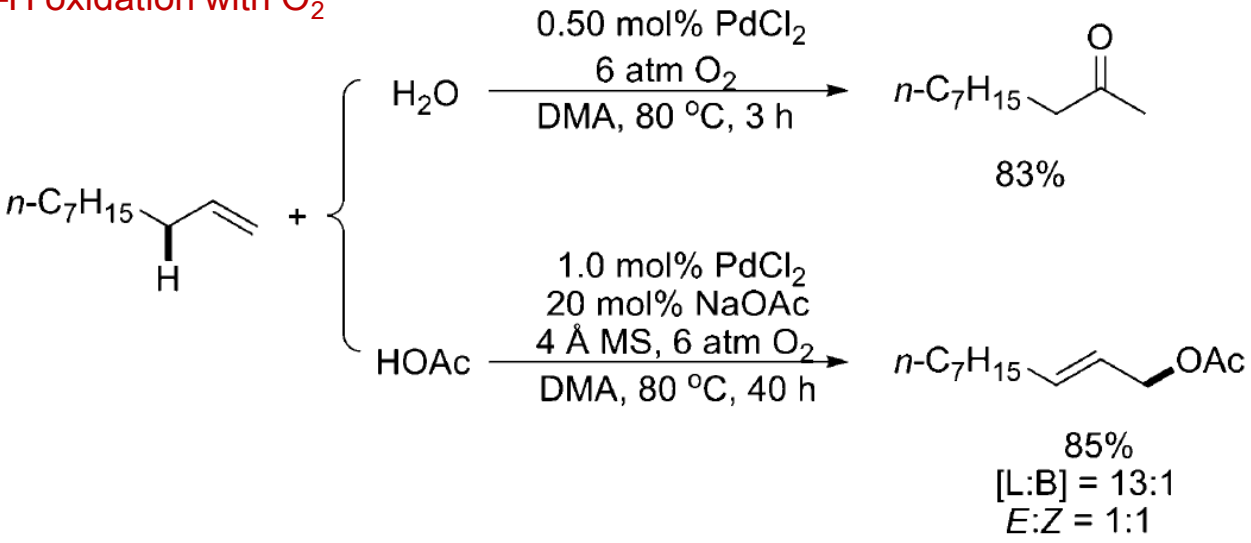
- allylic C–H oxidation with O_2



K. Kaneda, *Angew. Chem., Int. Ed.*, **2006**, *45*, 481.

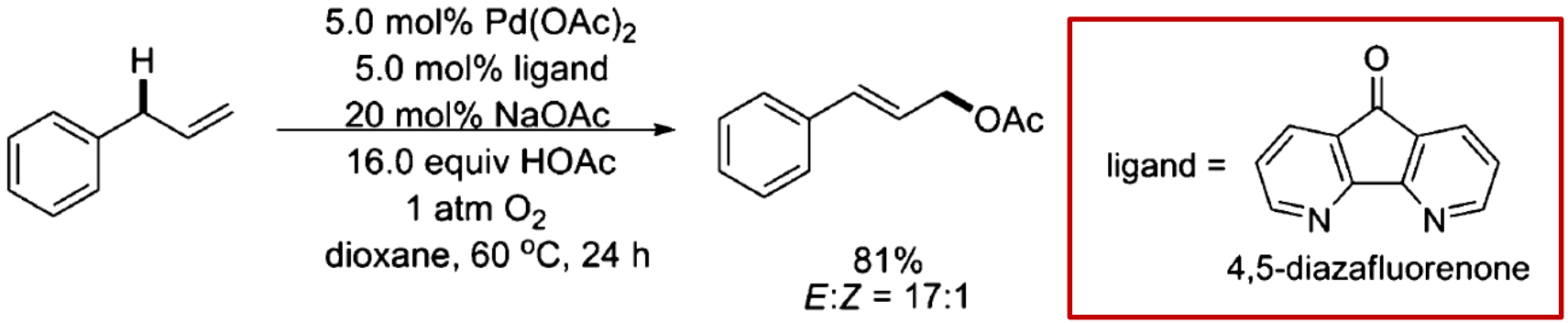
Allylic C–H activation: direct carboxylation

- allylic C–H oxidation with O_2



K. Kaneda, *Angew. Chem., Int. Ed.*, **2006**, *45*, 481.

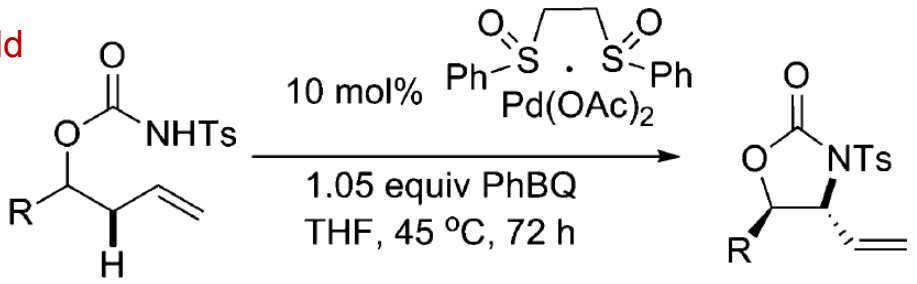
- allylic C–H acetoxylation



S. S. Stahl, *J. Am. Chem. Soc.*, **2010**, *132*, 15116.

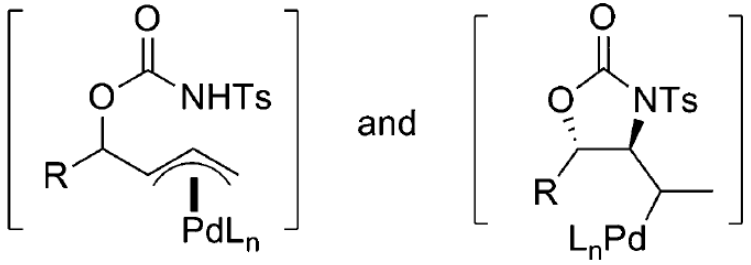
Allylic C–H activation: Direct amination

- 1,2-amino alcohol scaffold



R = ^{i}Pr: 72%, d.r. (*anti*/*syn*) = 6:1;
R = ^{n}Pr: 86%, d.r. (*anti*/*syn*) = 1.6:1.

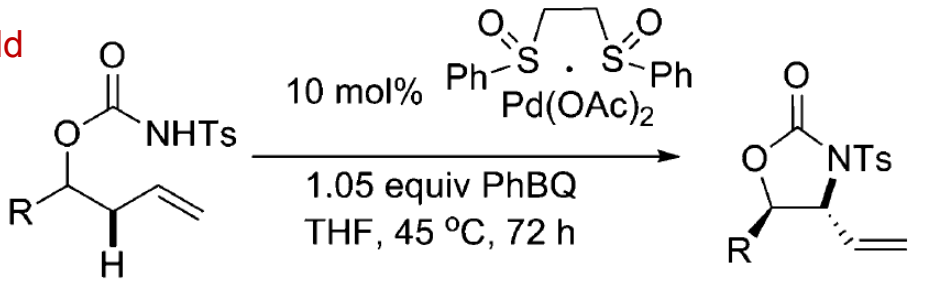
via:



M. C. White, *J. Am. Chem. Soc.*, **2007**, *129*, 7274.

Allylic C–H activation: Direct amination

- 1,2-amino alcohol scaffold



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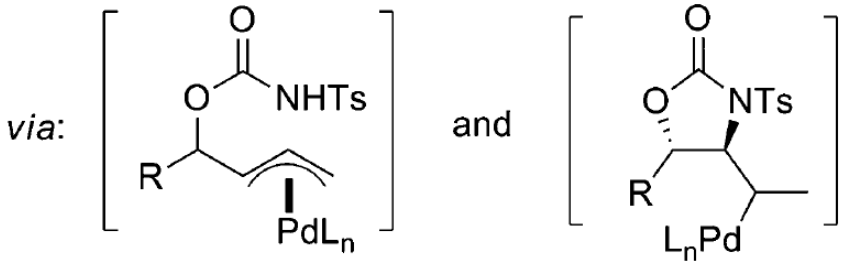
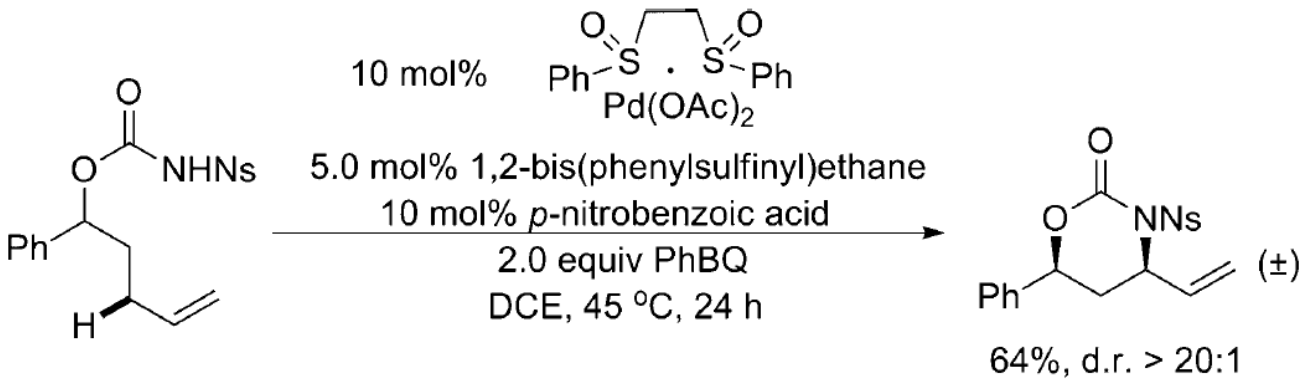


M. C. White, *J. Am. Chem. Soc.*, **2007**, *129*, 7274.

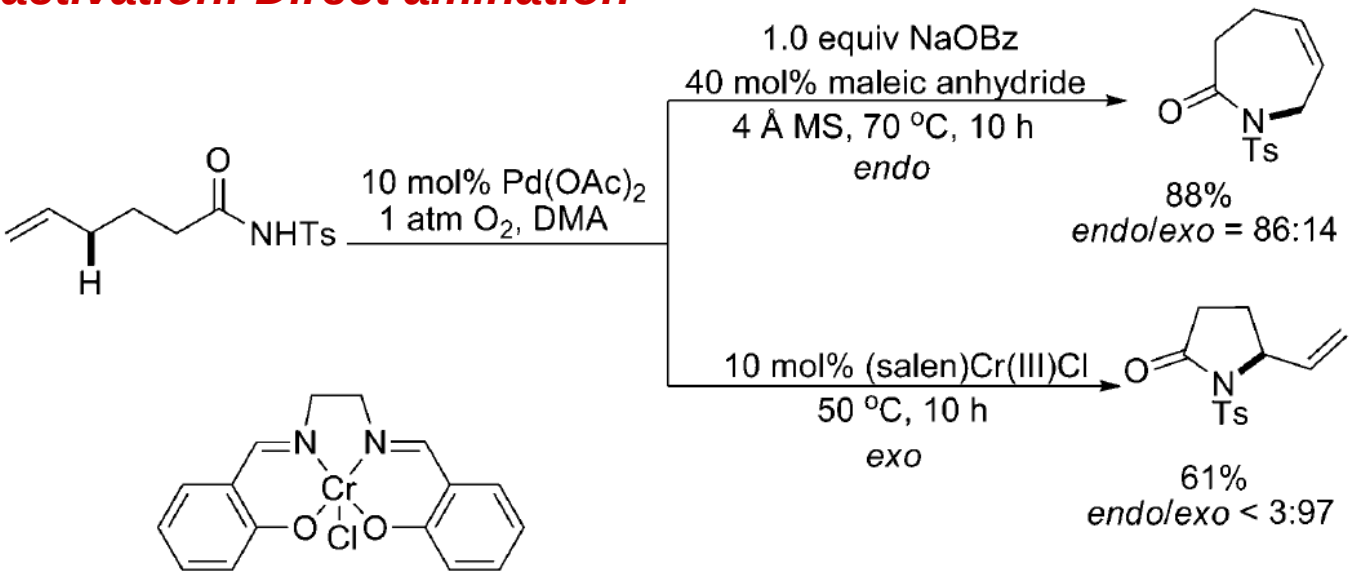
- 1,3-amino alcohol scaffold



64%, d.r. > 20:1

M. C. White, *J. Am. Chem. Soc.*, **2009**, *131*, 11707.

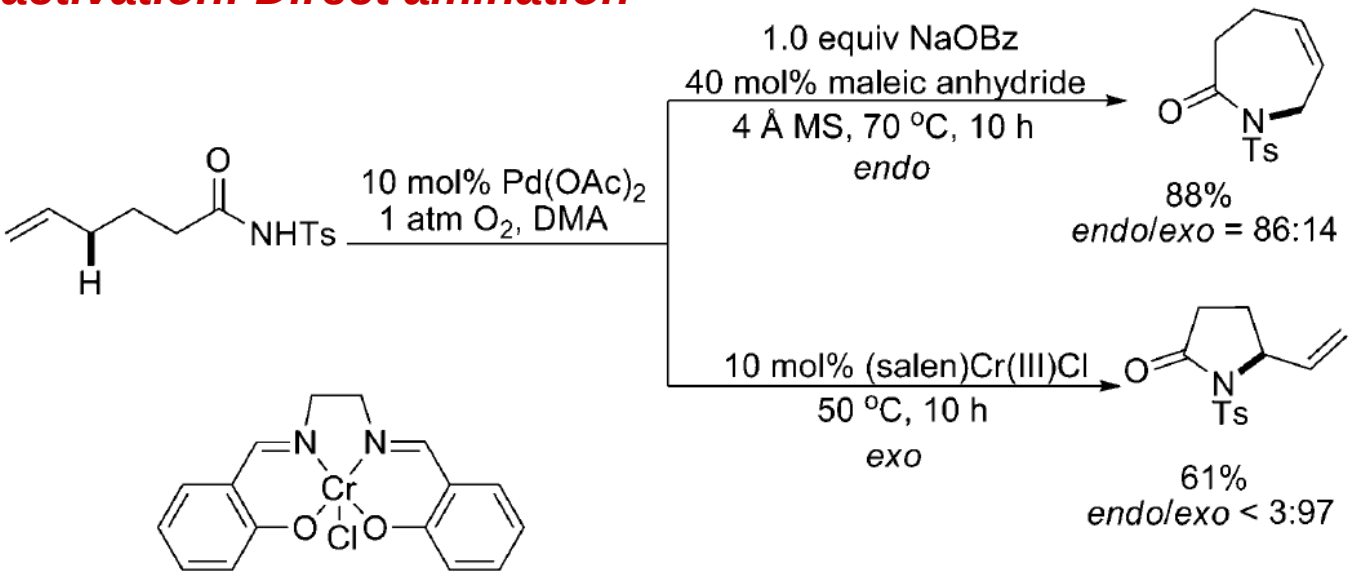
Allylic C–H activation: Direct amination



(salen)Cr(III)Cl

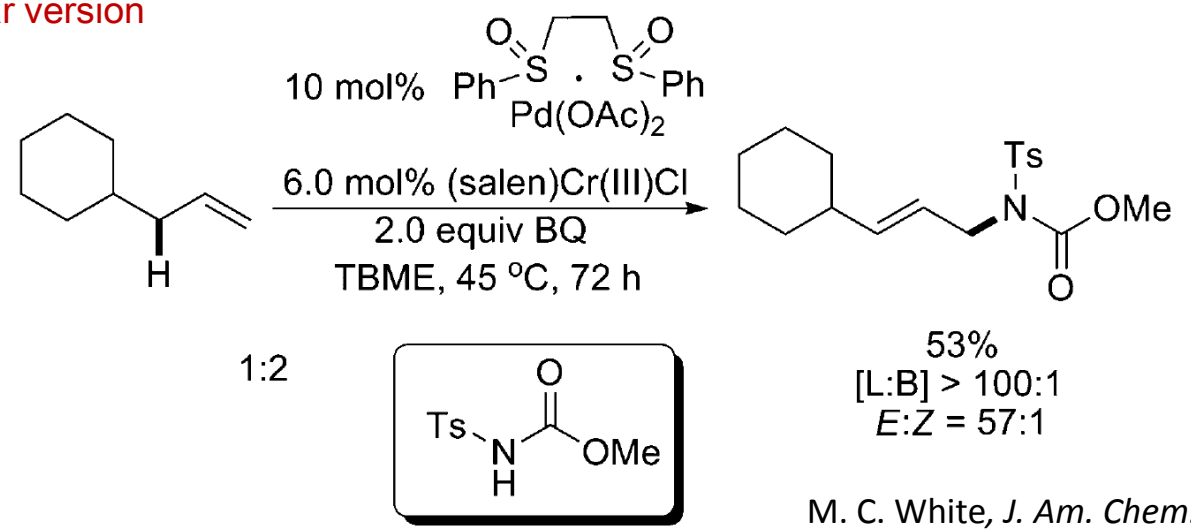
G. Liu, *Org. Lett.*, **2009**, *11*, 2707

Allylic C–H activation: Direct amination



G. Liu, *Org. Lett.*, **2009**, *11*, 2707

- Intermolecular version



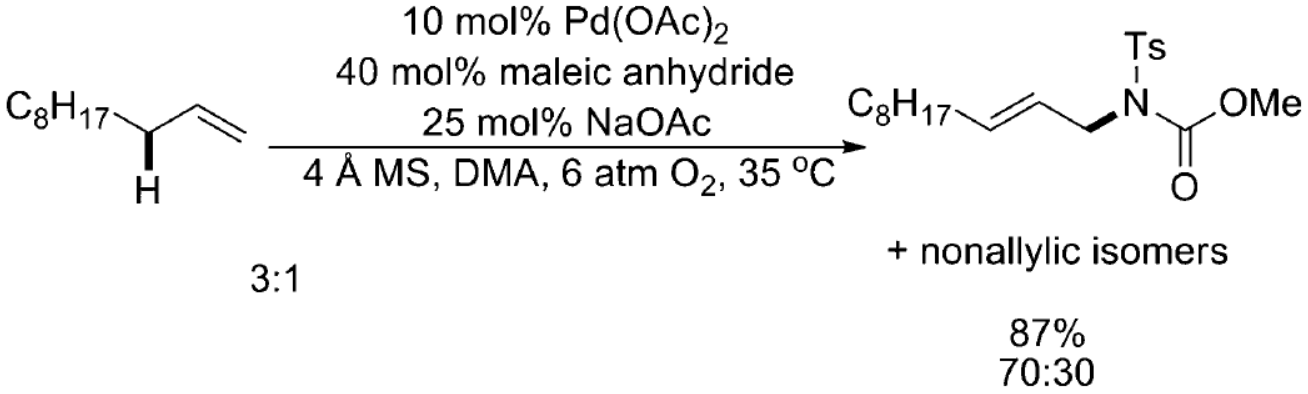
M. C. White, *J. Am. Chem. Soc.*, **2008**, *130*, 3316.

Cr(III) can be replaced by 6% DIPEA, see:

M. C. White, *J. Am. Chem. Soc.*, **2009**, *131*, 11701.

Allylic C–H activation: Direct amination

- Intermolecular C-H amination



3:1

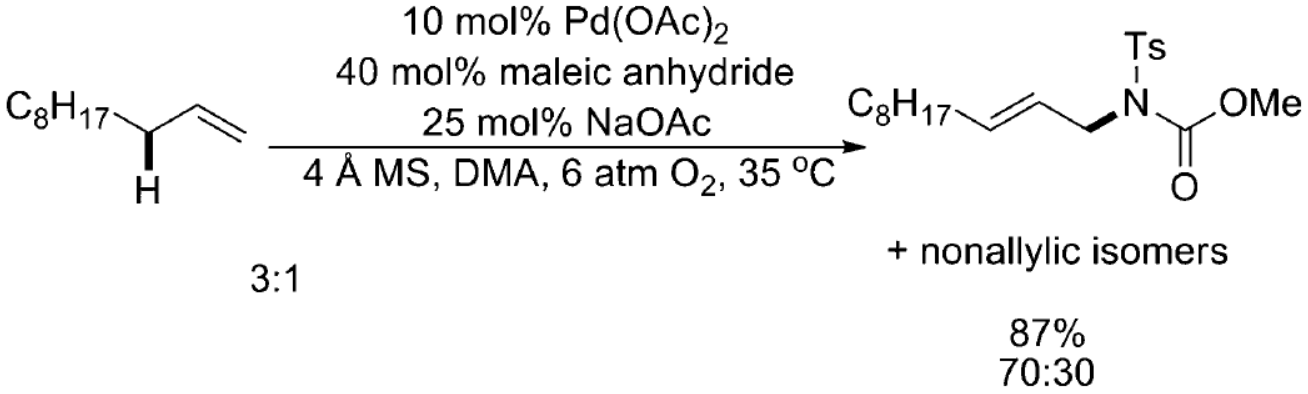
+ nonallylic isomers

87%
70:30

G. Liu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4733.

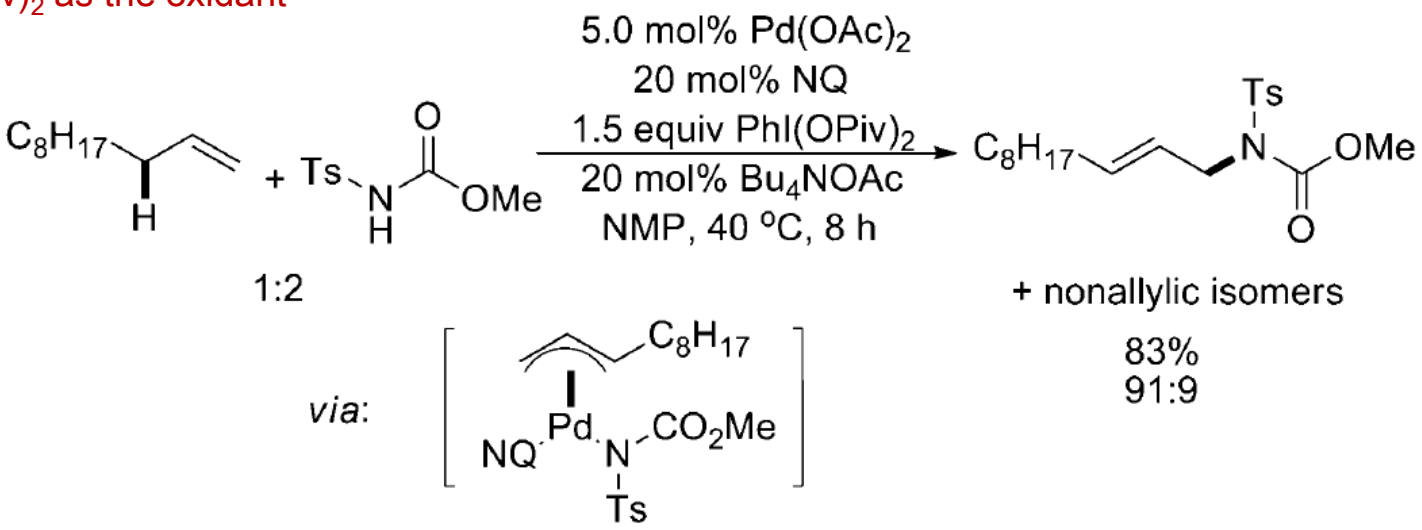
Allylic C–H activation: Direct amination

- Intermolecular C-H amination



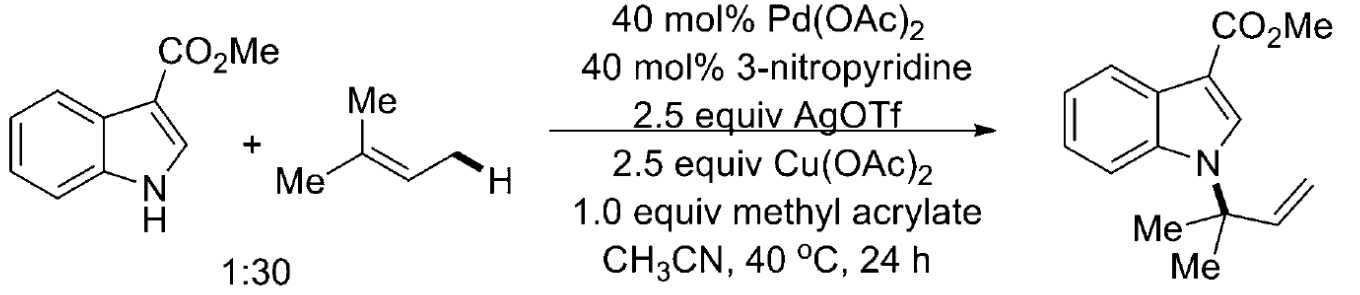
G. Liu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4733.

- $PhI(OPiv)_2$ as the oxidant

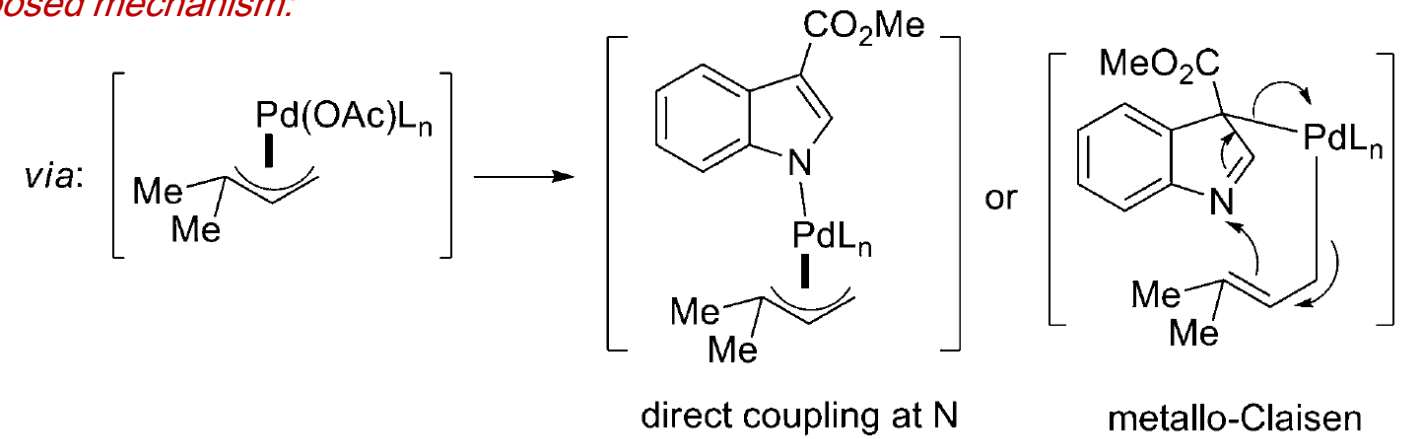


G. Liu, *J. Am. Chem. Soc.*, **2010**, *132*, 11978.

Allylic C–H activation: Direct amination



Proposed mechanism:

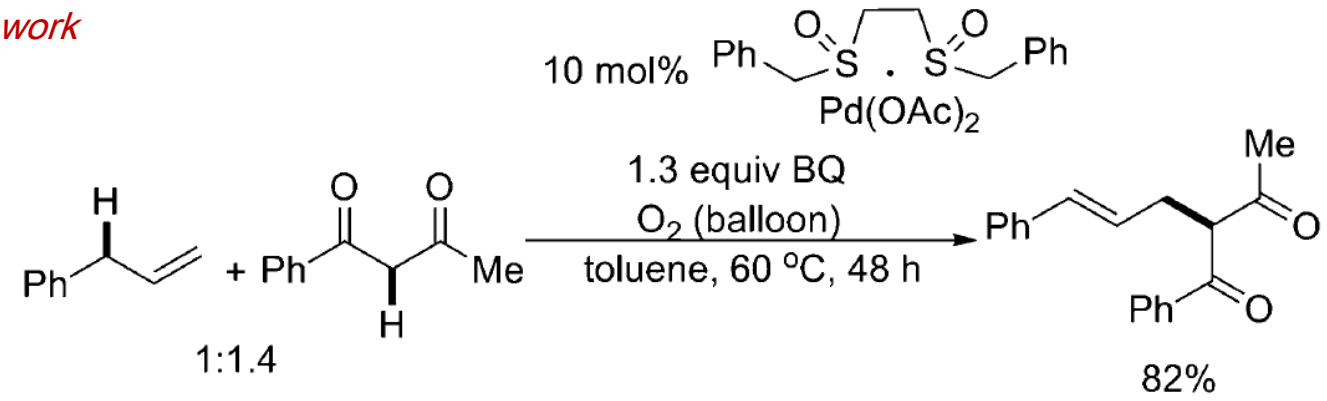


P. S. Baran, *Angew. Chem., Int. Ed.*, **2009**, *48*, 7025.

Allylic C–H activation: Direct C–C bond formation

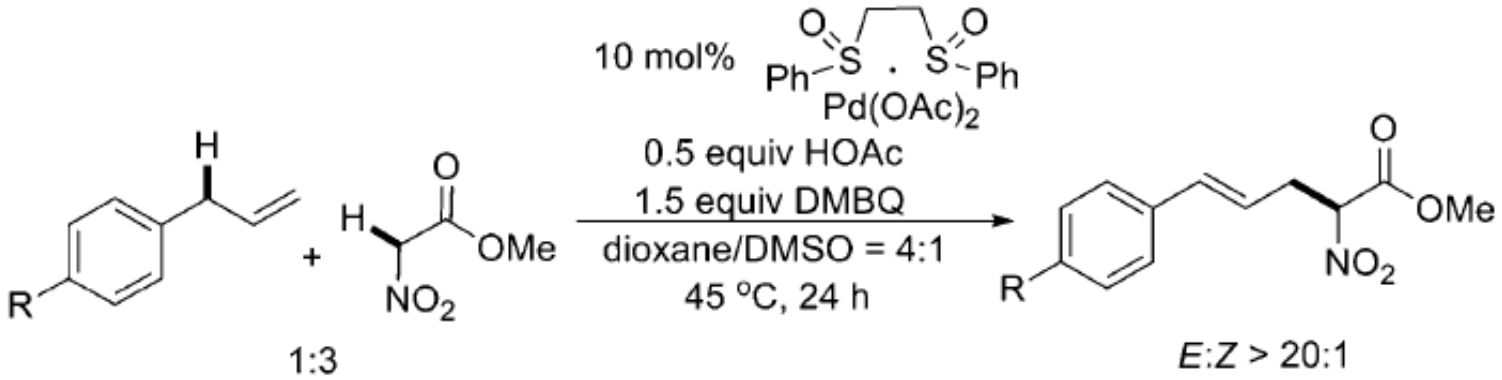
- Intermolecular C-H alkylation

Shi's work



Z.-J. Shi, *J. Am. Chem. Soc.*, **2008**, *130*, 12901.

White's work



R = H: 62%, [L:B] = 4:1;

M. C. White, *J. Am. Chem. Soc.*, **2008**, *130*, 14090

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Palladium-catalyzed sp^3 C–H activation

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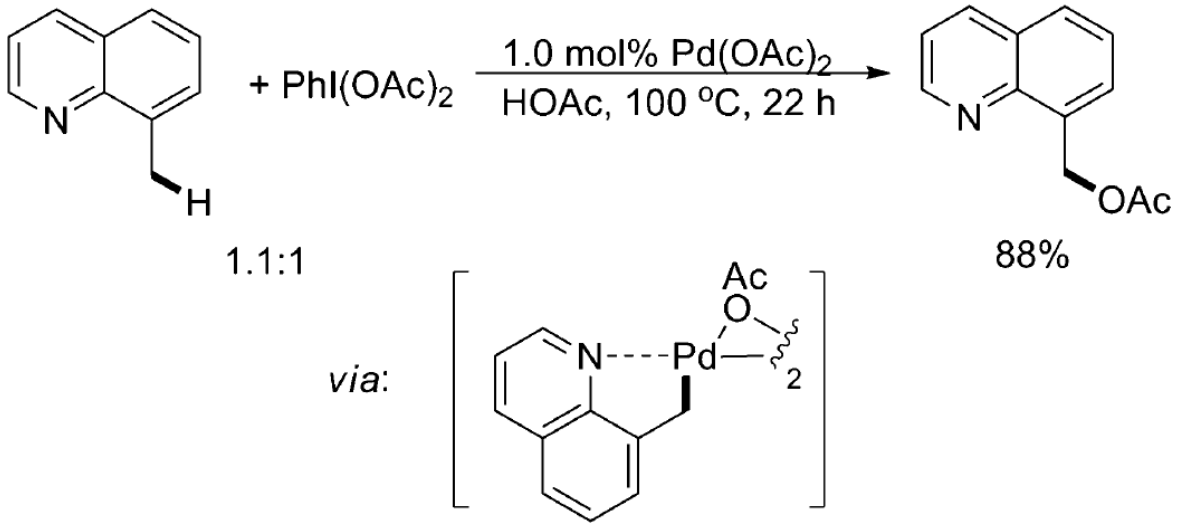
Palladium-catalyzed sp^3 C–H activation

Benzylic C–H activation: Direct acetoxylation / fluorination

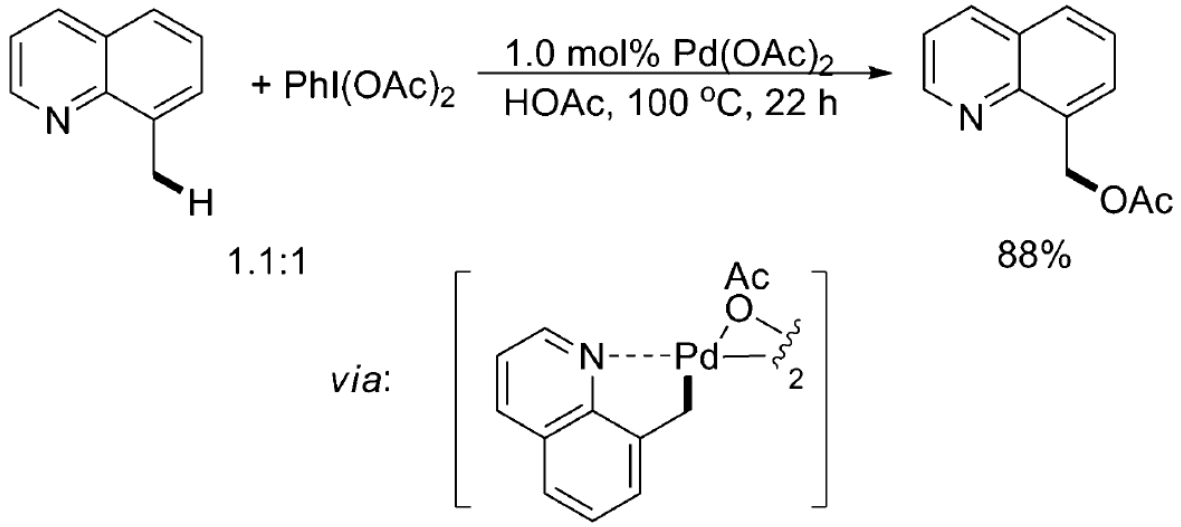
- C-H acetoxylation



M. S. Sanford, *J. Am. Chem. Soc.*, **2004**, *126*, 2300

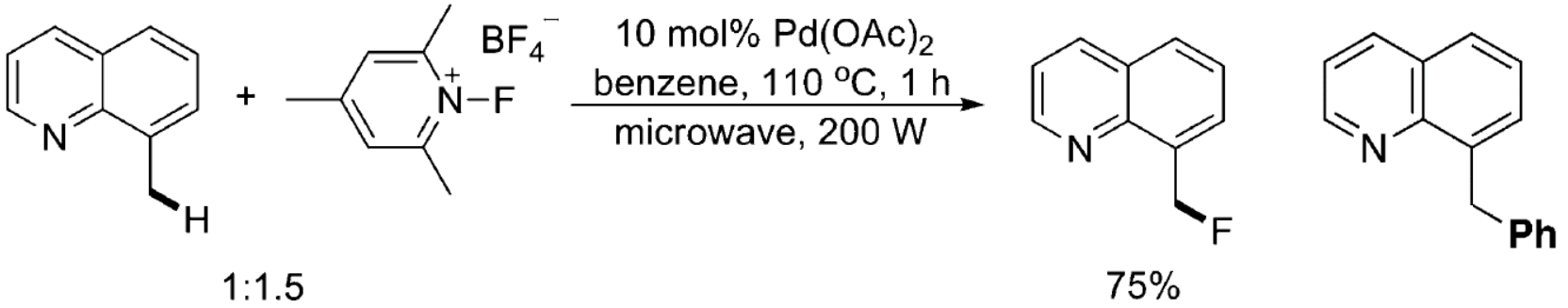
Benzylic C–H activation: Direct acetoxylation / fluorination

- C-H acetoxylation



M. S. Sanford, *J. Am. Chem. Soc.*, **2004**, *126*, 2300

- C-H fluorination

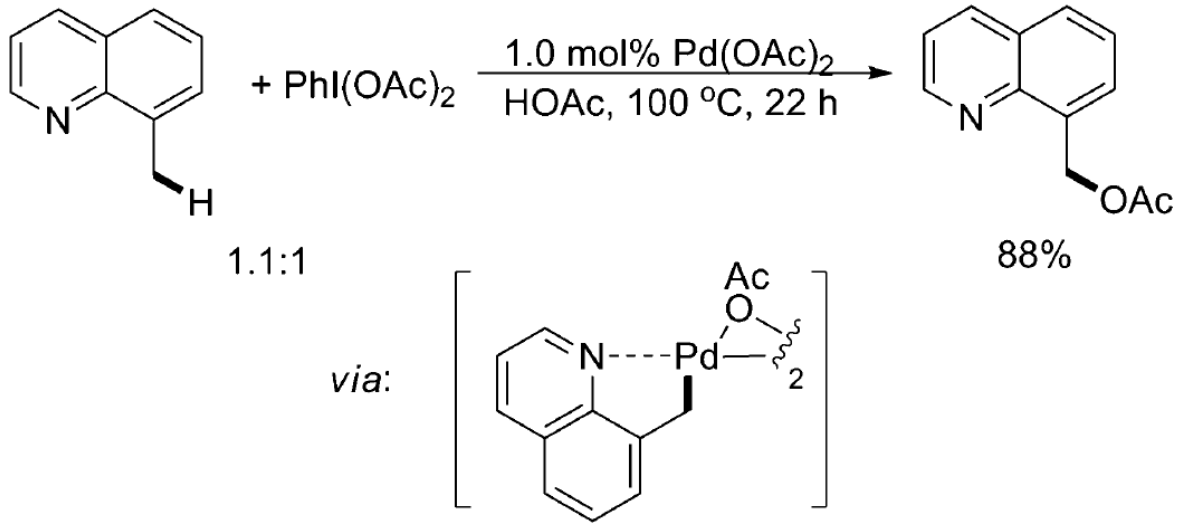


Thermo 110 °C: 36% out of 82% conversion
µwave 110 °C: 75% out of 97% conversion

M. S. Sanford, *J. Am. Chem. Soc.*, **2006**, *128*, 7134.

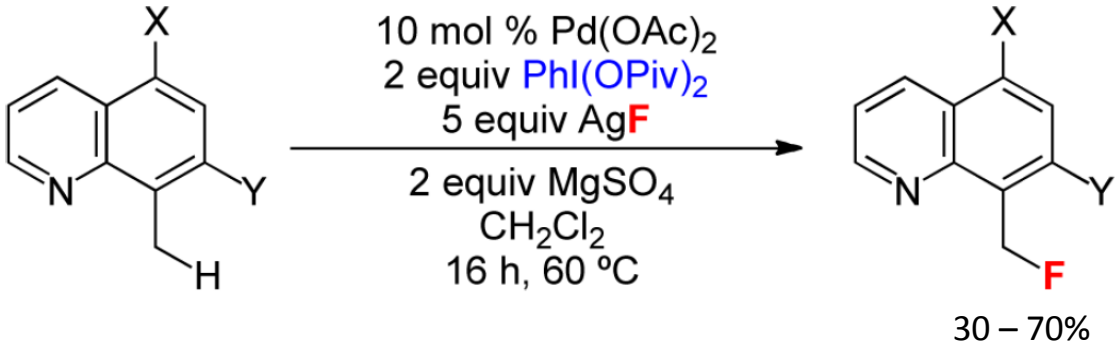
Benzylic C–H activation: Direct acetoxylation / fluorination

- C-H acetoxylation



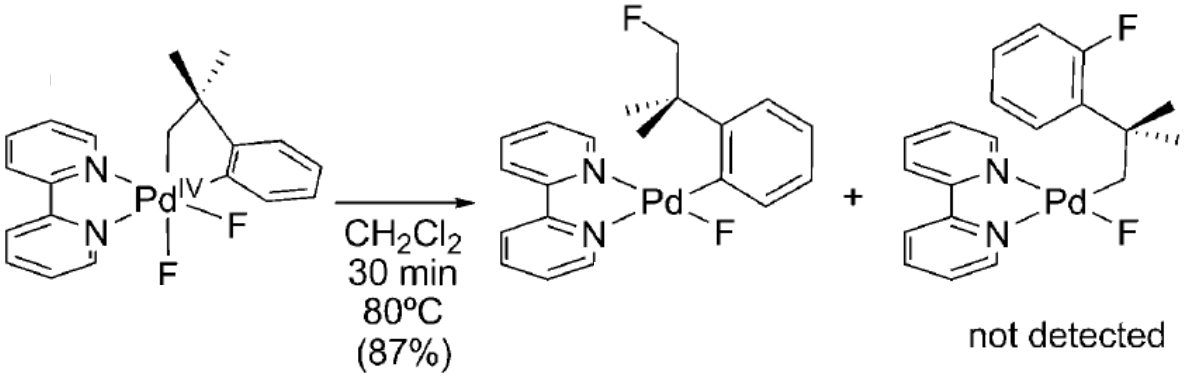
M. S. Sanford, *J. Am. Chem. Soc.*, **2004**, *126*, 2300

- C-H fluorination



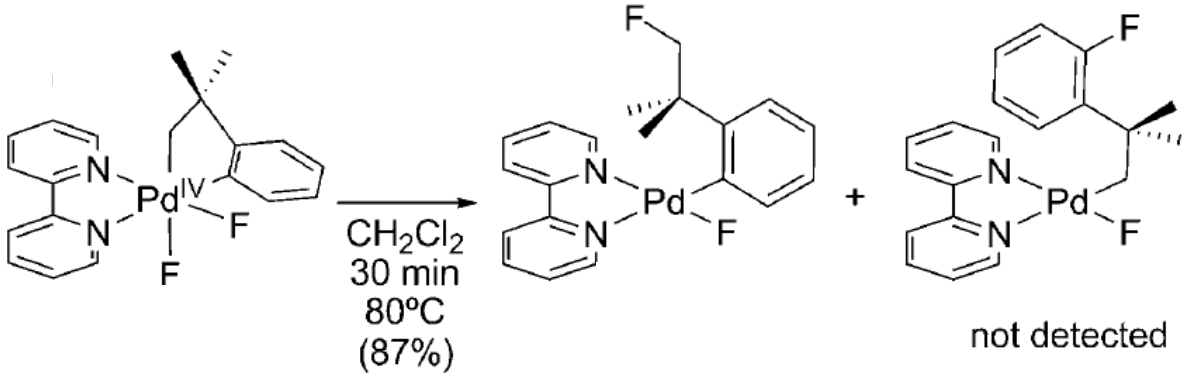
M. S. Sanford, *Org. Lett*. **2012**, *14*, 4094

Benzylic C–H activation: Direct acetoxylation / fluorination

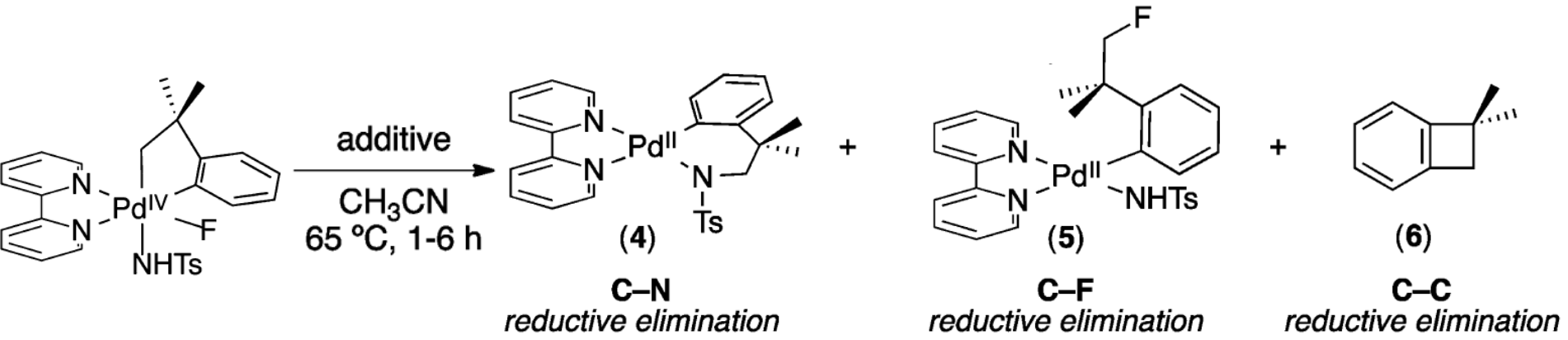


M. S. Sanford, *Angew. Chem. Int. Ed* **2012**, *51*, 3414

Benzylic C–H activation: Direct acetoxylation / fluorination



M. S. Sanford, *Angew. Chem. Int. Ed* **2012**, *51*, 3414



C–N *reductive elimination*

C–F *reductive elimination*

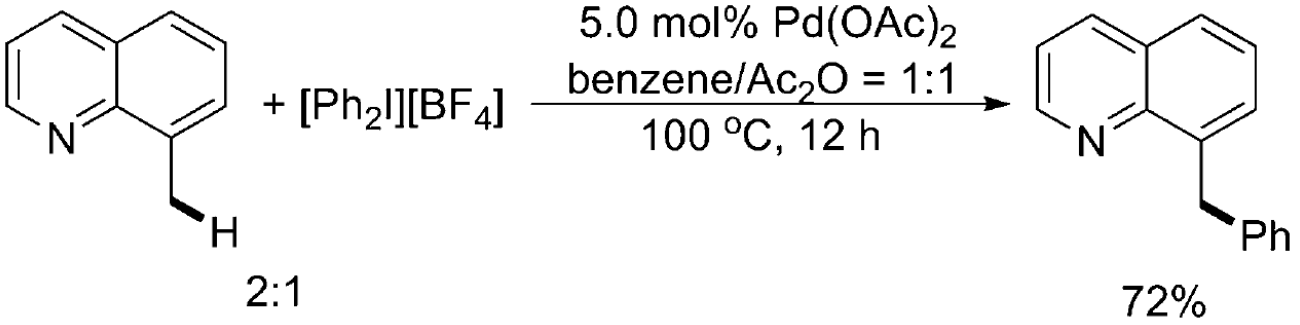
C–C *reductive elimination*

entry	additive	yield **4** (%)	yield **5** (%)	yield **6** (%)
1	none	9	49	29
2	1 equiv of NMe_4NHTs	85	<1	<1
3	1 equiv of NMe_4NHTs + 2 equiv of bpy	98	<1	<1

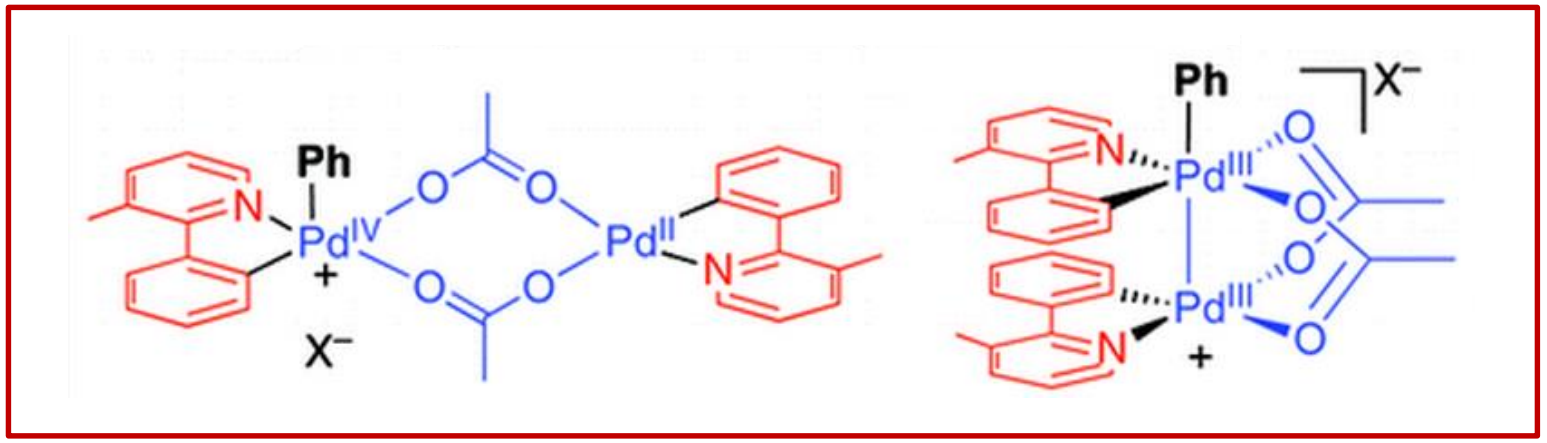
M. S. Sanford, *J. Am. Chem. Soc*. **2014**, *136*, 4097

Benzylic C–H activation: Direct C–C bond formation

- C-H arylation



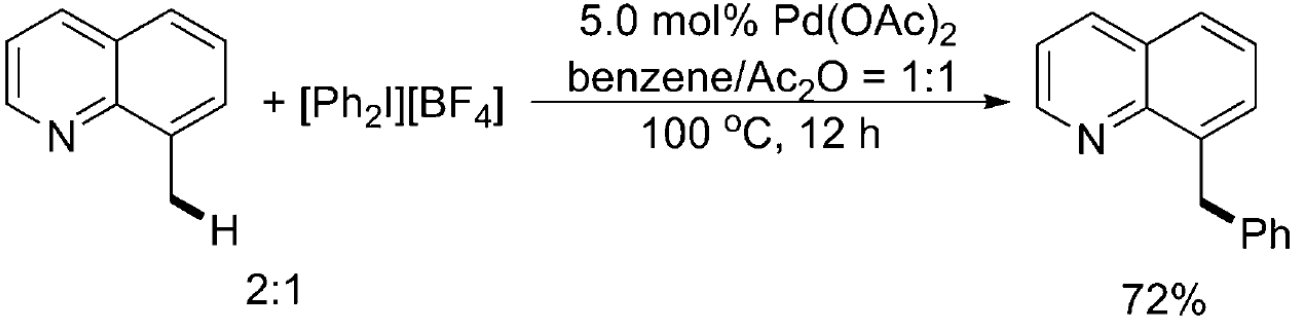
M. S. Sanford, *J. Am. Chem. Soc.*, **2005**, *127*, 7330.



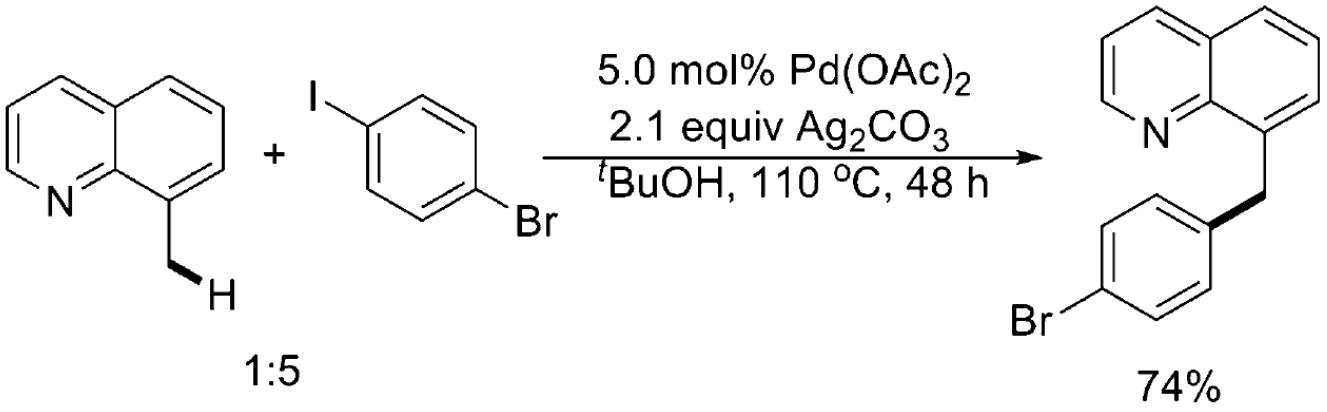
M. S. Sanford, *J. Am. Chem. Soc.*, **2009**, *131*, 11234.

Benzylic C–H activation: Direct C–C bond formation

- C-H arylation

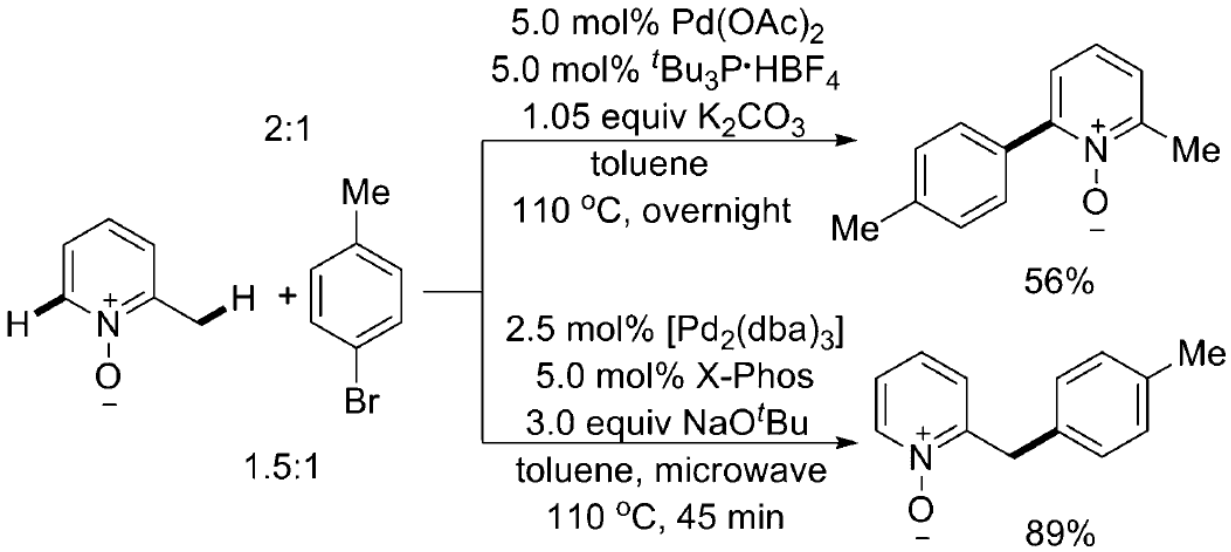


M. S. Sanford, *J. Am. Chem. Soc.*, **2005**, *127*, 7330.



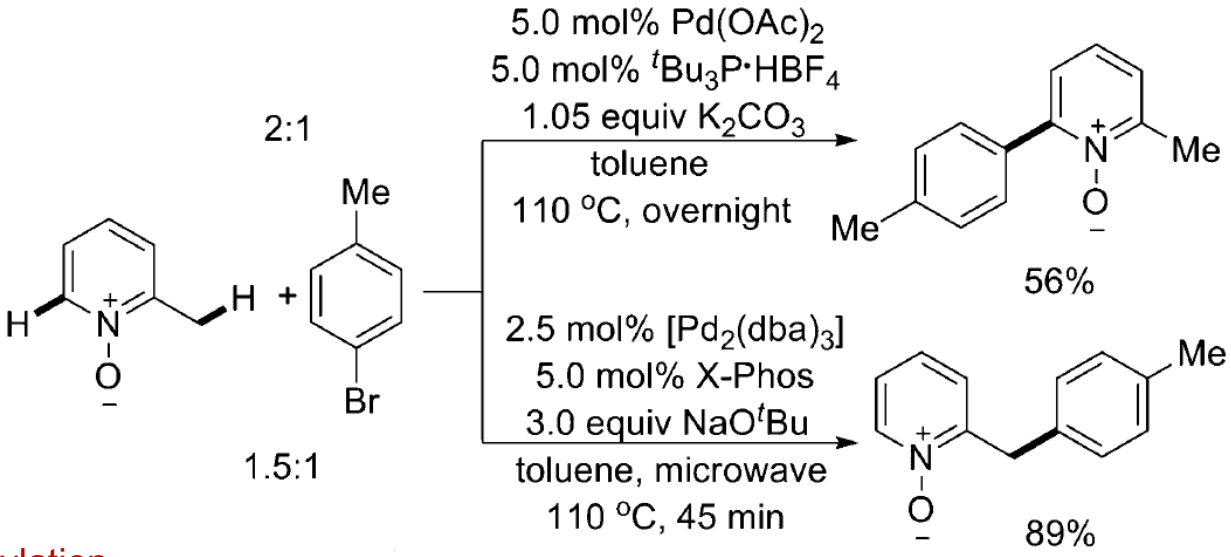
O. Daugulis, *Org. Lett.*, **2005**, *7*, 3657.

Benzylic C–H activation: Direct C–C bond formation



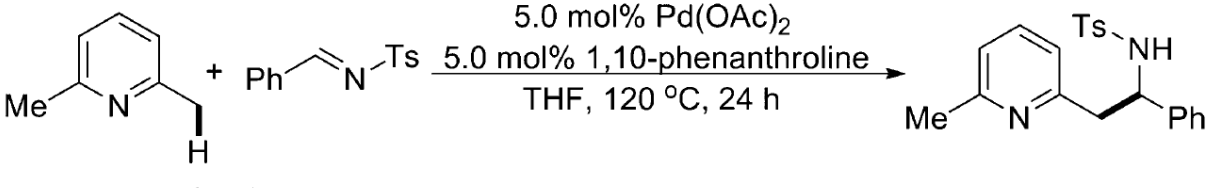
K. Fagnou, *J. Am. Chem. Soc.*, **2008**, *130*, 3266.

Benzylic C–H activation: Direct C–C bond formation

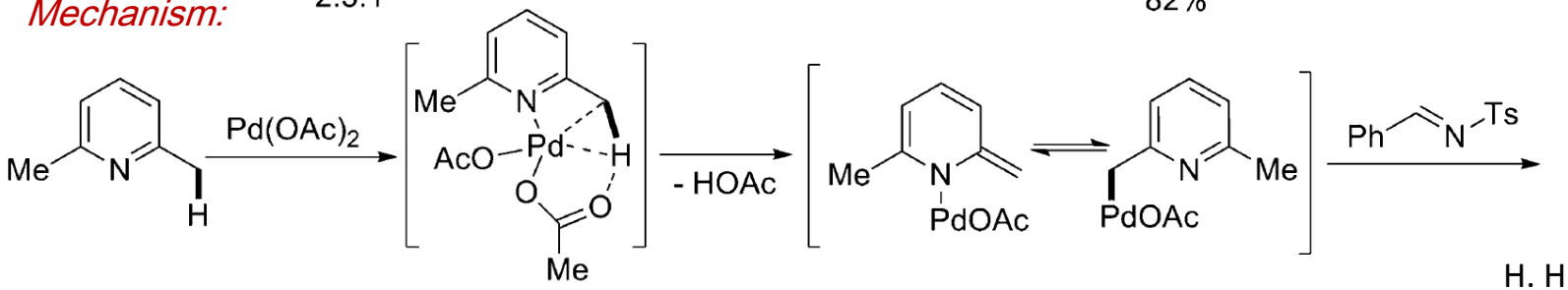


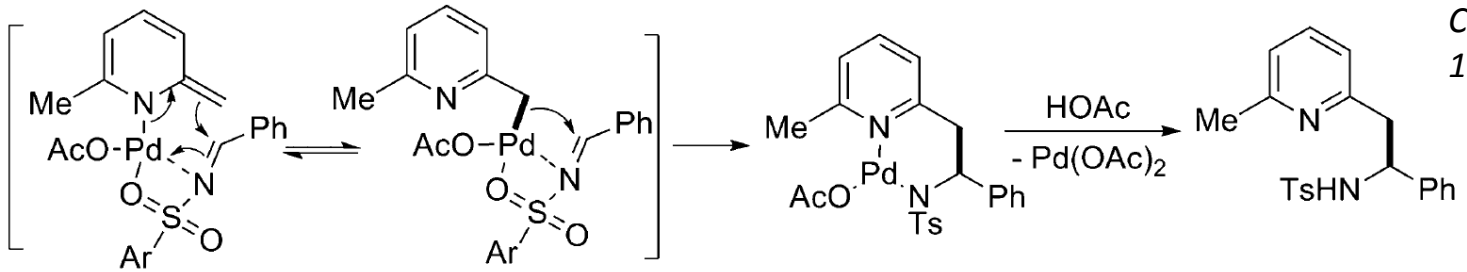
K. Fagnou, *J. Am. Chem. Soc.*, **2008**, *130*, 3266.

C-H alkylation



Mechanism:





H. Huang, *J. Am. Chem. Soc.*, **2010**, *132*, 3650.

Content

Palladium-catalyzed sp^3 C–H activation

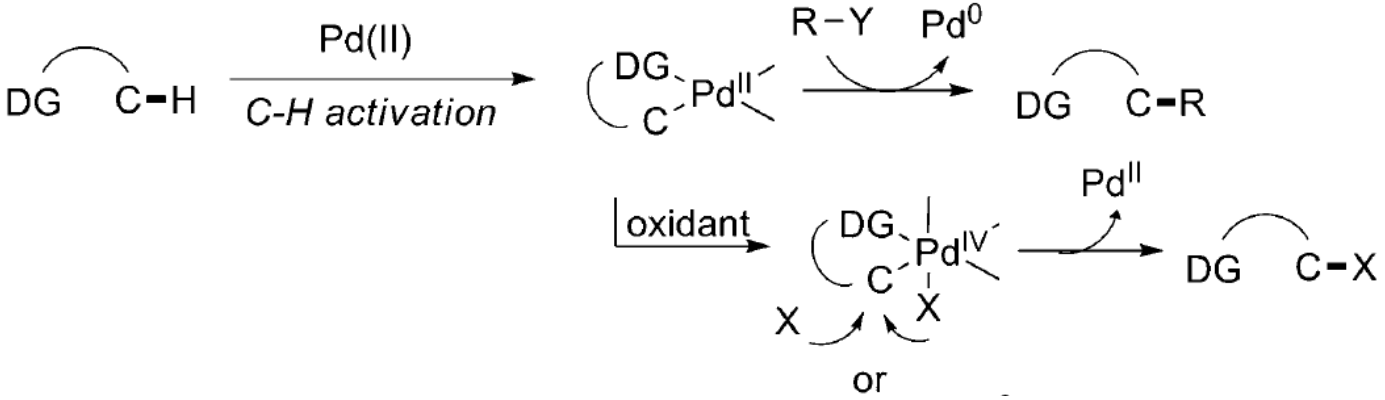
Content

Palladium-catalyzed sp^3 C–H activation

Common C–H activation: Direct C–X bond formation

- General model

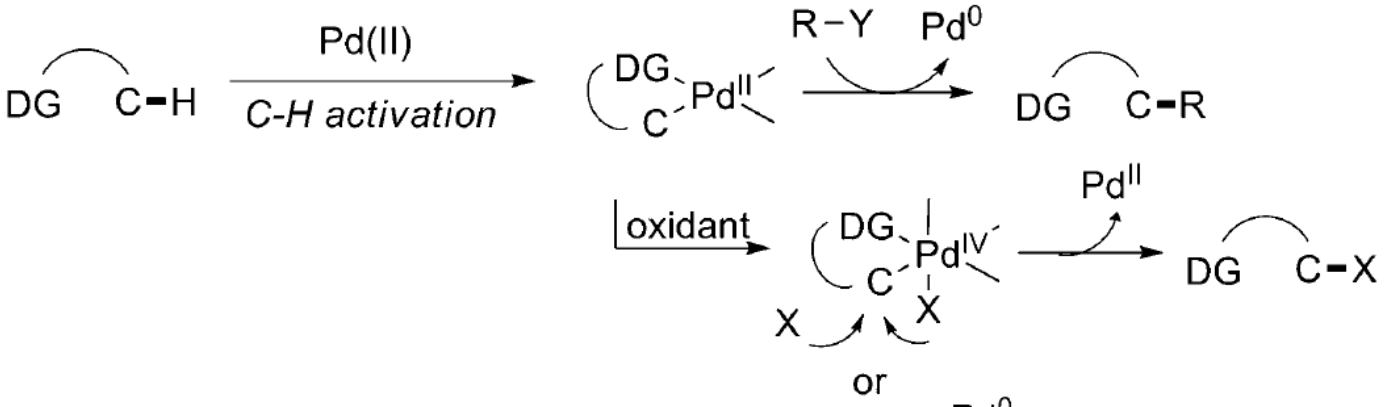
***Pathway A*: triggered by C-H cleavage**



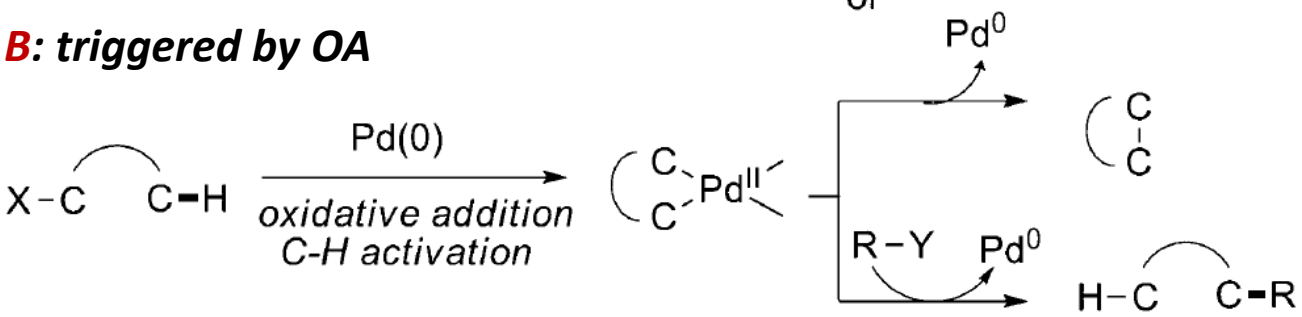
Common C–H activation: Direct C–X bond formation

- General model

***Pathway A*: triggered by C-H cleavage**

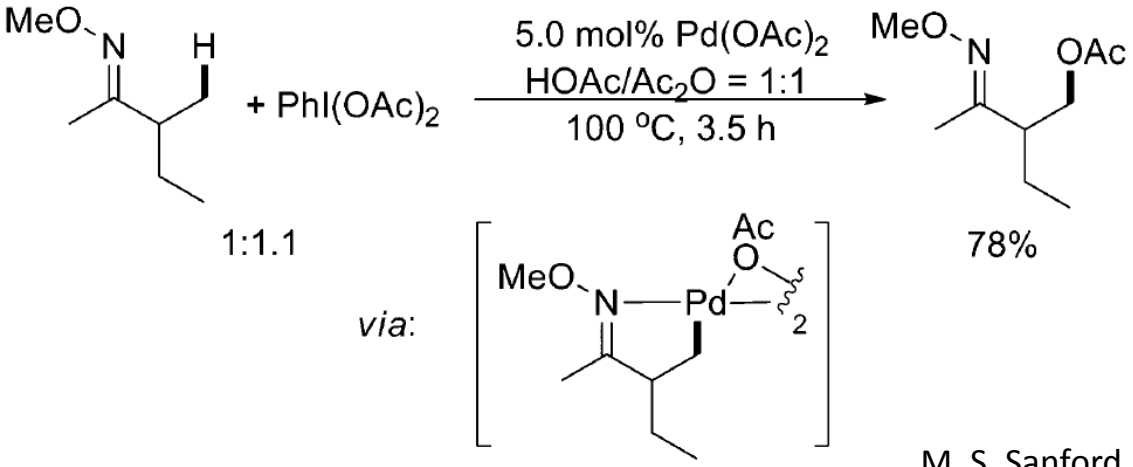


***Pathway B*: triggered by OA**



Common C–H activation: Direct C–X bond formation

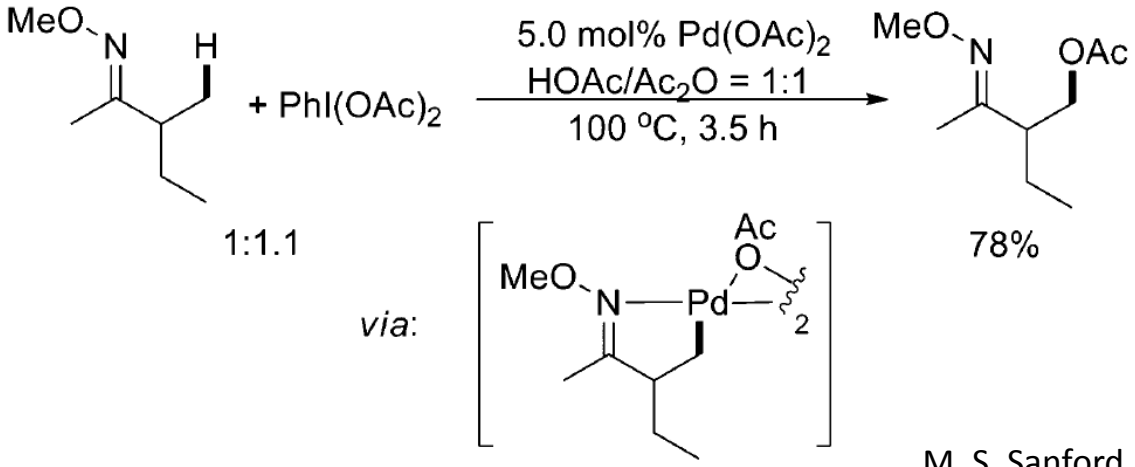
- C-H actoxylation



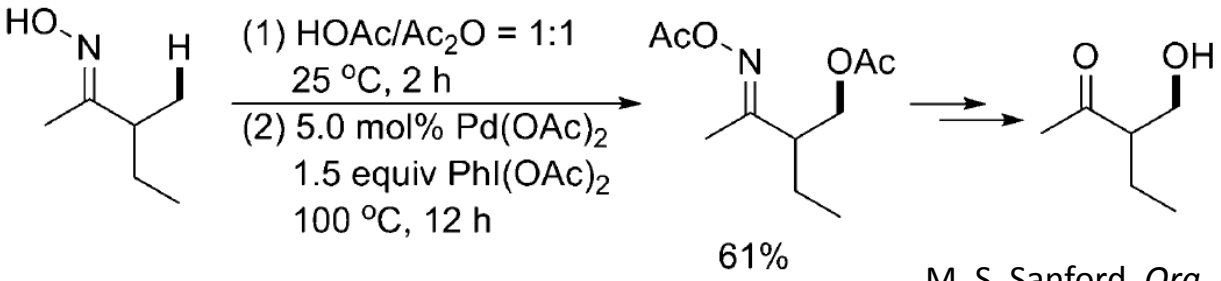
M. S. Sanford, *JACS.*, **2004**, *126*, 9542.

Common C–H activation: Direct C–X bond formation

- C-H actoxylation



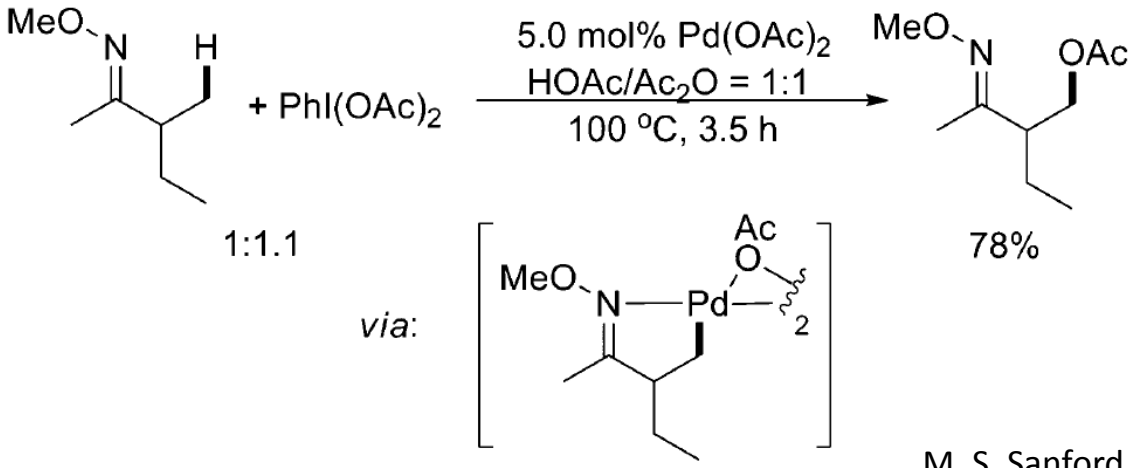
M. S. Sanford, *JACS.*, **2004**, *126*, 9542.



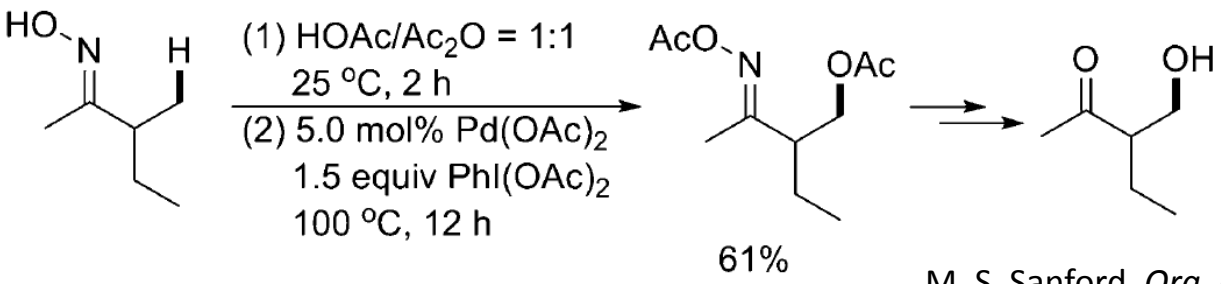
M. S. Sanford, *Org. Lett.*, **2010**, *12*, 532

Common C–H activation: Direct C–X bond formation

- C-H actoxylation

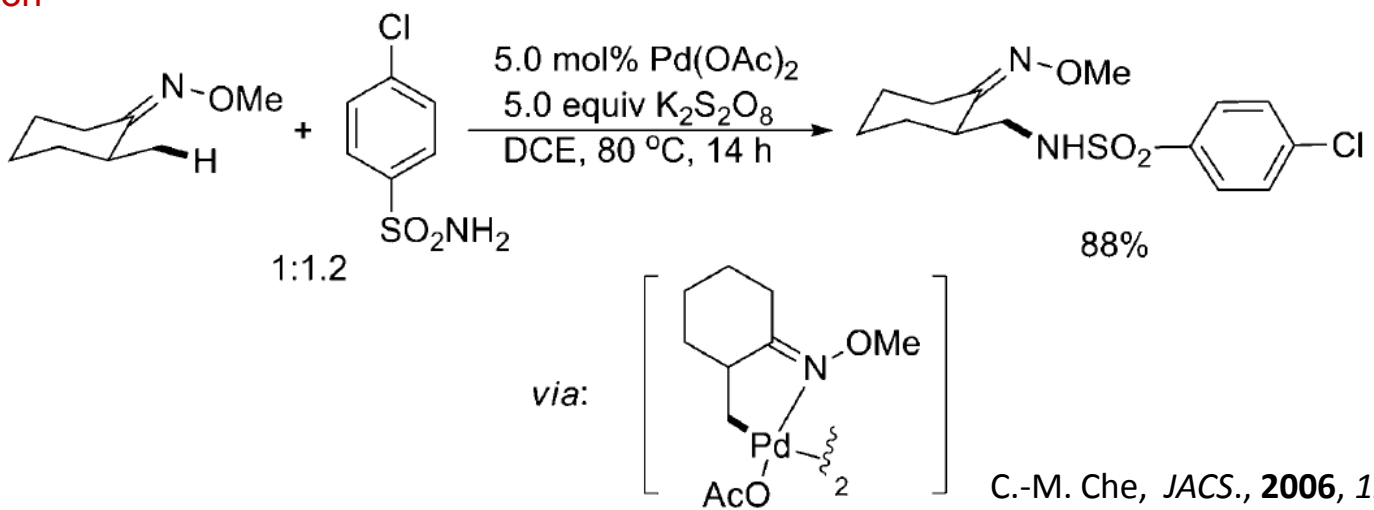


M. S. Sanford, *JACS.*, **2004**, *126*, 9542.



M. S. Sanford, *Org. Lett.*, **2010**, *12*, 532

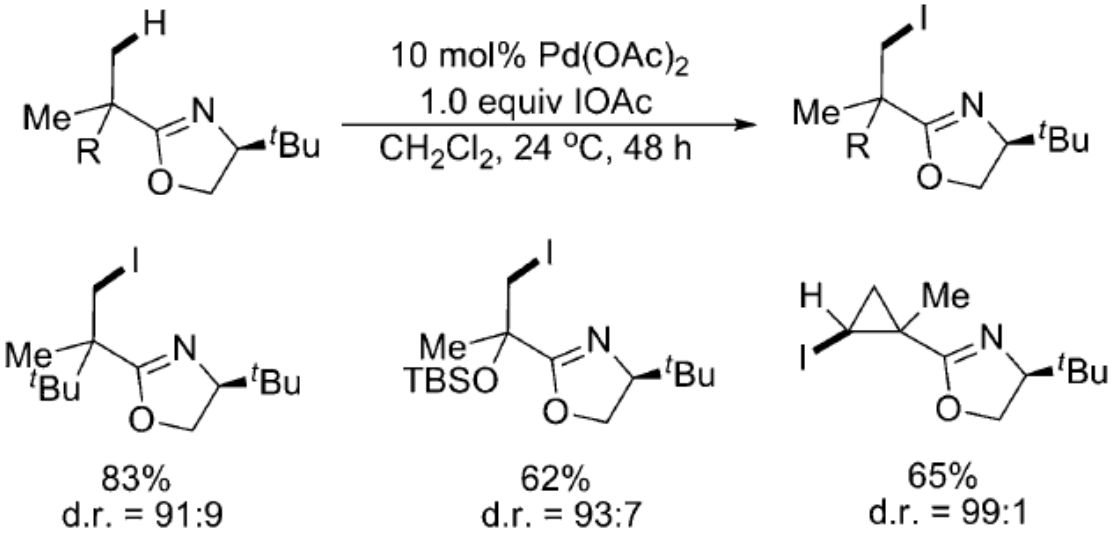
- C-H amidation



C.-M. Che, *JACS.*, **2006**, *128*, 9048.

Common C–H activation: Direct C–X bond formation

- C-H iododination

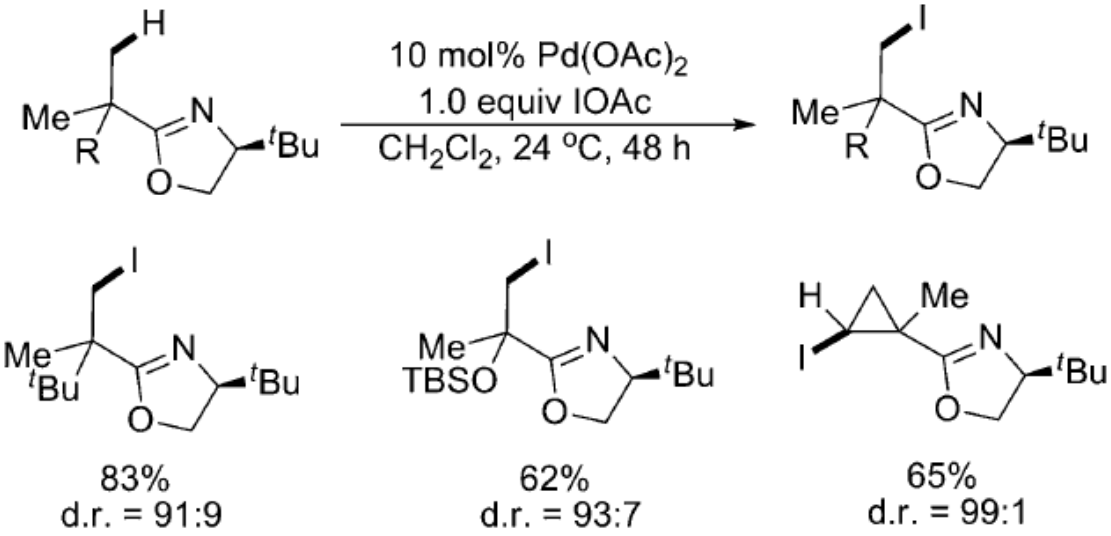


For a *diiodination version* followed by converting into *cyclopropane*, see:
J.-Q. Yu, *Org. Lett.*, **2006**, *8*, 5685.

J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2005**, *44*, 2112

Common C–H activation: Direct C–X bond formation

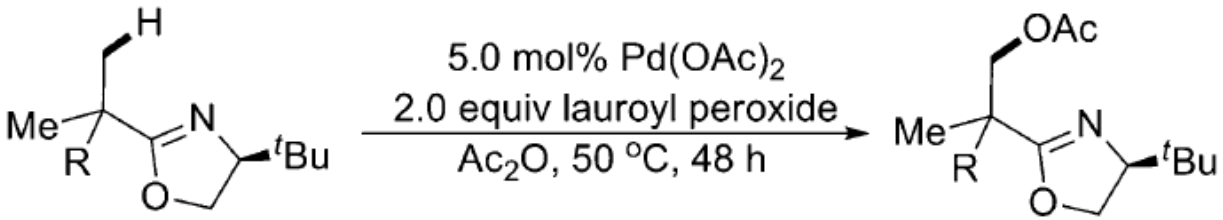
- C-H iododination



For a *diiodination version* followed by converting into *cyclopropane*, see:
J.-Q. Yu, *Org. Lett.*, **2006**, *8*, 5685.

J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2005**, *44*, 2112

- C-H acetoxylation

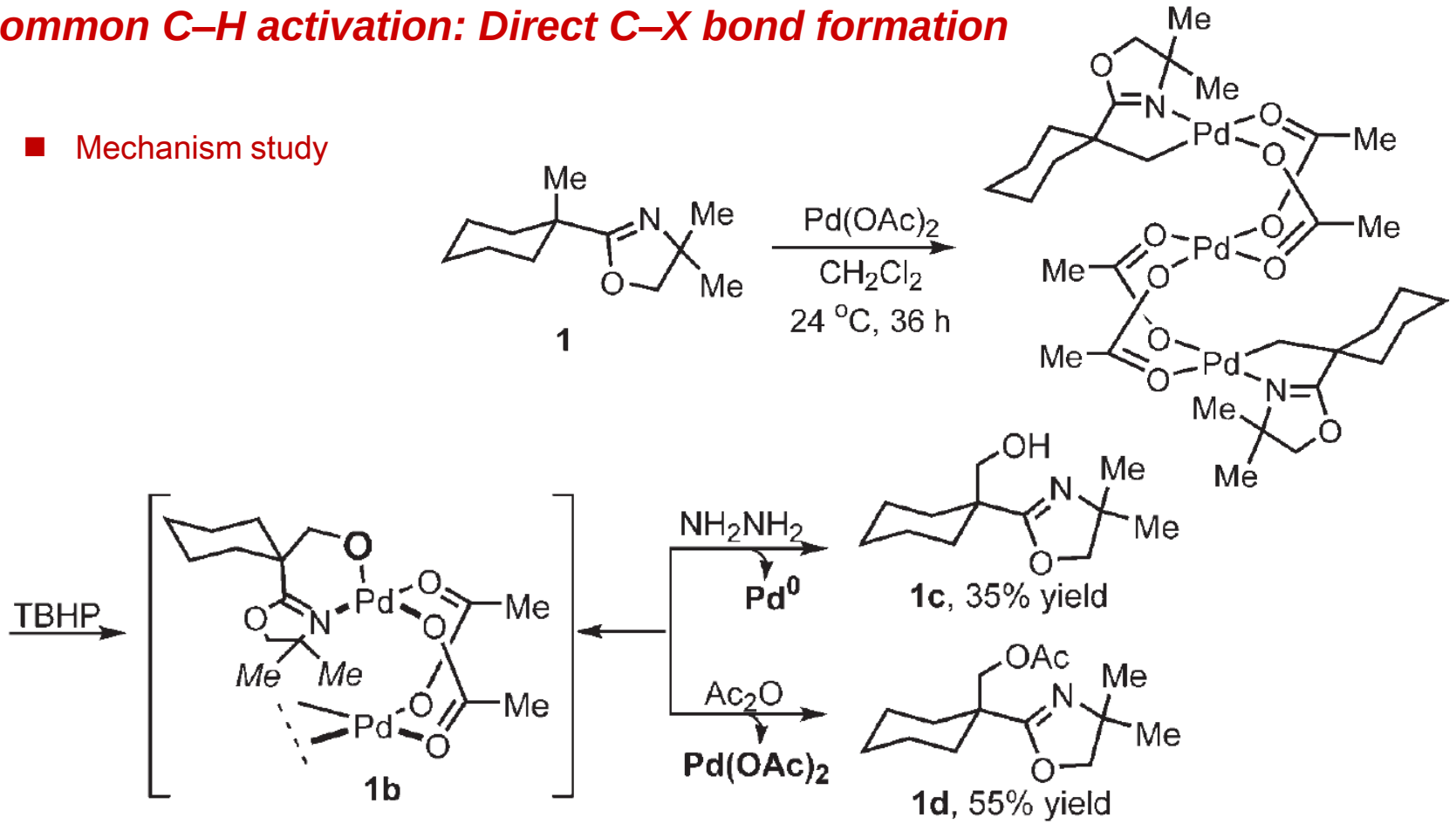


R = Et: 67% yield, 18% *de*;
R = ^{t}Bu: 49% yield, 82% *de*.

J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7420.

Common C–H activation: Direct C–X bond formation

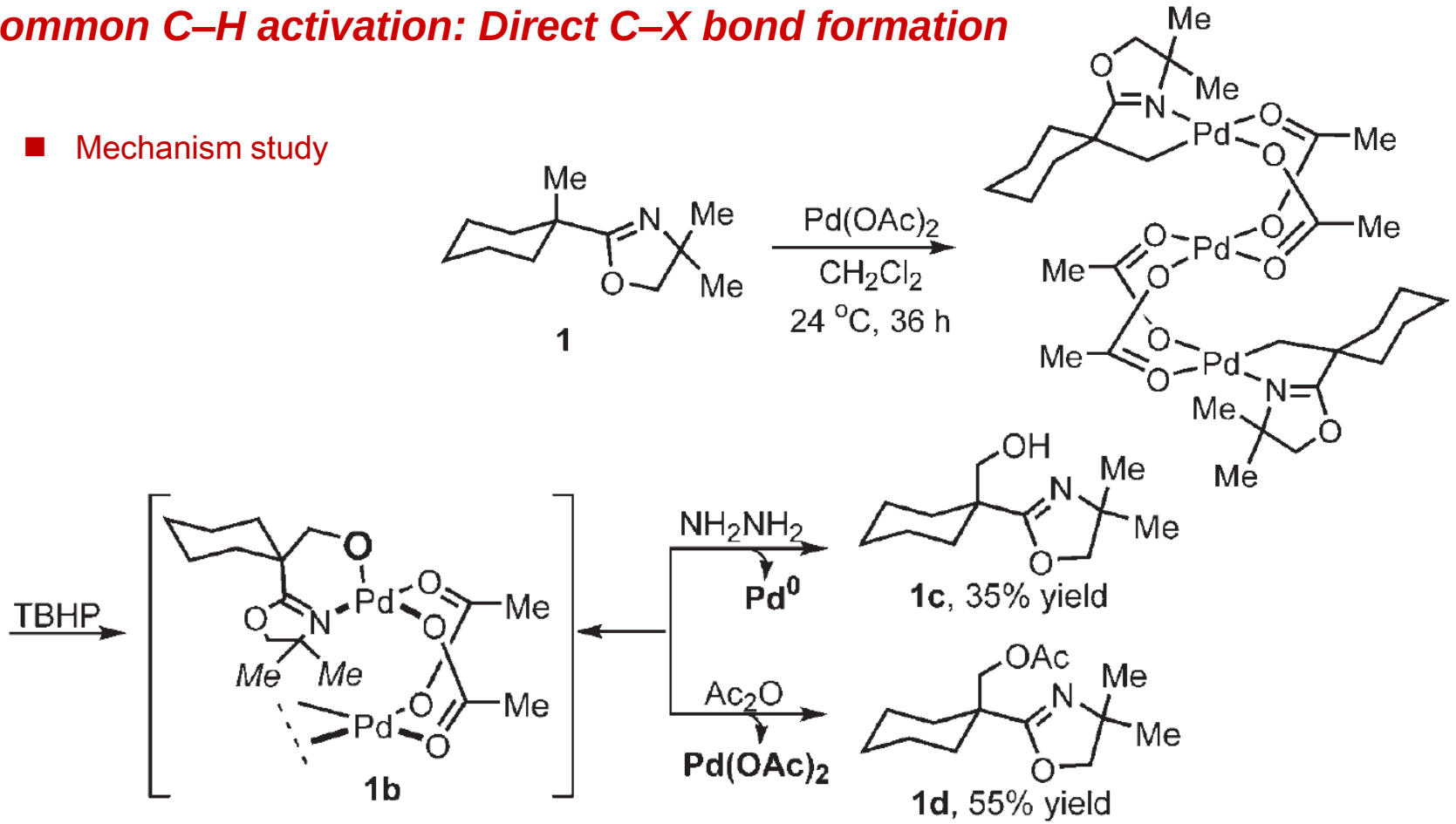
- Mechanism study



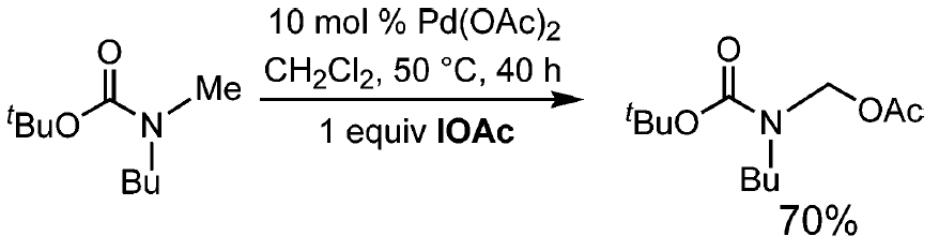
J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7420.

Common C–H activation: Direct C–X bond formation

- Mechanism study



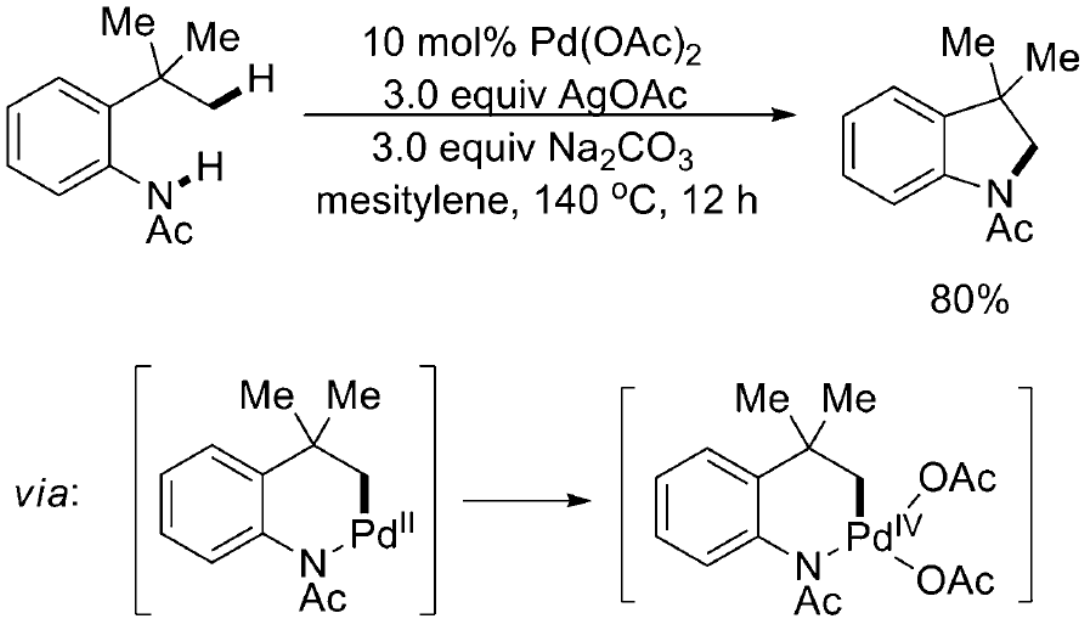
J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7420.

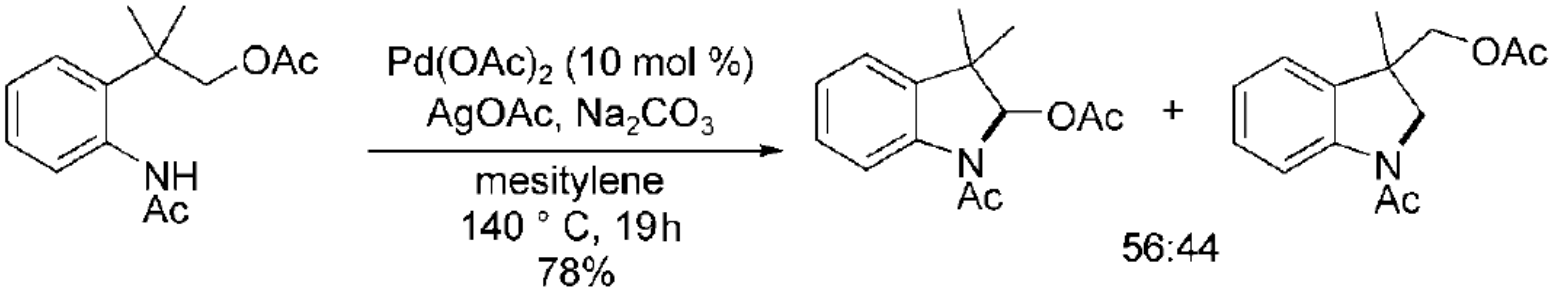


J.-Q. Yu, *Org. Lett.*, **2006**, *8*, 3387.

Common C–H activation: Direct C–X bond formation

- intramolecular direct amidation



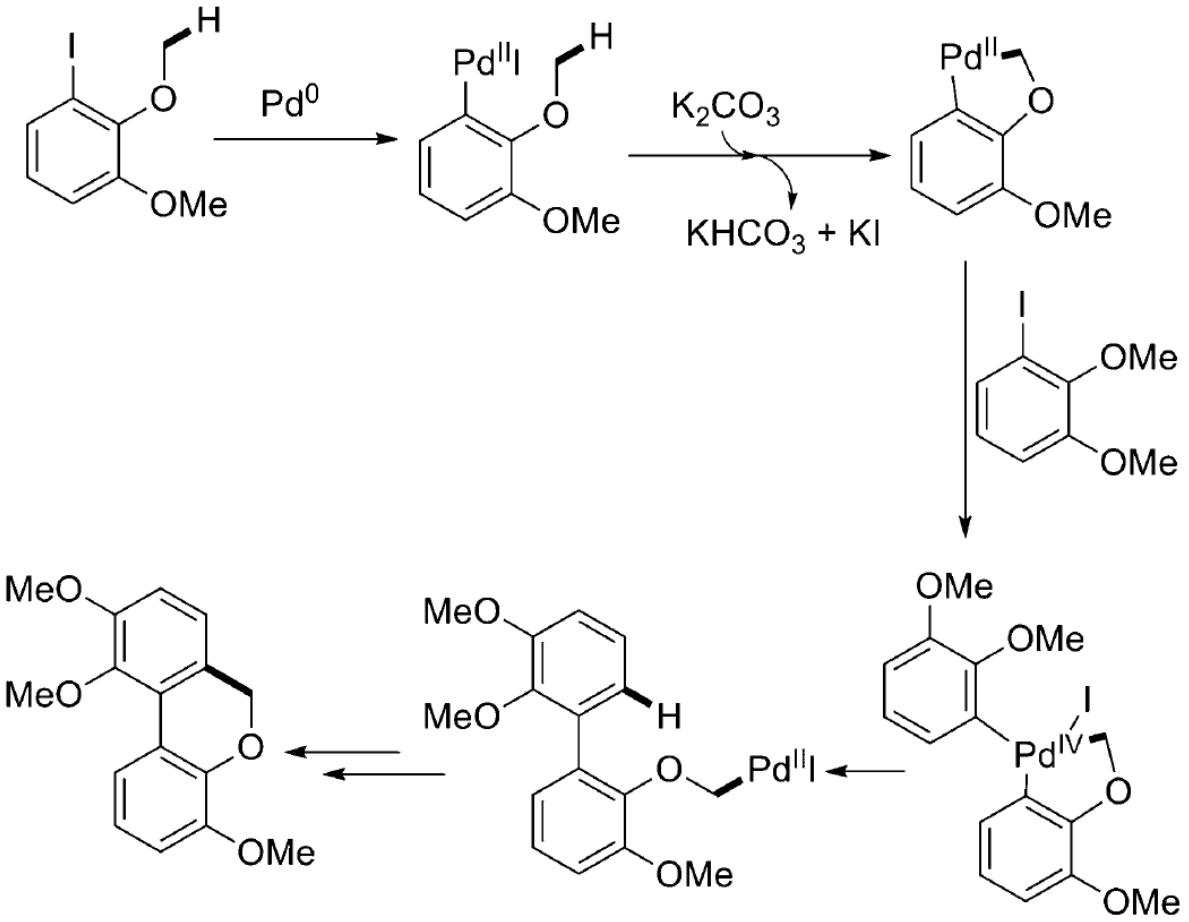


F. Glorius, *Angew. Chem., Int. Ed.*, **2009**, *48*, 6892.

Common C–H activation: Direct C–C bond formation ***triggered by OA***

G. Dyker, *Angew. Chem., Int. Ed*.., **1992**, *31*, 1023.

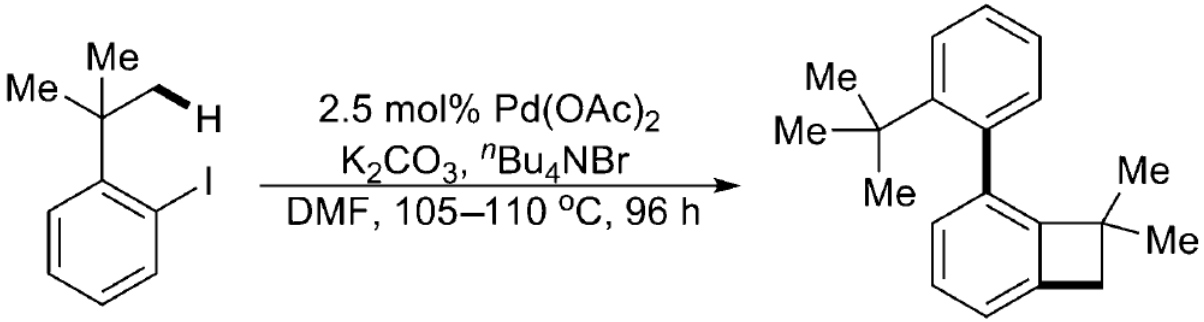
Mechanism:



Common C–H activation: Direct C–C bond formation ***triggered by OA***

87%

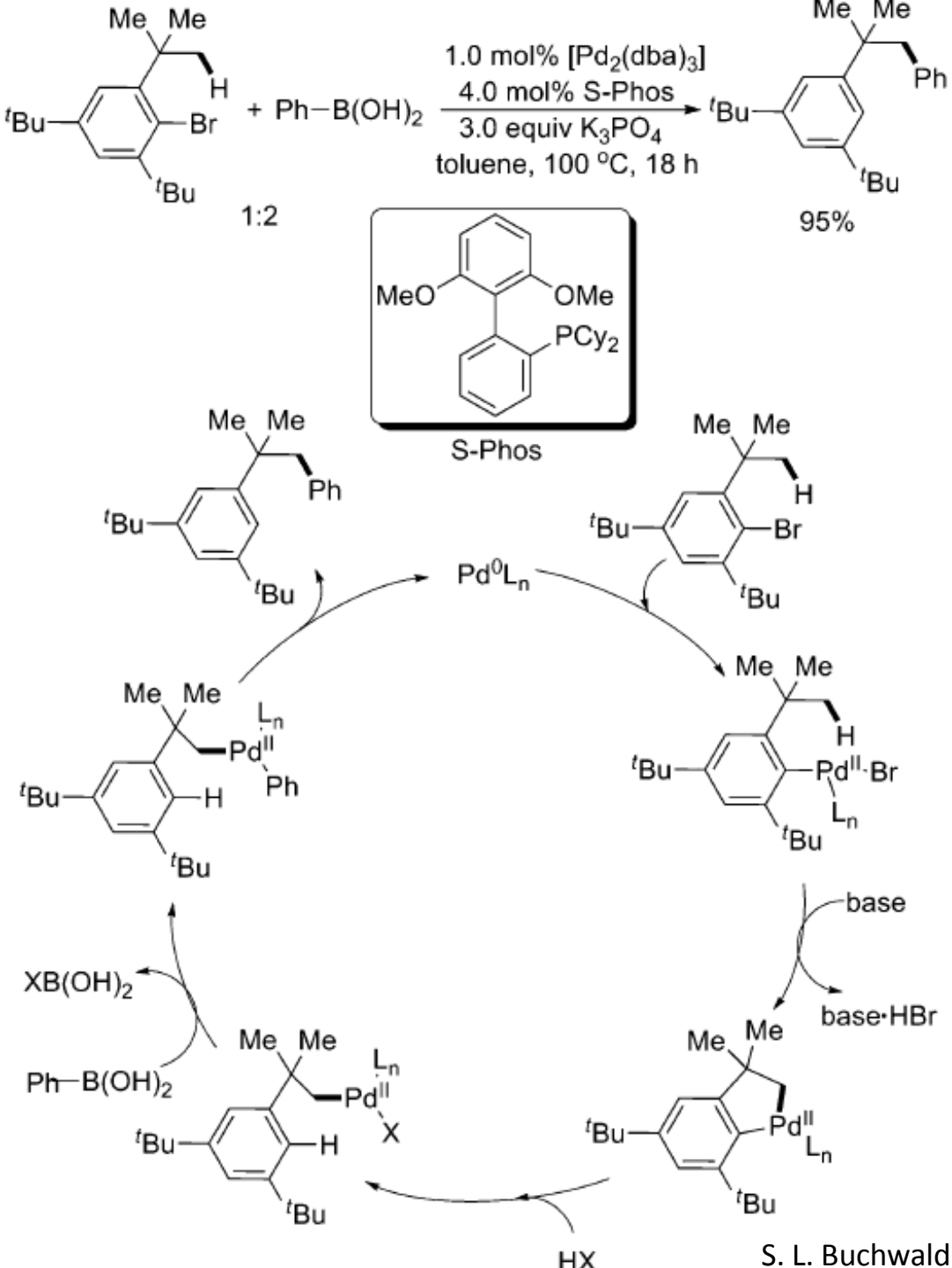
G. Dyker, *Angew. Chem., Int. Ed*.., **1992**, *31*, 1023.



75%

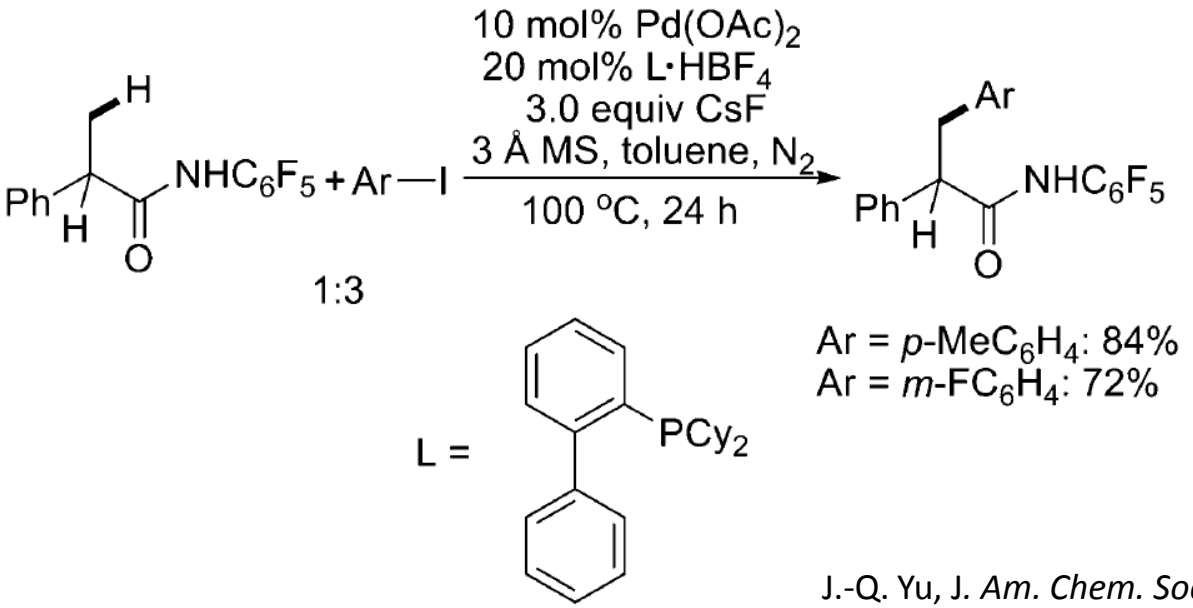
G. Dyker, *Angew. Chem., Int. Ed*., **1994**, *33*, 103.

Common C–H activation: Direct C–C bond formation triggered by OA



S. L. Buchwald, *JACS*., **2005**, *127*, 4685

Common C–H activation: Direct C–C bond formation ***triggered by OA***

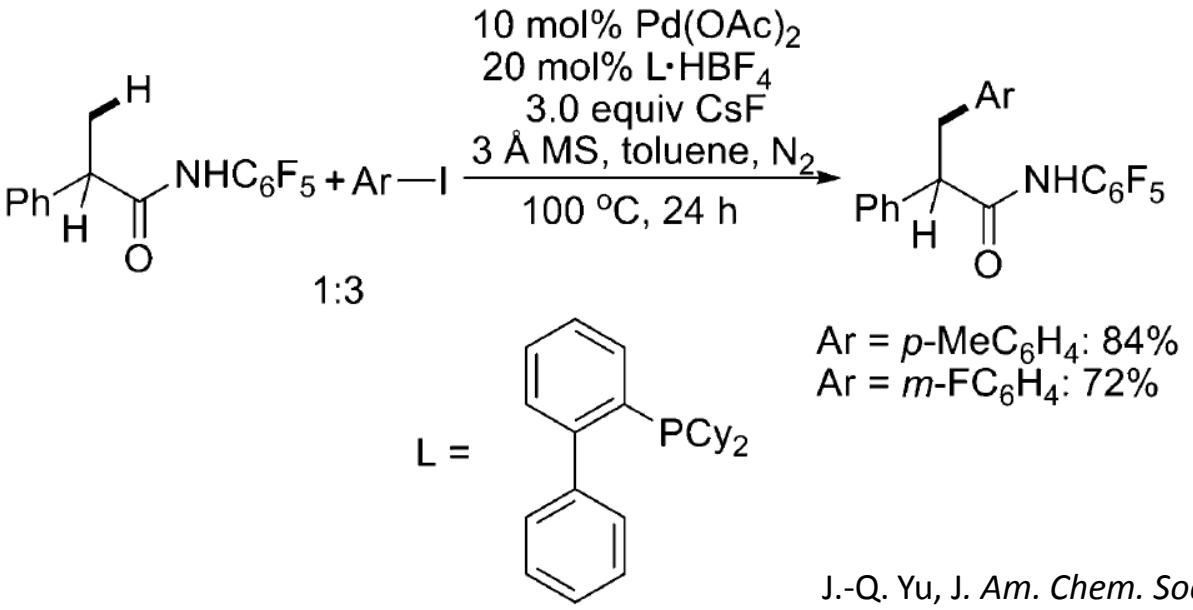


J.-Q. Yu, J. *Am. Chem. Soc.*, **2009**, *131*, 9886

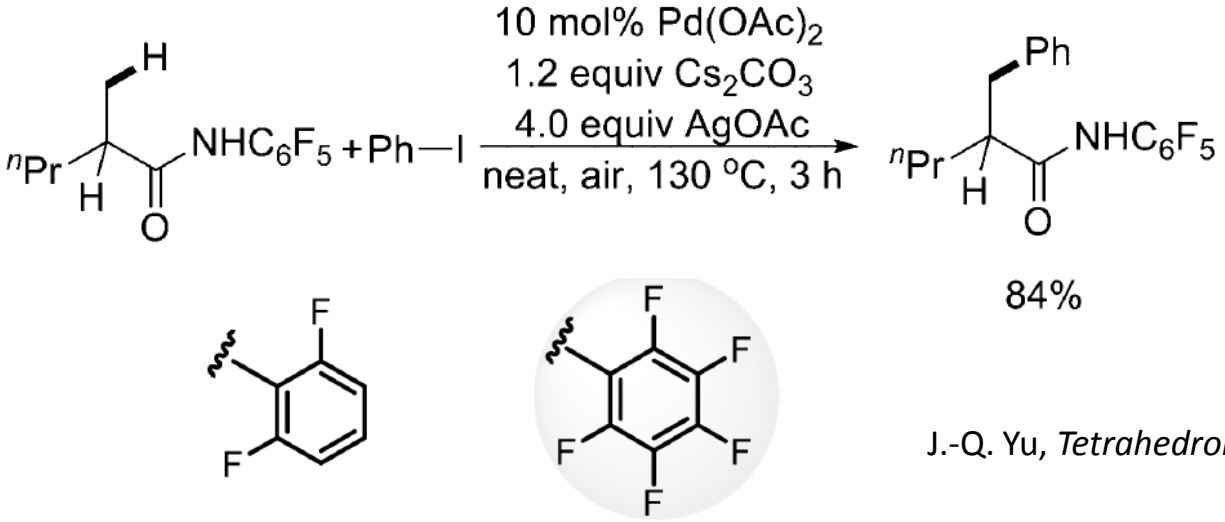
For detailed discussion for *cation-promoted Pd insertion* into C-H bonds, see:

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

Common C–H activation: Direct C–C bond formation triggered by OA

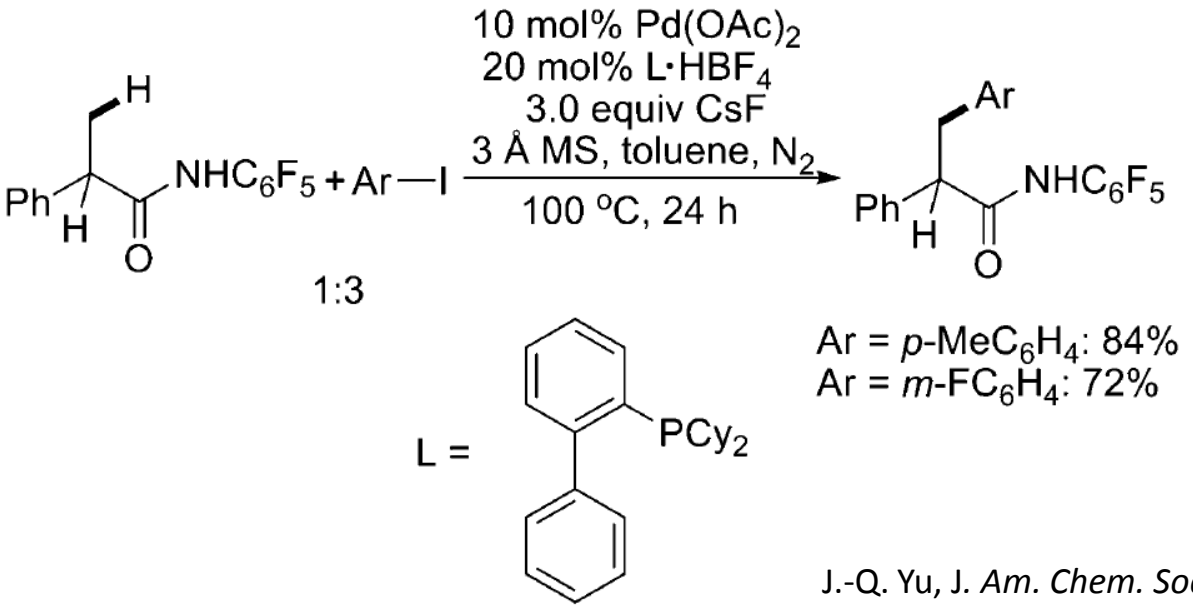


J.-Q. Yu, J. *Am. Chem. Soc.*, **2009**, *131*, 9886

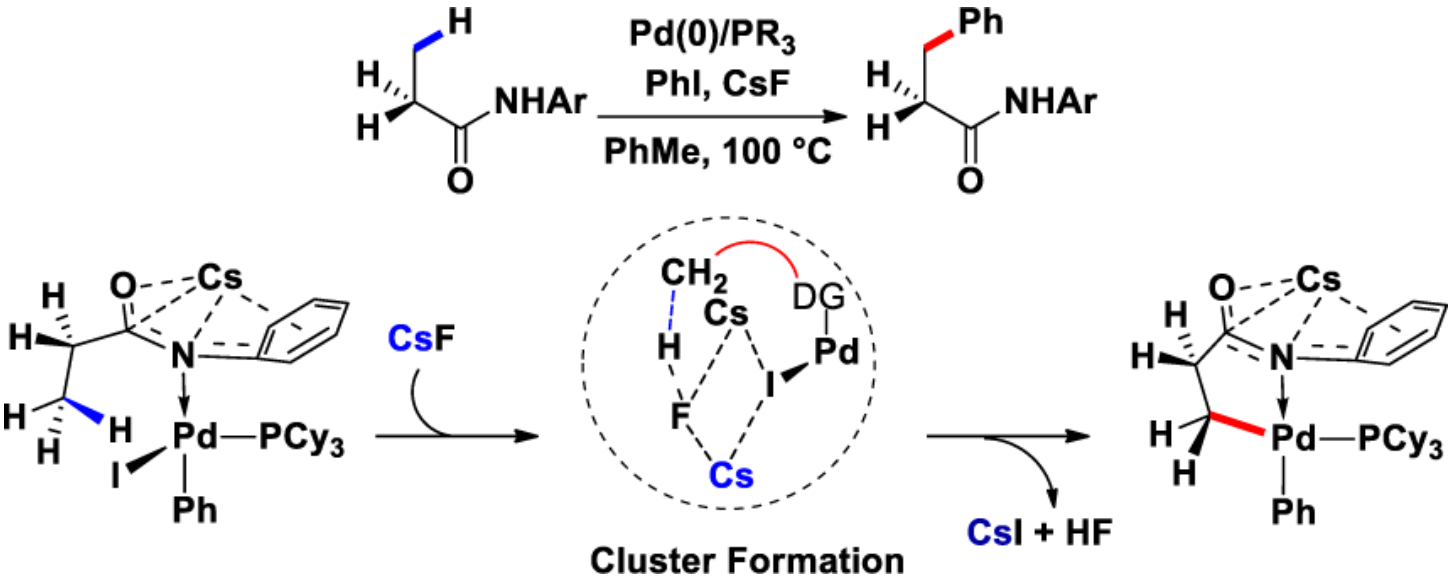


J.-Q. Yu, *Tetrahedron*, **2010**, *66*, 4811.

Common C–H activation: Direct C–C bond formation triggered by OA

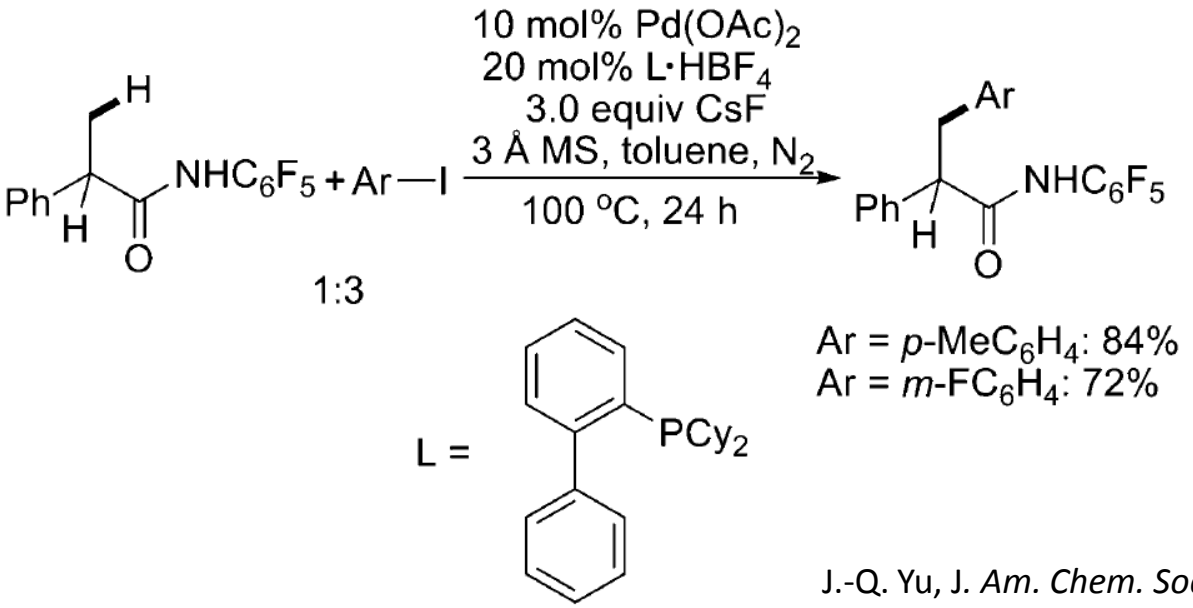


J.-Q. Yu, J. *Am. Chem. Soc.*, **2009**, *131*, 9886



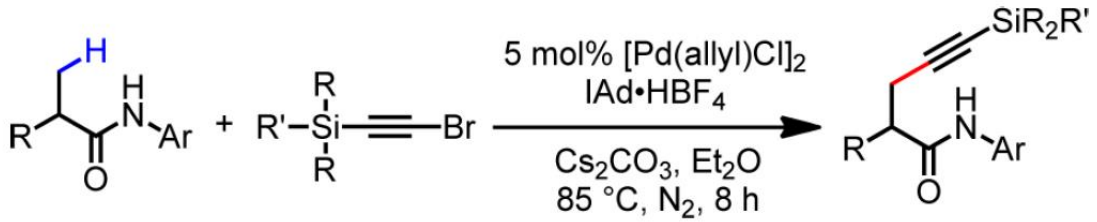
J.-Q. Yu, G. Musaev, *J. Am. Chem. Soc*. **2013**, *135*, 14206

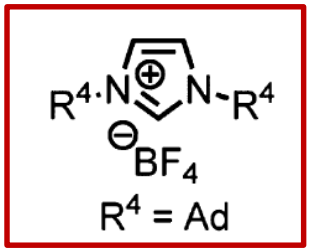
Common C–H activation: Direct C–C bond formation ***triggered by OA***

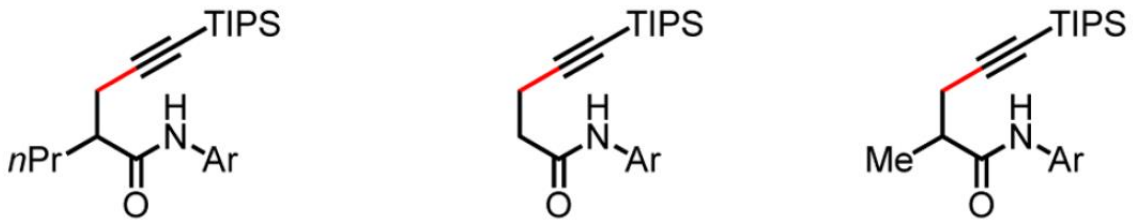


Ar = *p*-MeC_6H_4: 84%
Ar = *m*-FC_6H_4: 72%

J.-Q. Yu, J. *Am. Chem. Soc.*, **2009**, *131*, 9886







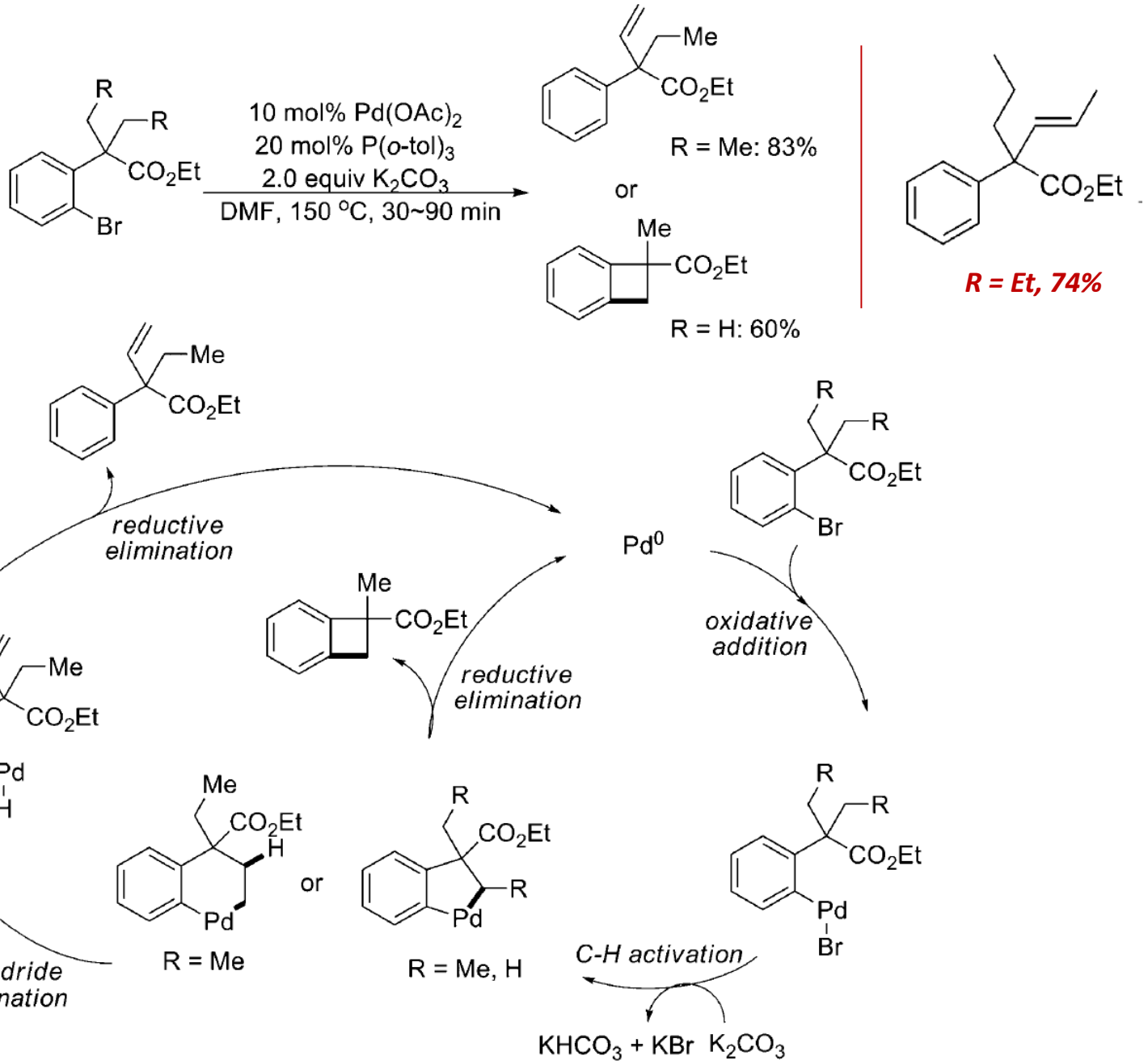
2a, 81% **2b**, 62% **2c**, 70%

For alkynylation, also see:

M. Tobisu, N. Chatani *J. Am. Chem. Soc.*, **2011**, *133*, 12984.

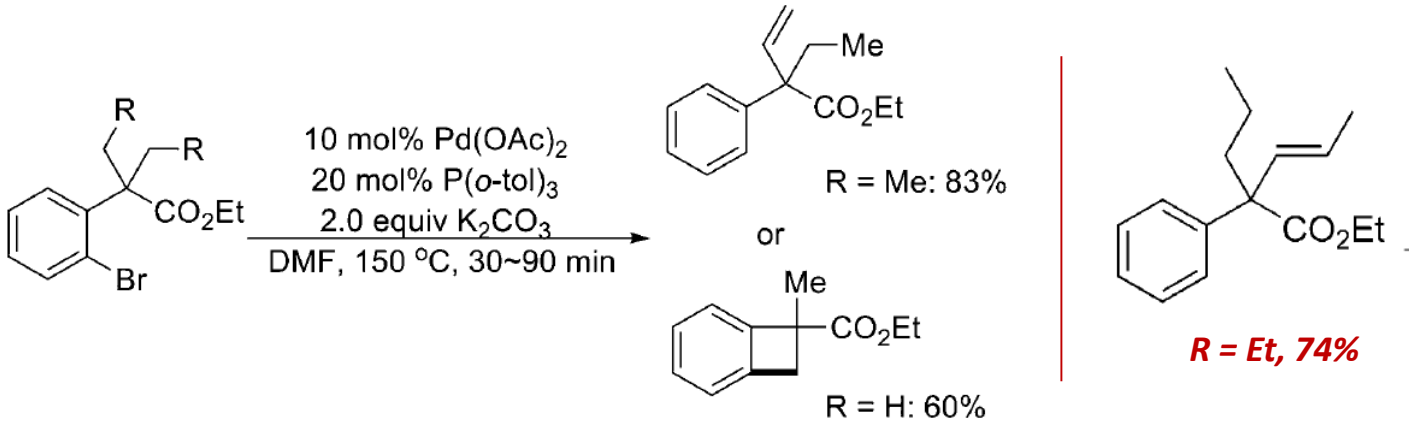
J.-Q. Yu, , *J. Am. Chem. Soc*. **2013**, *135*, 3387

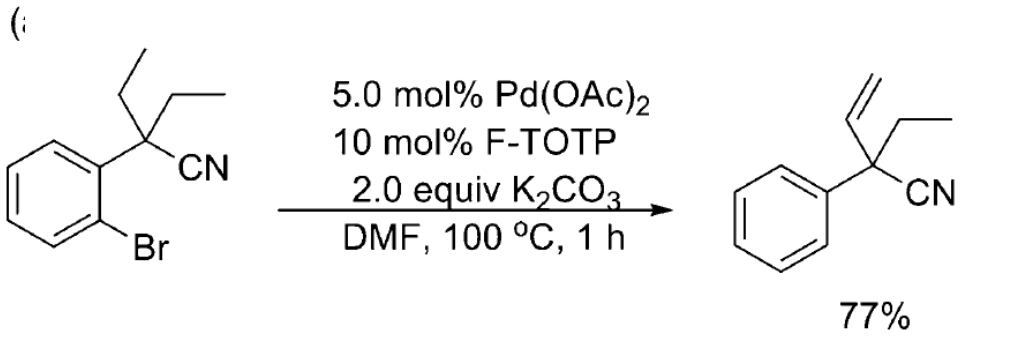
Common C–H activation: Direct C–C bond formation triggered by OA

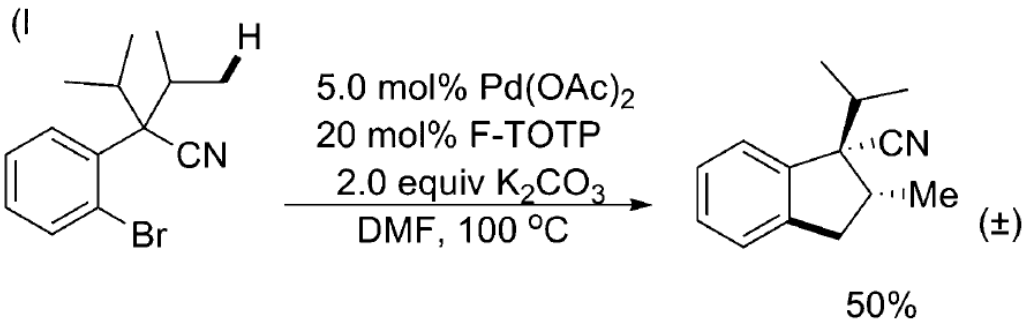


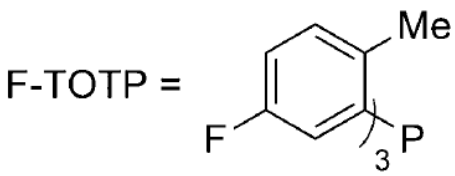
O. Baudoin, *Angew. Chem., Int. Ed.*, **2003**, *42*, 5736.

Common C–H activation: Direct C–C bond formation triggered by OA



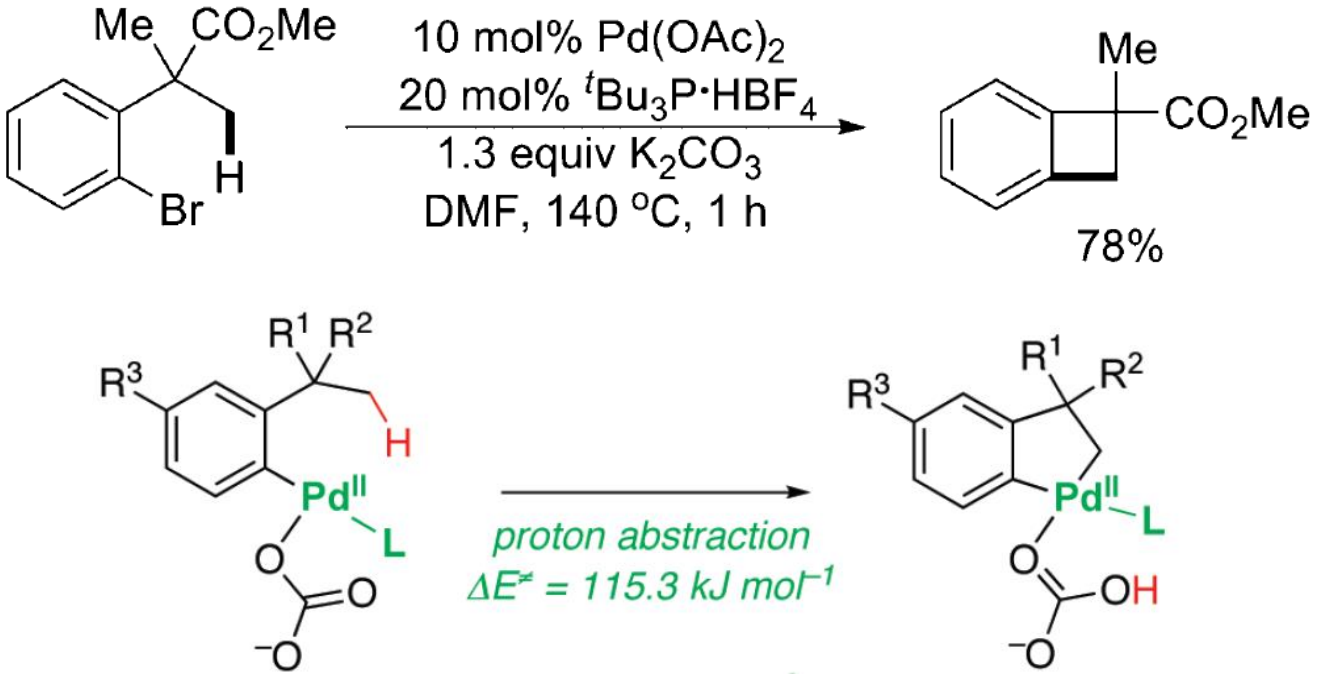






O. Baudoin, *Chem.–Eur. J.*, **2007**, *13*, 792.

Common C–H activation: Direct C–C bond formation ***triggered by OA***



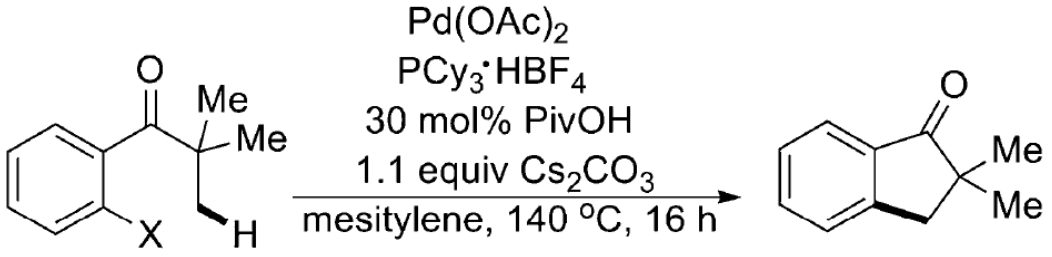
For other *computationally mechanistic studies* of CMD, see:

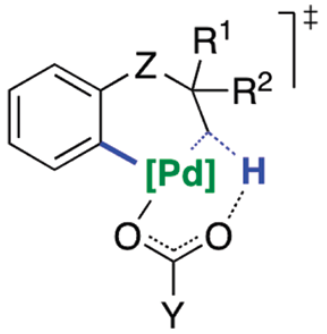
(a) A. M. Echavarren, *J. Am. Chem. Soc.*, **2006**, *128*, 1066;

(b) K. Fagnou, J. *Am. Chem. Soc.*, **2006**, *128*, 8754.

O. Baudoin, *J. Am. Chem. Soc.*, **2008**, *130*, 15157.

Common C–H activation: Direct C–C bond formation triggered by OA

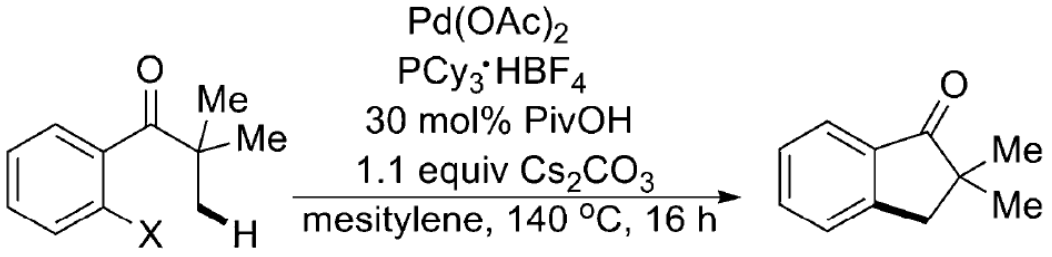


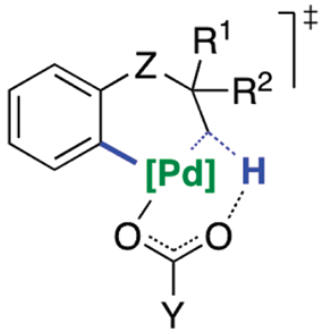


X = Br: 98% (5.0 mol% cat., 10 mol% ligand);
X = Cl: 93% (2.0 mol% cat., 4.0 mol% ligand).

K. Fagnou, *J. Am. Chem. Soc.*, **2007**, *129*, 14570.

Common C–H activation: Direct C–C bond formation triggered by OA





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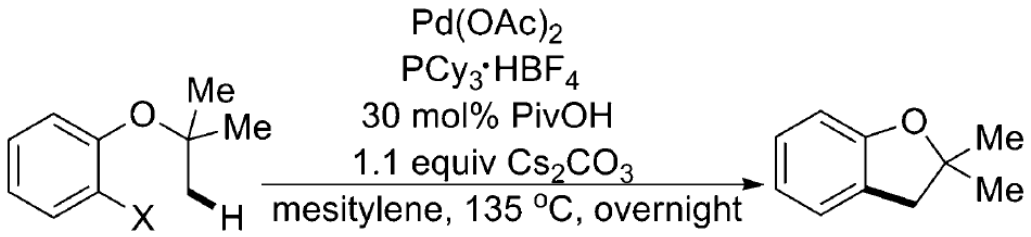
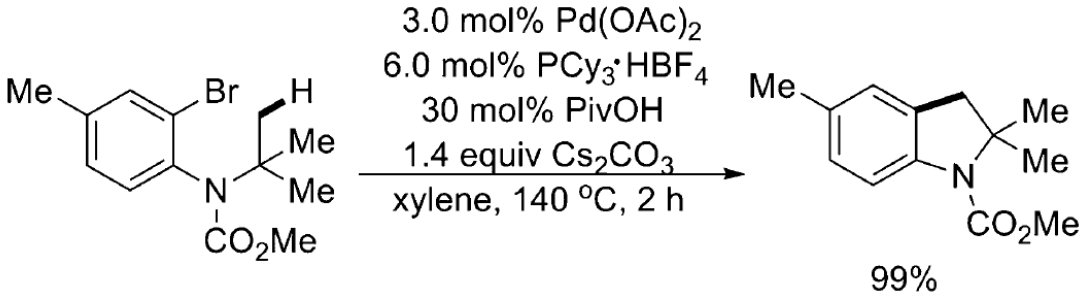
X = Cl: 93% (2.0 mol% cat., 4.0 mol% ligand).

K. Fagnou, *J. Am. Chem. Soc.*, **2007**, *129*, 14570.



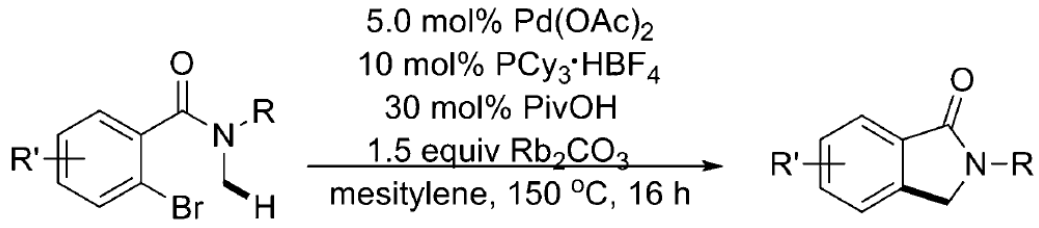
X = Br: 97% (3.0 mol% cat., 6.0 mol% ligand);
X = Cl: 77% (5.0 mol% cat., 10 mol% ligand).

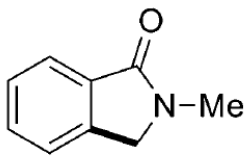
K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, **2010**, *132*, 10706.



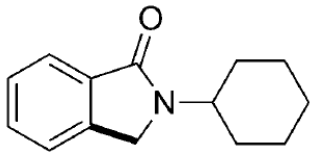
H. Ohno, *Org. Lett.*, **2008**, *10*, 1759.

Common C–H activation: Direct C–C bond formation ***triggered by OA***

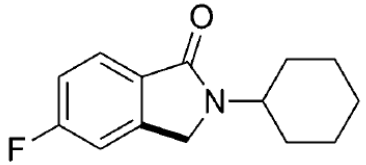




76%

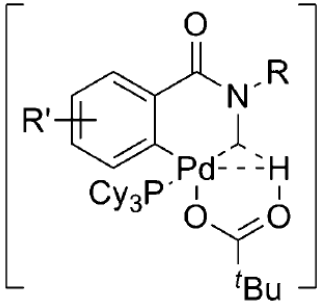


83%



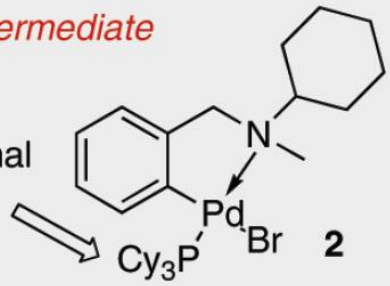
70%

via:



Unreactive intermediate

^{31}P NMR signal at 47 ppm

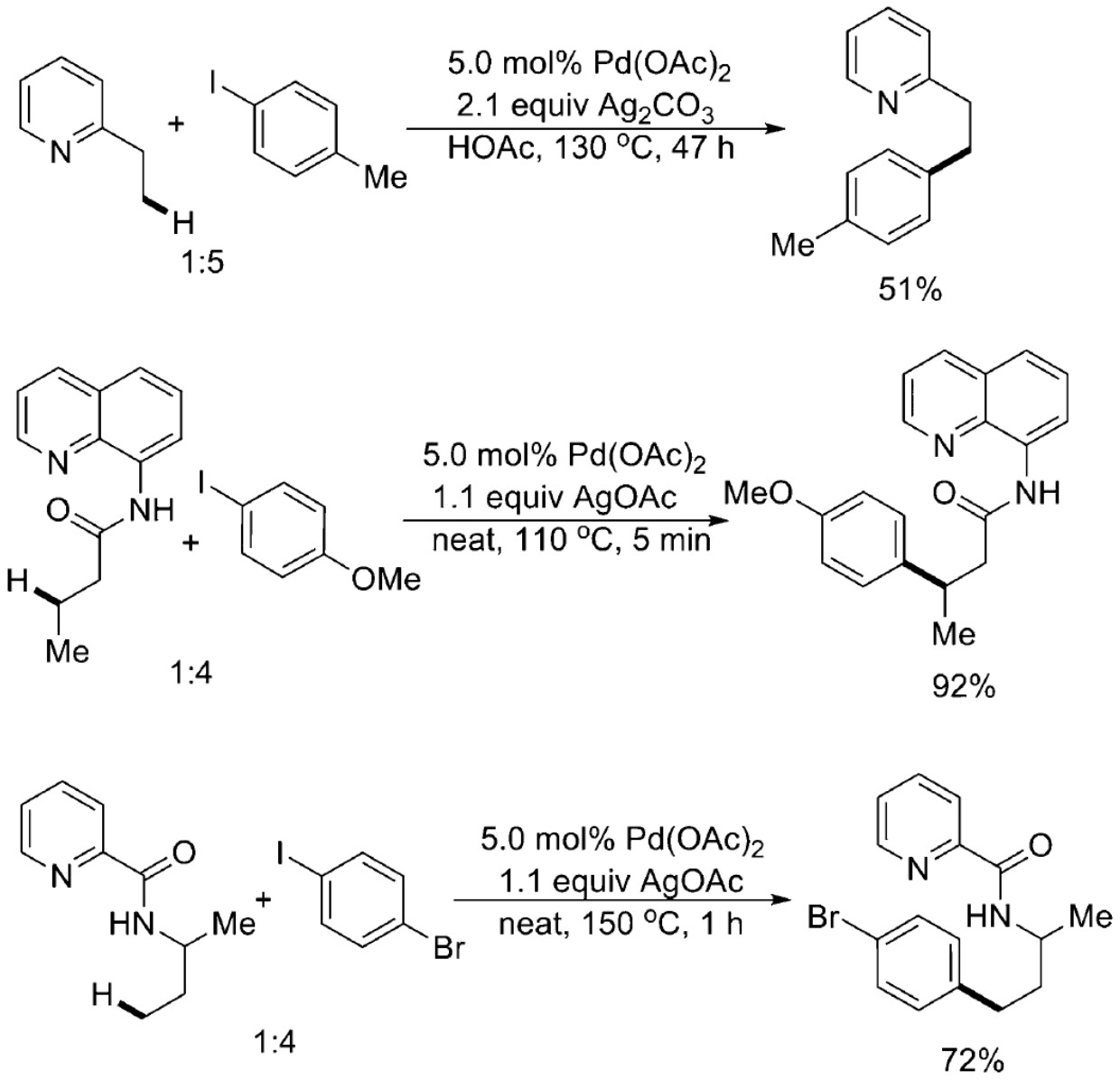


2

K. Fagnou, *J. Am. Chem. Soc.*, **2010**, *132*, 10692.

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

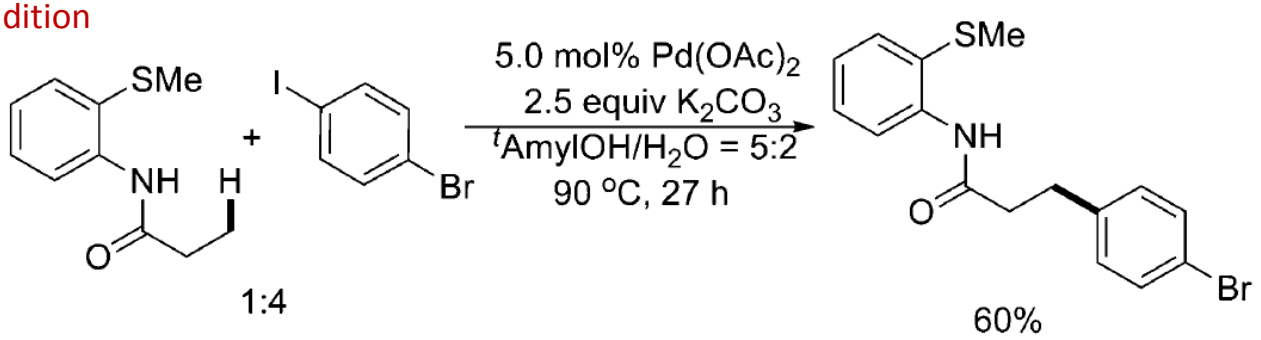
- C-H arylation



O. Daugulis, *J. Am. Chem. Soc.*, **2005**, *127*, 13154.
Also see: E. J. Corey, *Org. Lett.*, **2006**, *8*, 3391.

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

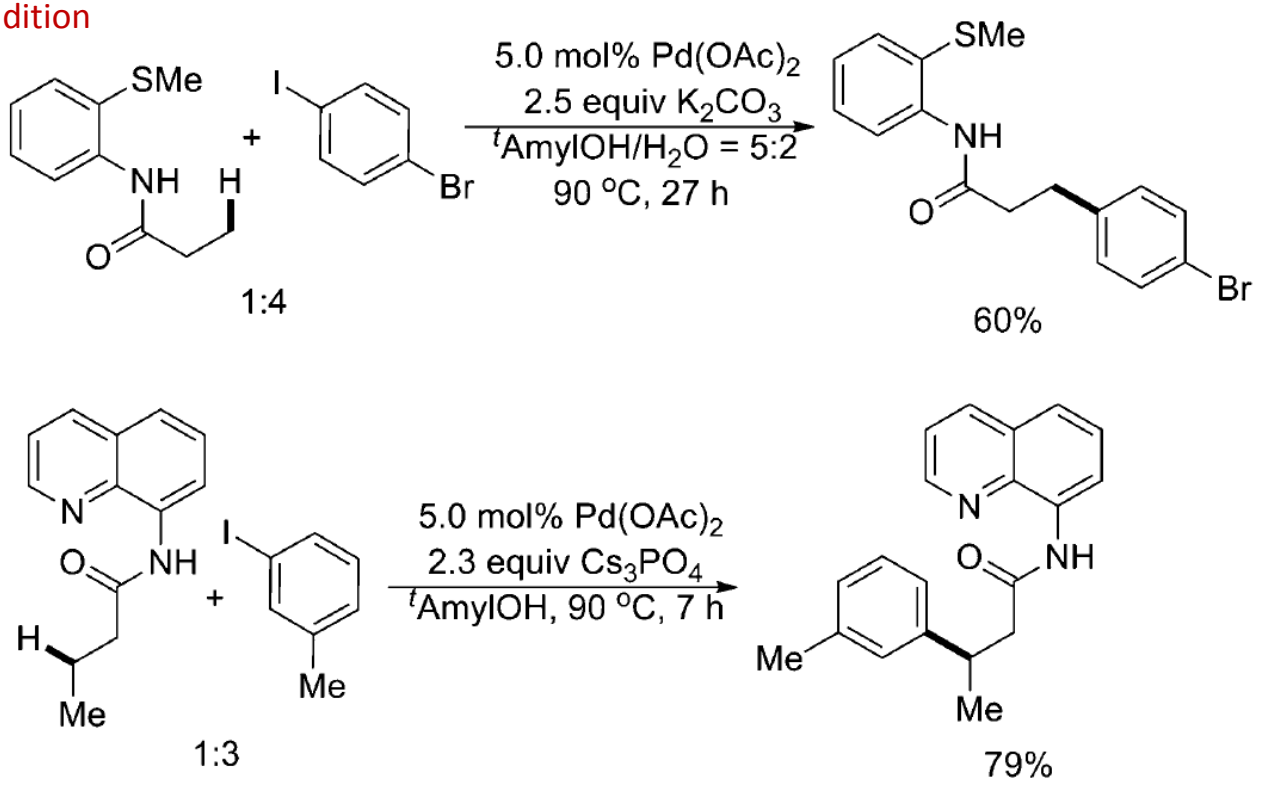
- Silver-free condition



O. Daugulis, J. *Am. Chem. Soc*., **2010**, *132*, 3965.

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

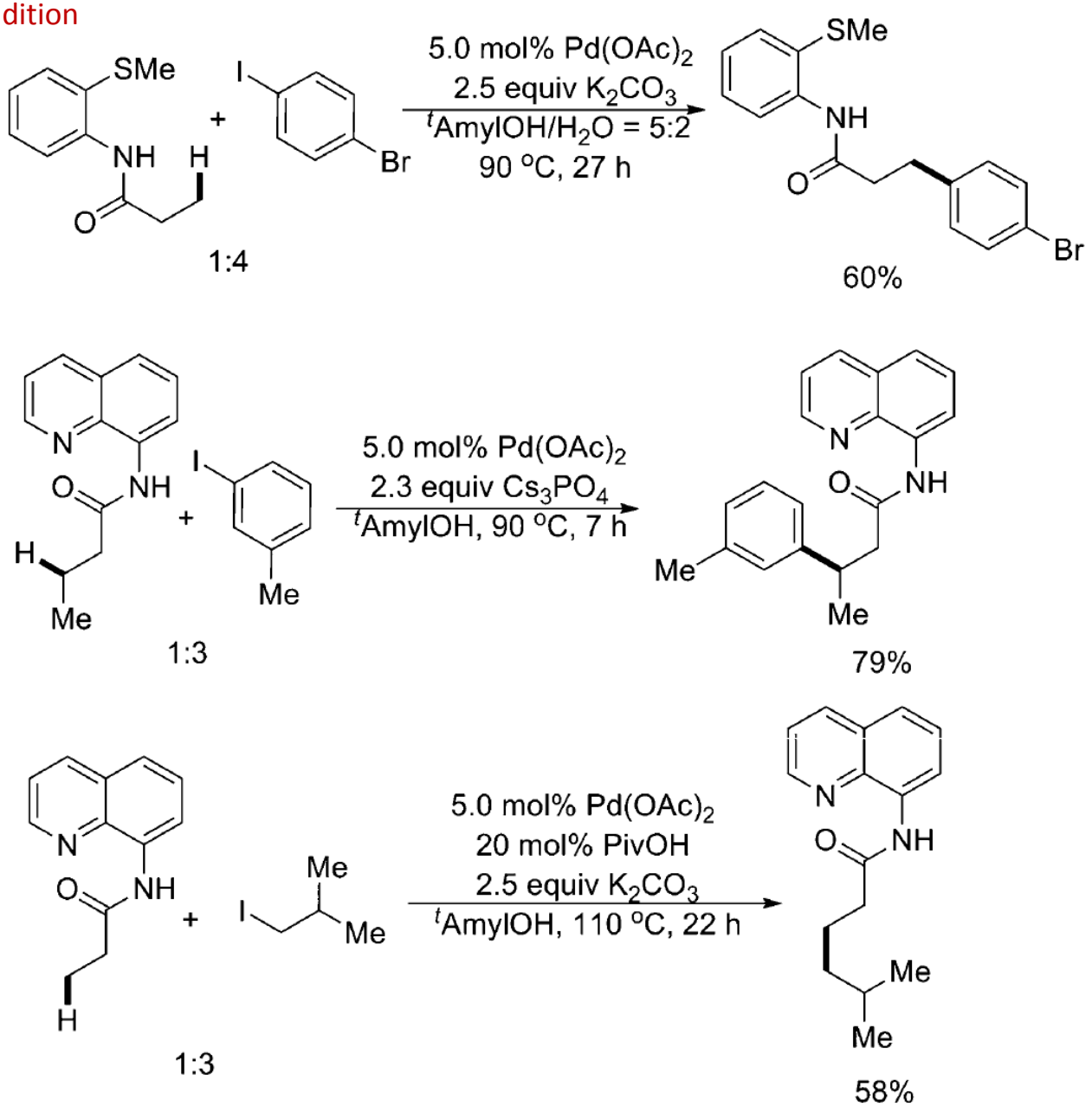
- Silver-free condition



O. Daugulis, J. *Am. Chem. Soc*., **2010**, *132*, 3965.

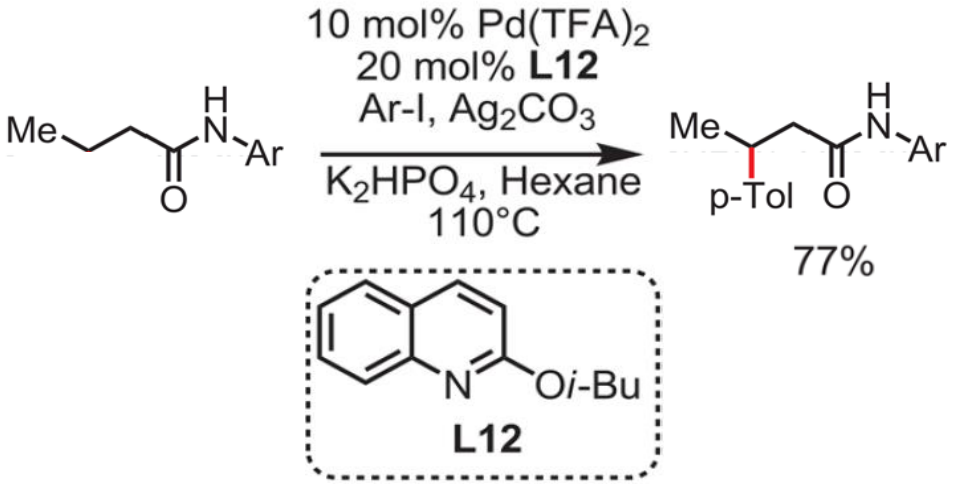
Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

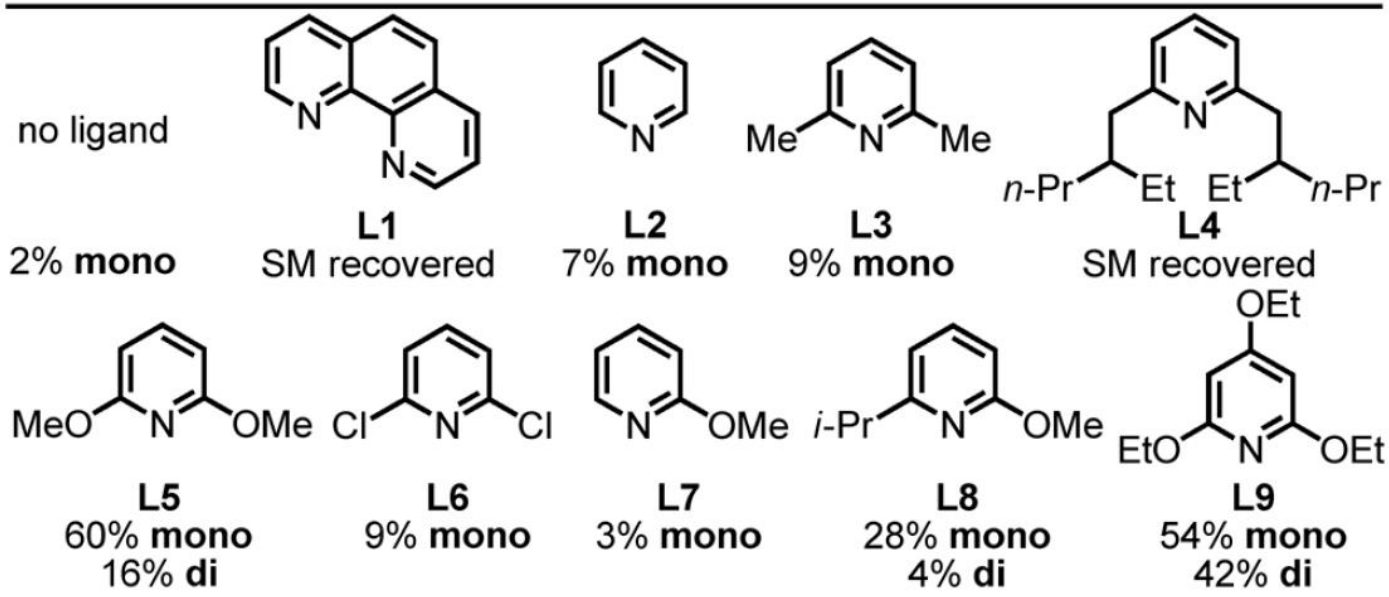
- Silver-free condition



O. Daugulis, J. *Am. Chem. Soc.*, **2010**, *132*, 3965.

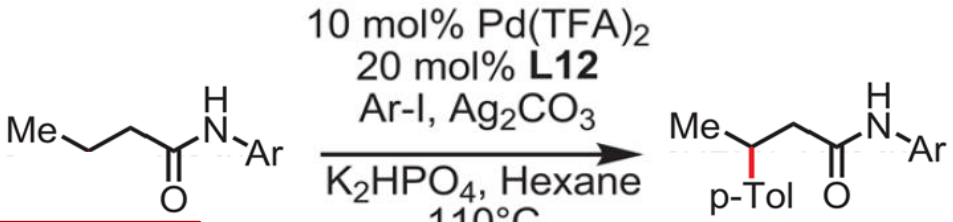
Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



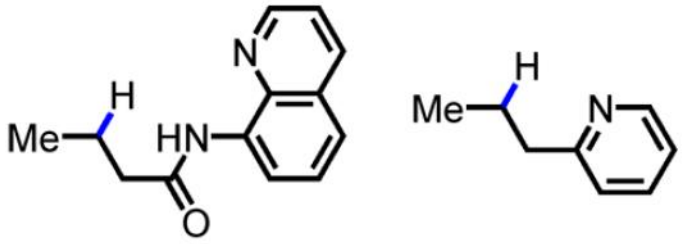


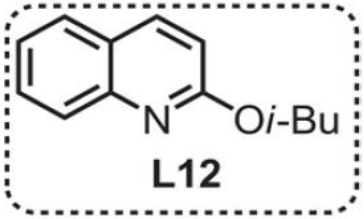
J.-Q. Yu, *J. Am. Chem. Soc*. **2012**, *134*, 18570

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

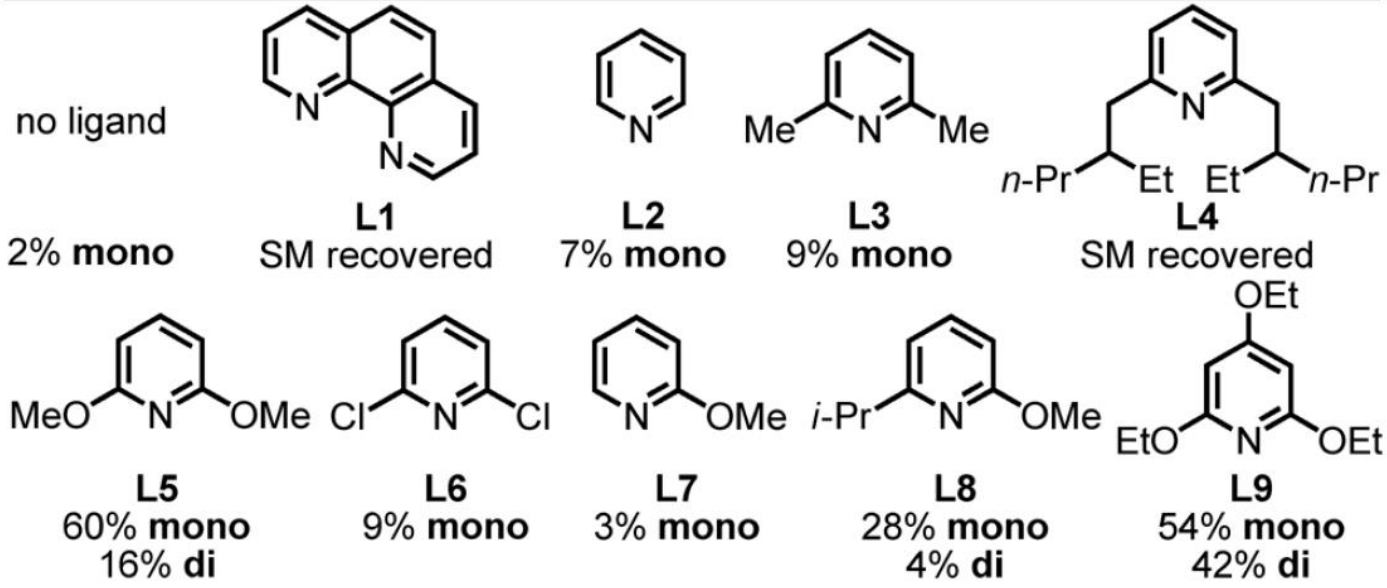


■ Previous achievement



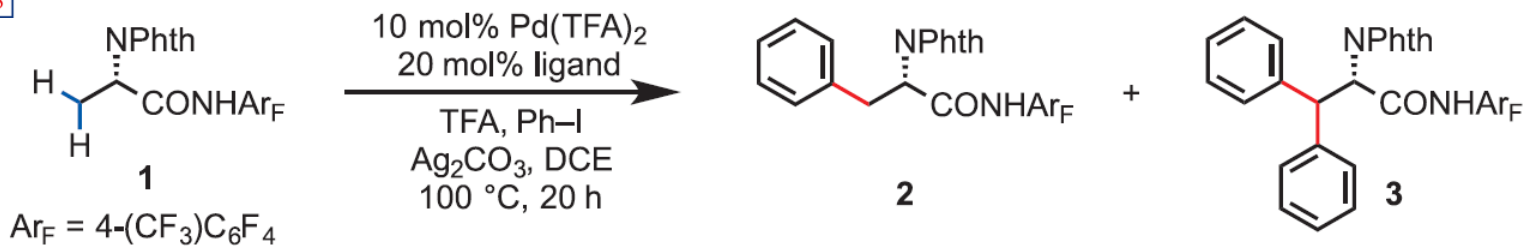


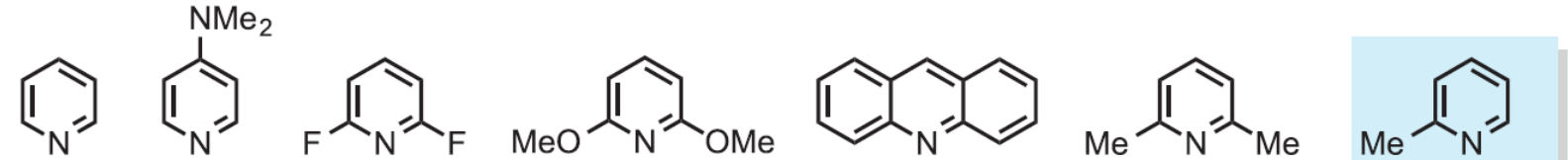
L12



J.-Q. Yu, *J. Am. Chem. Soc*. **2012**, *134*, 18570

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

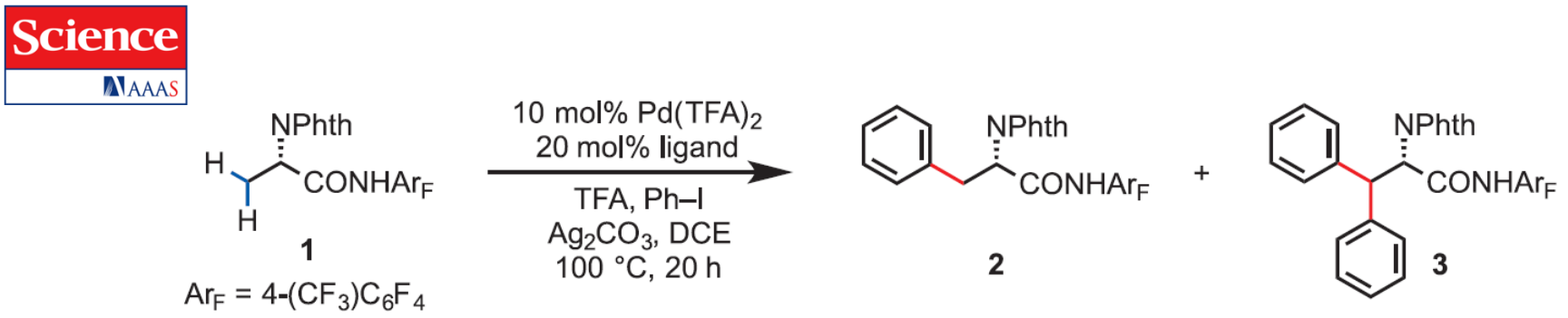


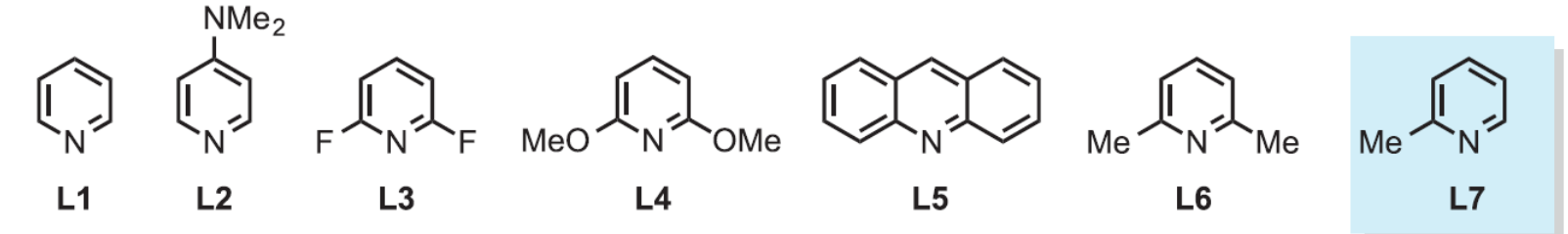


	—	L1	L2	L3	L4	L5	L6	L7
2:	47%	29%	52%	65%	87%	88%	91%	94%
3:	1%	0%	0%	2%	13%	12%	9%	2%

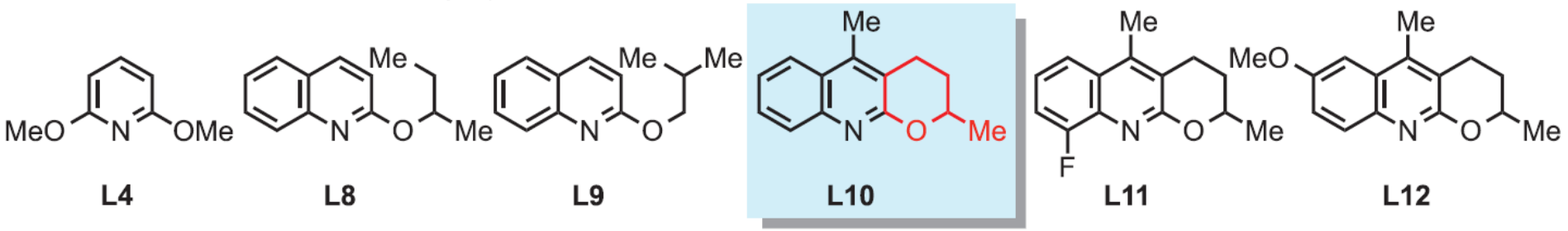
J.-Q. Yu, *Science* **2014**, *343*, 1216

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



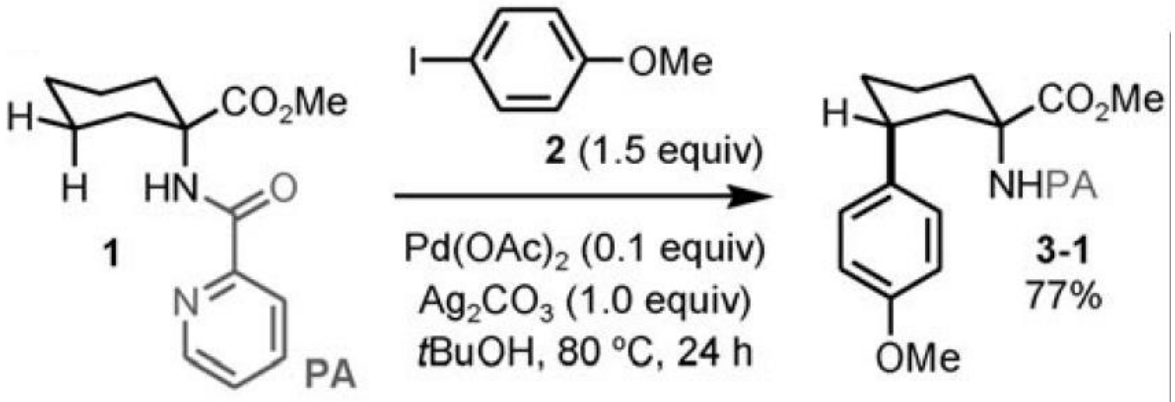


	—	L1	L2	L3	L4	L5	L6	L7
2:	47%	29%	52%	65%	87%	88%	91%	94%
3:	1%	0%	0%	2%	13%	12%	9%	2%



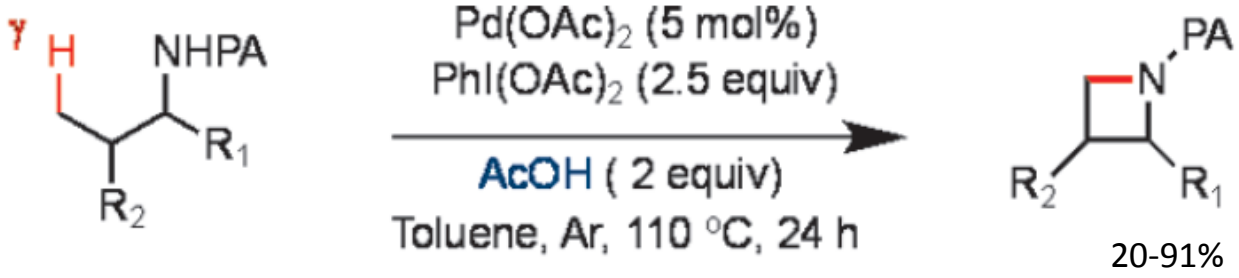
J.-Q. Yu, *Science* **2014**, *343*, 1216

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

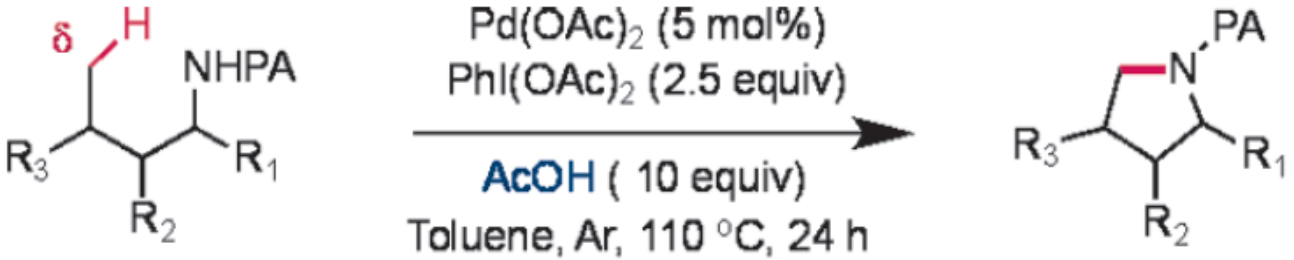


Chen, G. *Angew. Chem. Int. Ed*. **2011**, *50*, 5192.

For the alkylation using alkyl iodide, see : *J. Am. Chem. Soc*. **2013**, *135*, 2124



20-91%

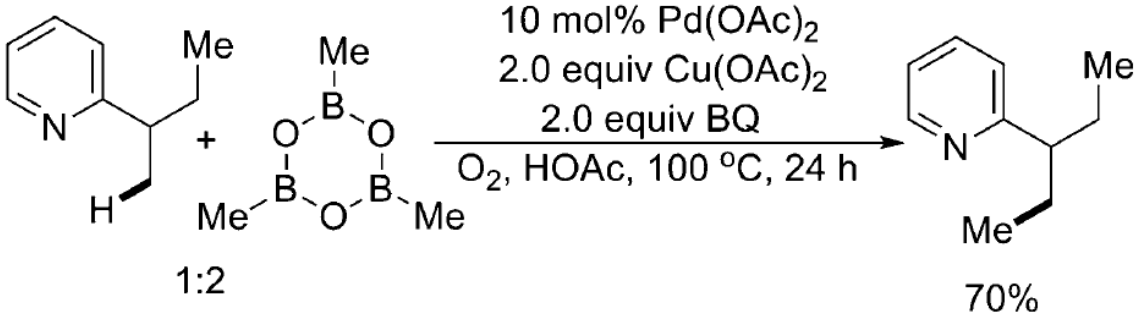


17-82%

Chen, G. *J. Am. Chem. Soc*. **2012** , *134*, 3

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

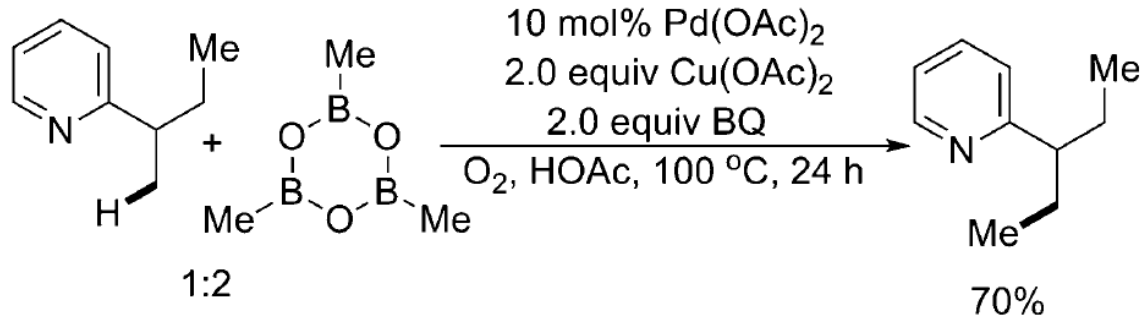
- C-H alkylation

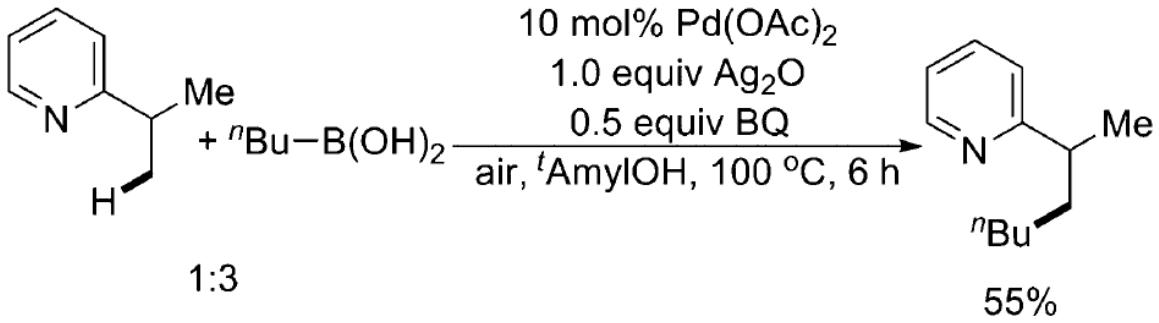


J.-Q. Yu, *J. Am. Chem. Soc.*, **2006**, *128*, 12634.

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

- C-H alkylation

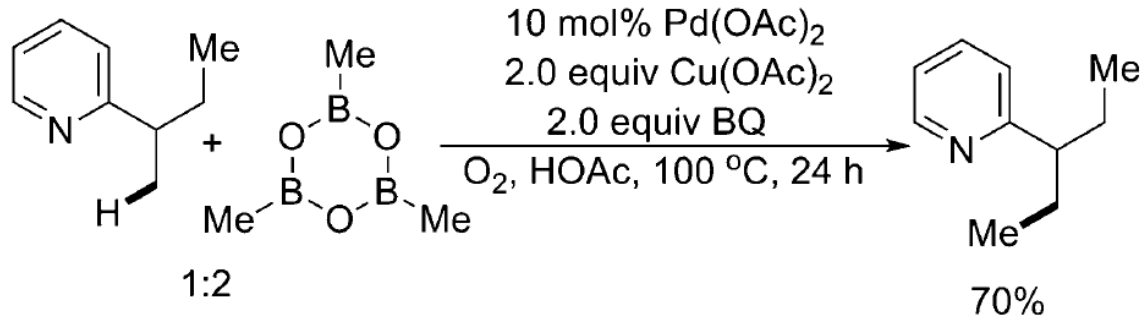


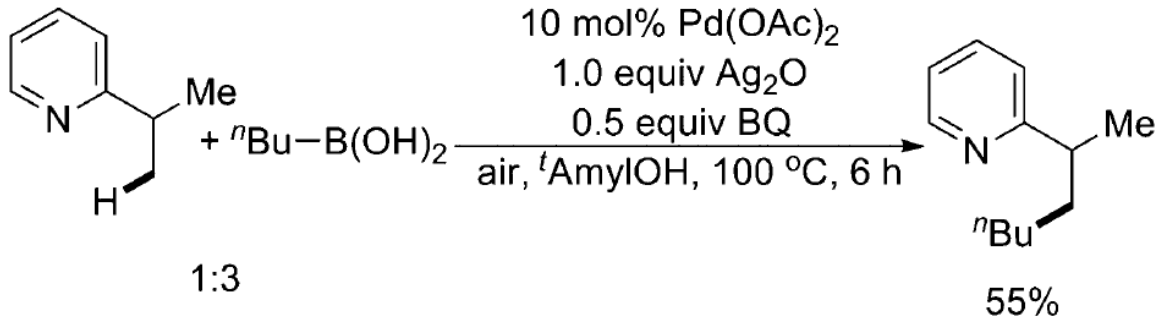


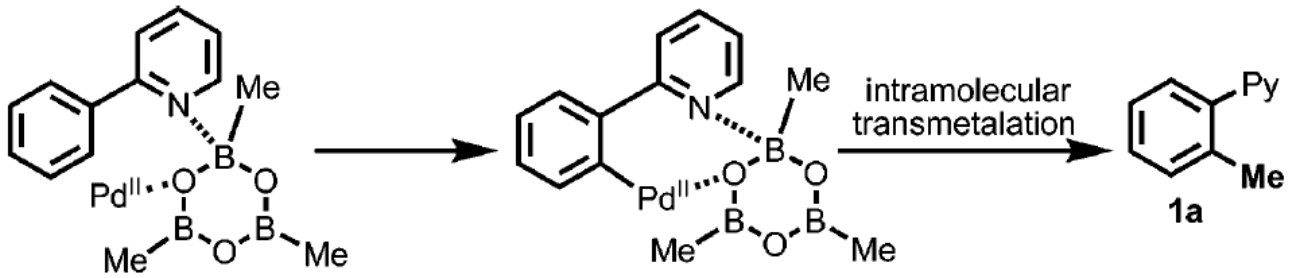
J.-Q. Yu, *J. Am. Chem. Soc.*, **2006**, *128*, 12634.

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage

- C-H alkylation

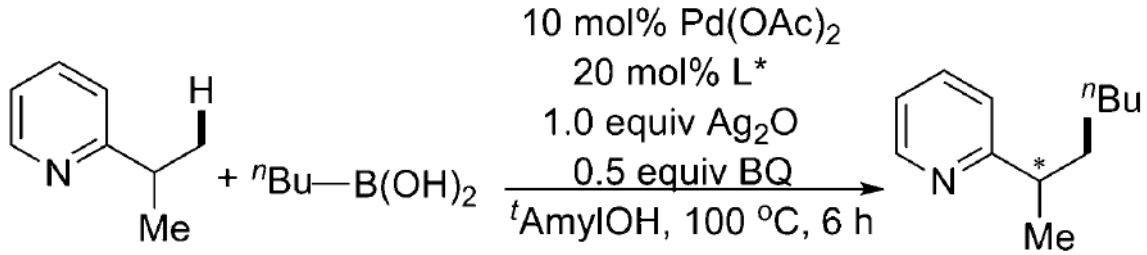






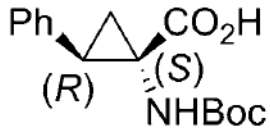
J.-Q. Yu, *J. Am. Chem. Soc.*, **2006**, *128*, 12634.

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***



1:3

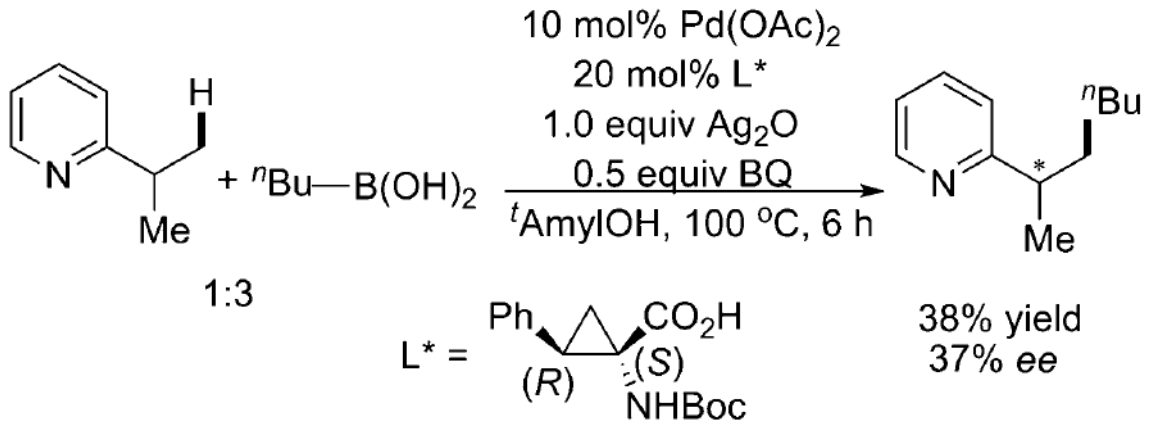
L* =



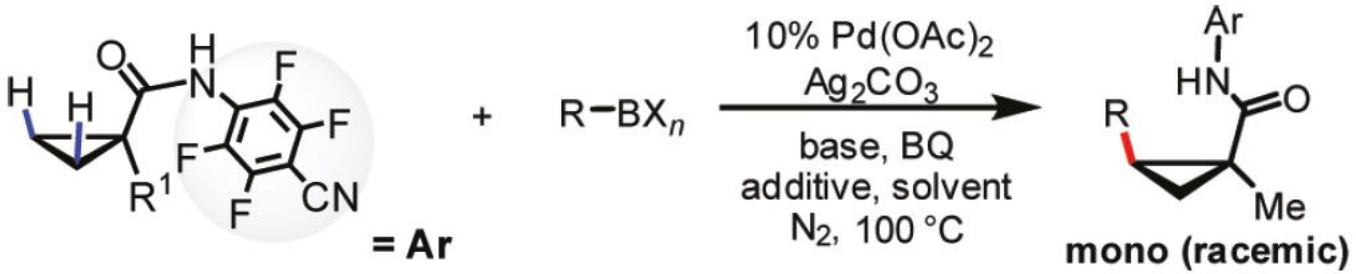
38% yield
37% *ee*

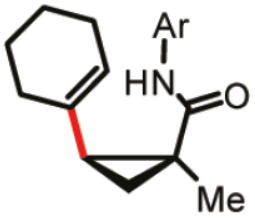
J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4882.

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

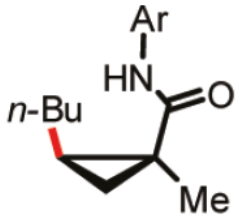


J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4882.





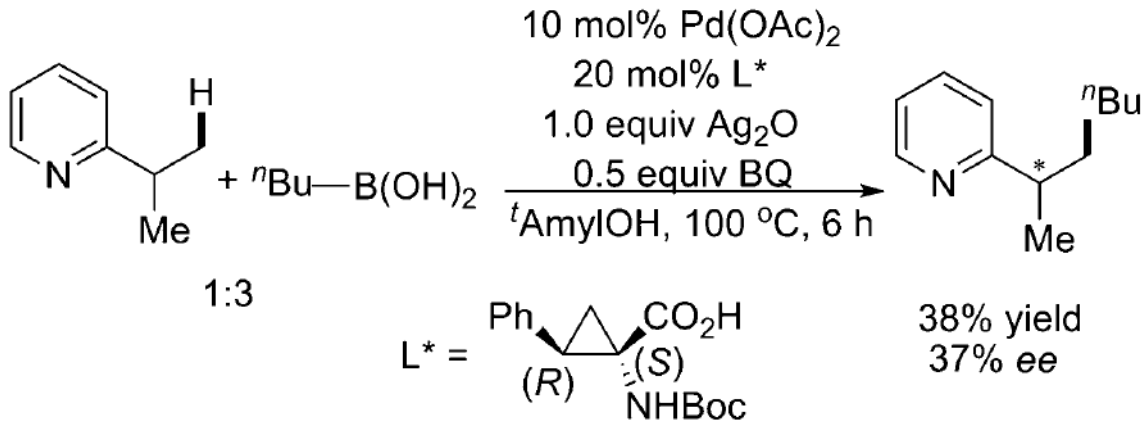
BX_n = BPin, base = $NaHCO_3$(3 eq.), additive = DMSO (0.4 eq)
Yield = 60%



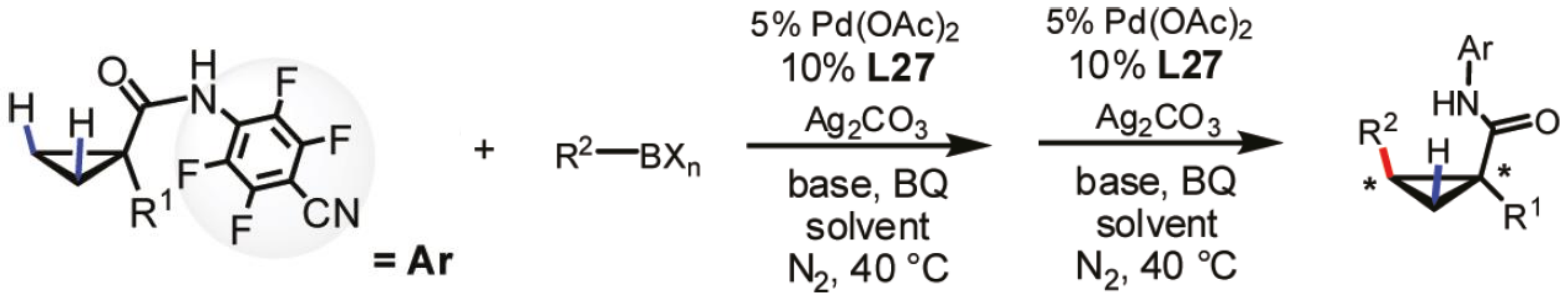
BX_n = BF_3K, base = Li_2CO_3(3 eq.), additive = DMF (0.1 ml)
Yield = 74%

J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 19598

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***

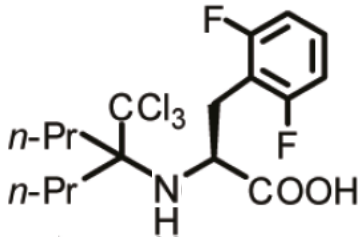


J.-Q. Yu, *Angew. Chem., Int. Ed.*, **2008**, *47*, 4882.



- **R = Aryl**: BX_n = *BPin*, base = $NaHCO_3$, solv = tAmyl-OH
- **R = vinyl**: BX_n = *BPin*, base = $NaHCO_3$, solv = THF
- **R = alkyl**: BX_n = *BF_3K*, base = Li_2CO_3, solv = THF

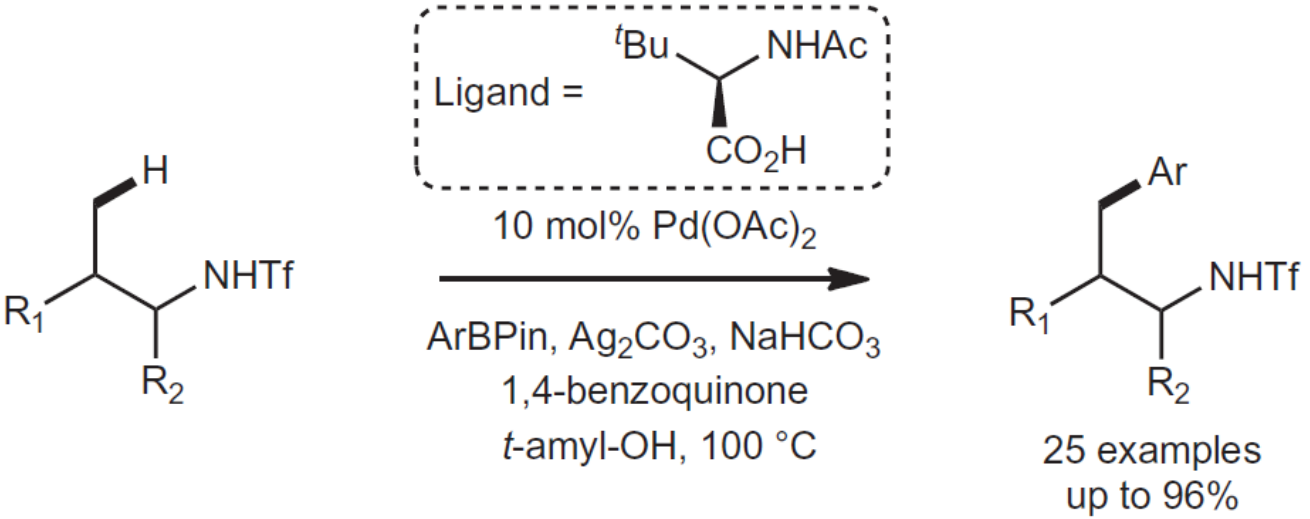
L27 =



R = Ph
81% yield, 91% *ee*
R = 1-cyclohexenyl
60% yield, 82% ee
R = *n*-Bu[d]
49% yield, 62% ee

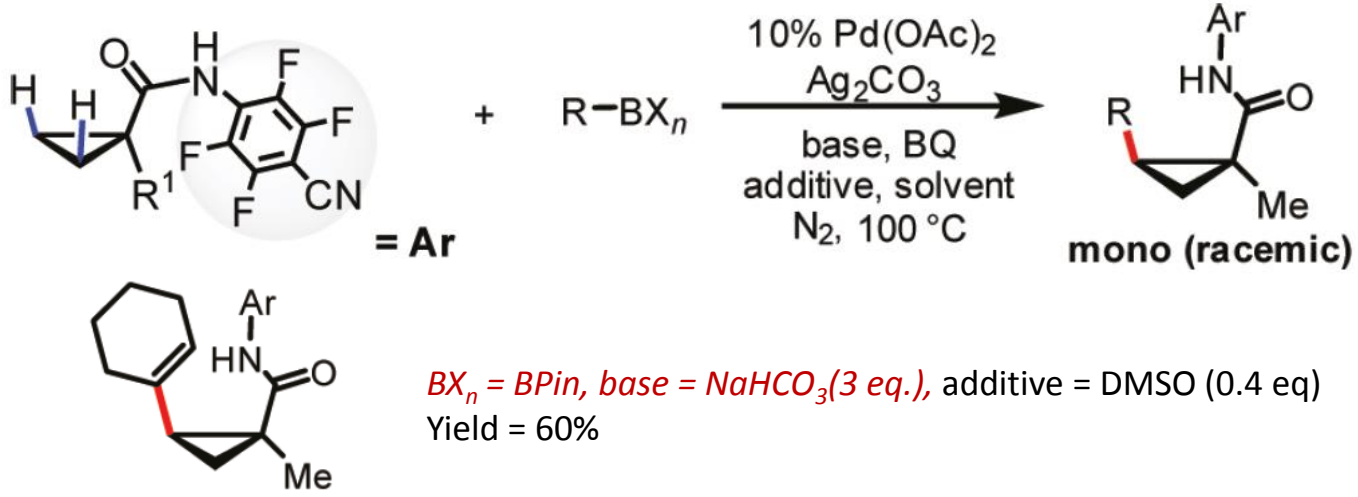
J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 19598

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***



J.-Q. Yu & Blackmond, D. G, *J. Am. Chem. Soc.* **2012**, *134*,
J.-Q. Yu, *Nature Chemistry* **2014**, *6*, 146.

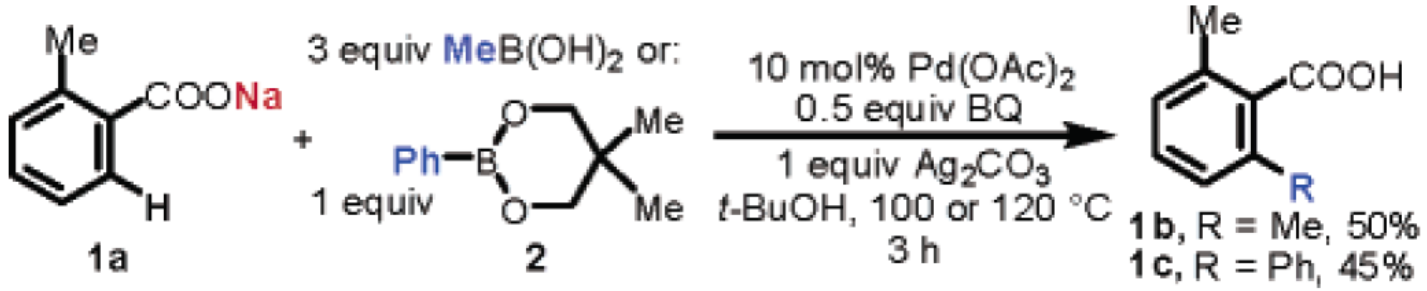
■ Previous work

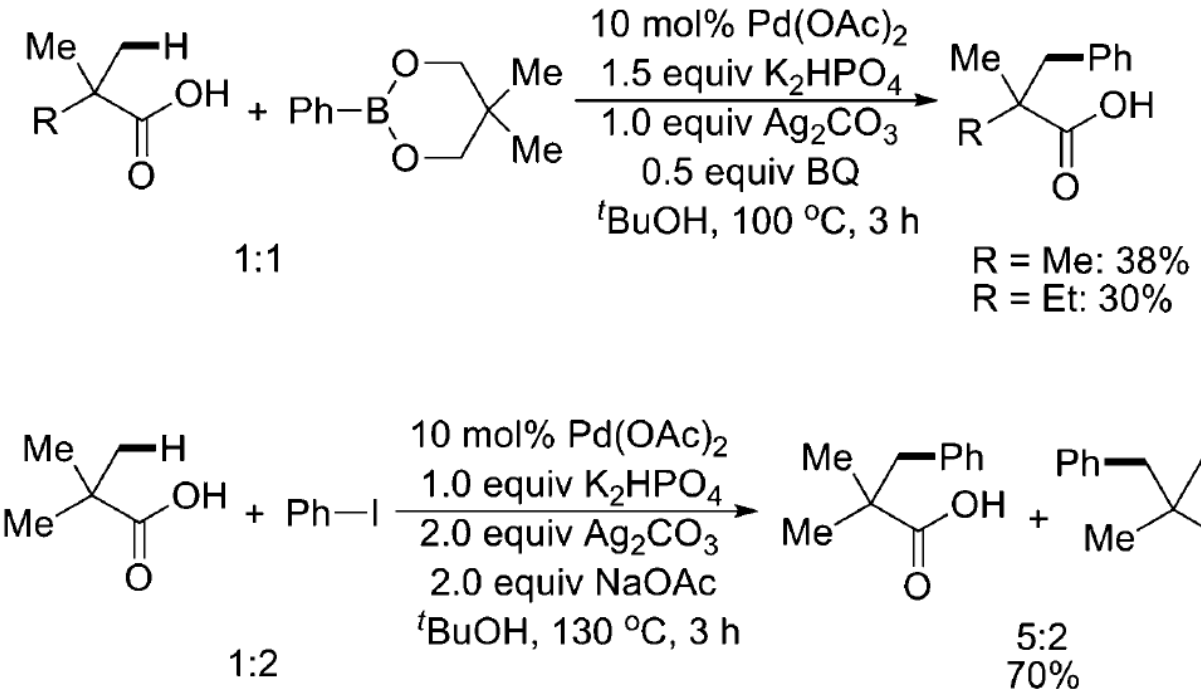


BX_n = BPin, base = $NaHCO_3$(3 eq.), additive = DMSO (0.4 eq)
Yield = 60%

J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 19598

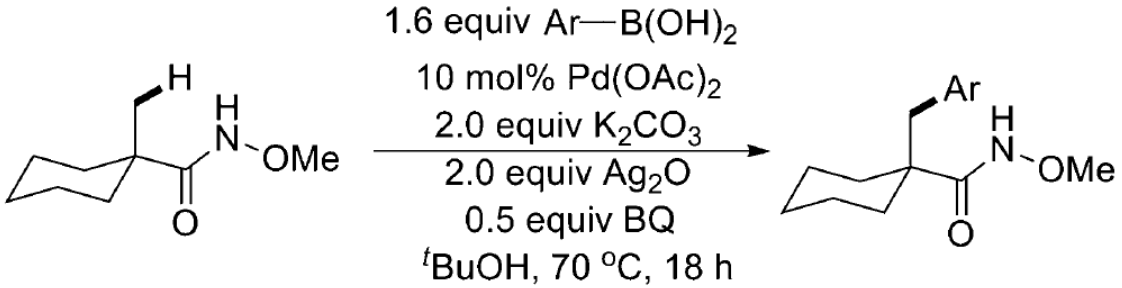
Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



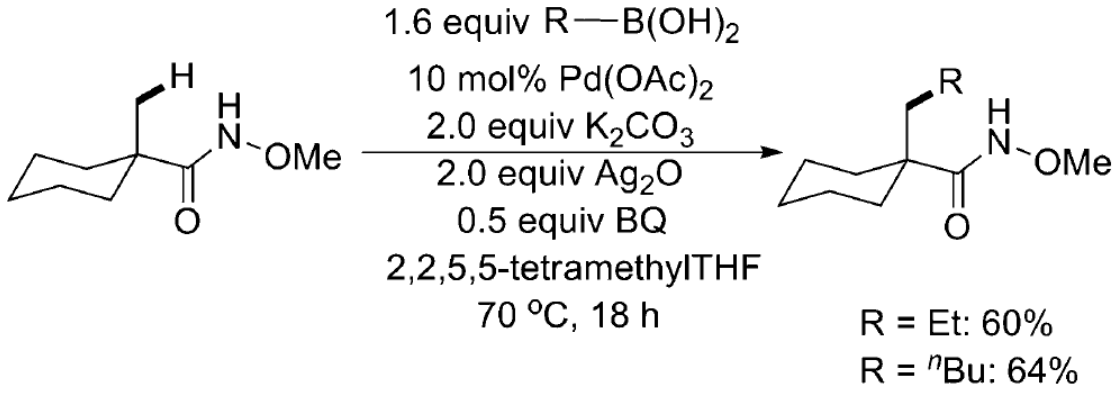


J.-Q. Yu, *J. Am. Chem. Soc.*, **2007**, *129*, 3510

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



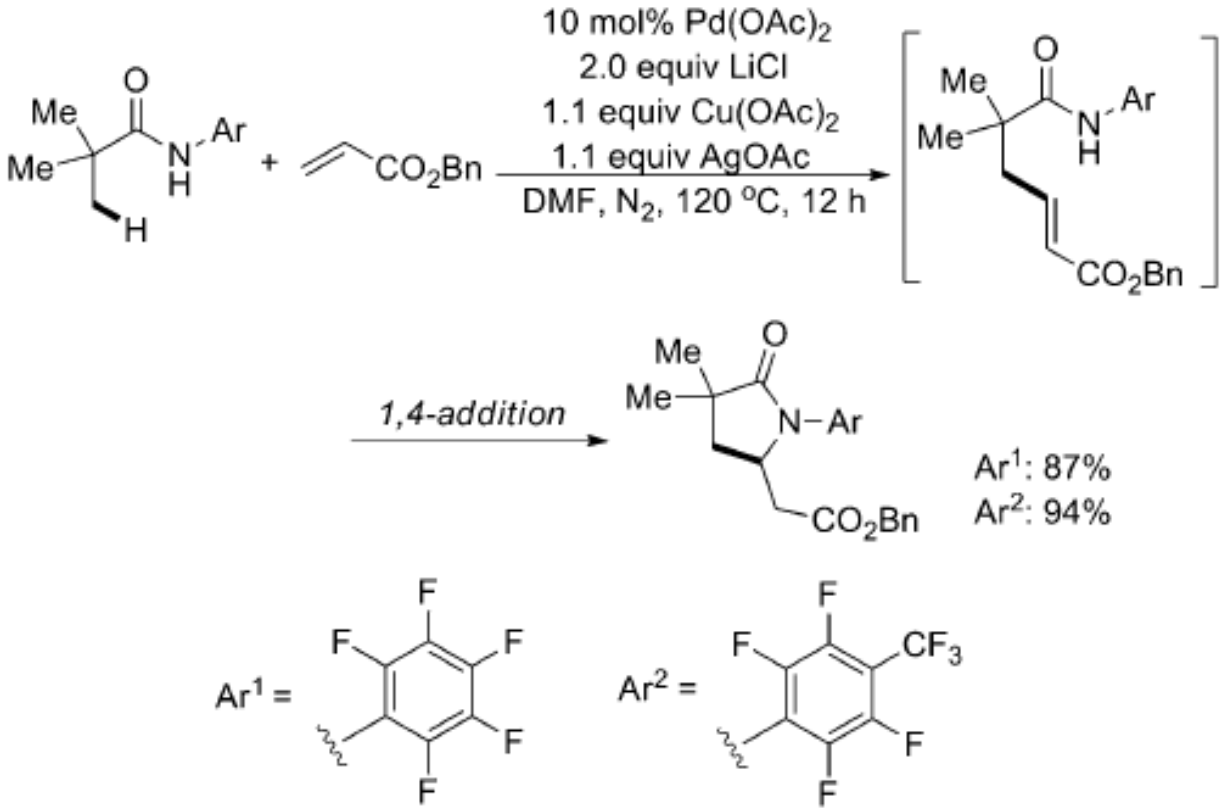
Ar = Ph: 94%
Ar = 4-$CO_2MeC_6H_4$: 62%



R = Et: 60%
R = ^{n}Bu: 64%

J.-Q. Yu, *J. Am. Chem. Soc.*, **2008**, *130*, 7190.

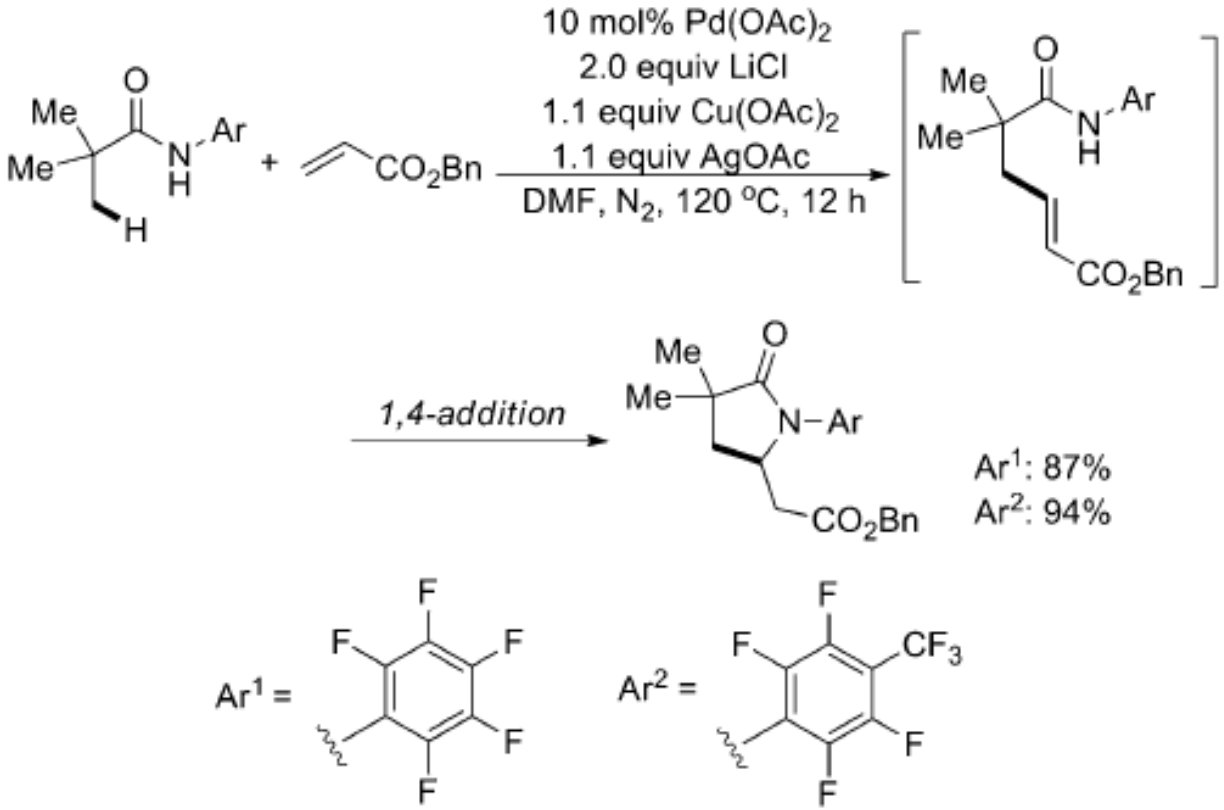
Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***



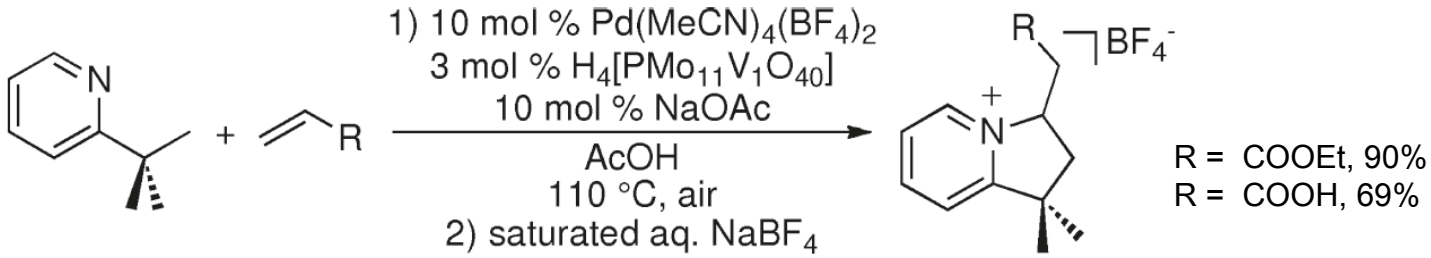
J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 3680.

J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 17378.

Common C–H activation: Direct C–C bond formation ***triggered by C-H cleavage***



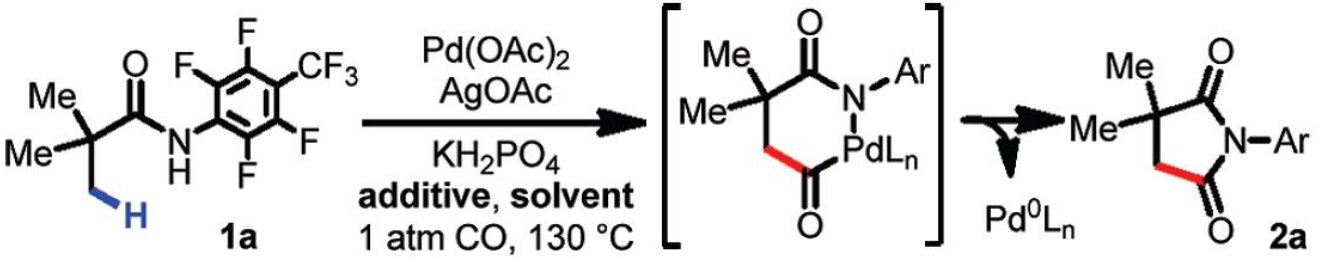
J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 3680.
J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 17378.



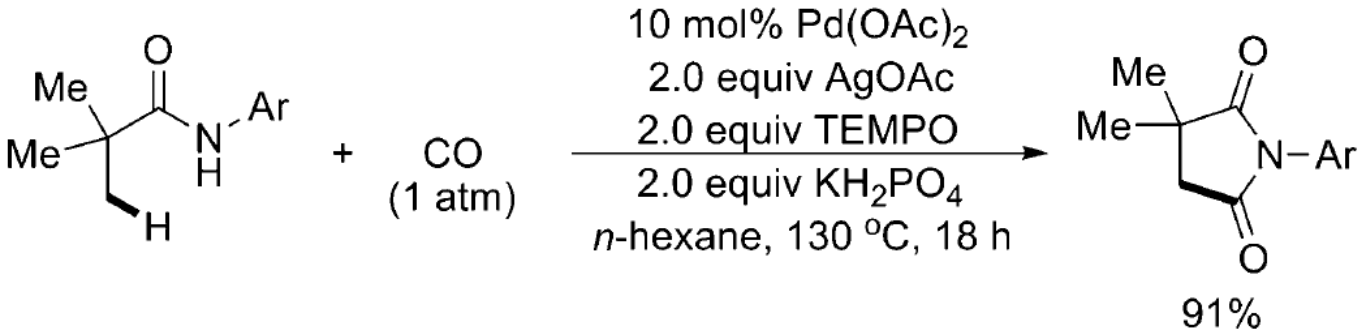
See: *Ishii, Y. Molecules* ***2010****, 15, 1487*
J.-Q. Yu, *Angew. Chem. Int. Ed*. **2013**, *53*, 2683

M. S. Sanford, *J. Am. Chem. Soc*. **2011**, *133*, 6541.

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



entry	additive	solvent	yield (%)[b]	entry	additive	solvent	yield (%)[b]
1	none	DMF	<1	6	$Cu(OAc)_2$	*n*-hexane	4
2	none	toluene	7	7	DMF	*n*-hexane	54
3	none	C_6F_6	8	8	PivOH	*n*-hexane	50
4	none	*n*-hexane	30	9	TEMPO[c]	*n*-hexane	80
5	BQ	*n*-hexane	13	10	TEMPO	*n*-hexane	95



J.-Q. Yu, *J. Am. Chem. Soc.*, **2010**, *132*, 17378.

Content

Palladium-catalyzed sp^3 C–H activation

Content

Palladium-catalyzed sp^3 C–H activation

Summary

via several pathways to construct synthetically useful C–C/C–X bonds.

allylic sp3 C–H bonds:
pre-coordination of the Pd faciltate the activation

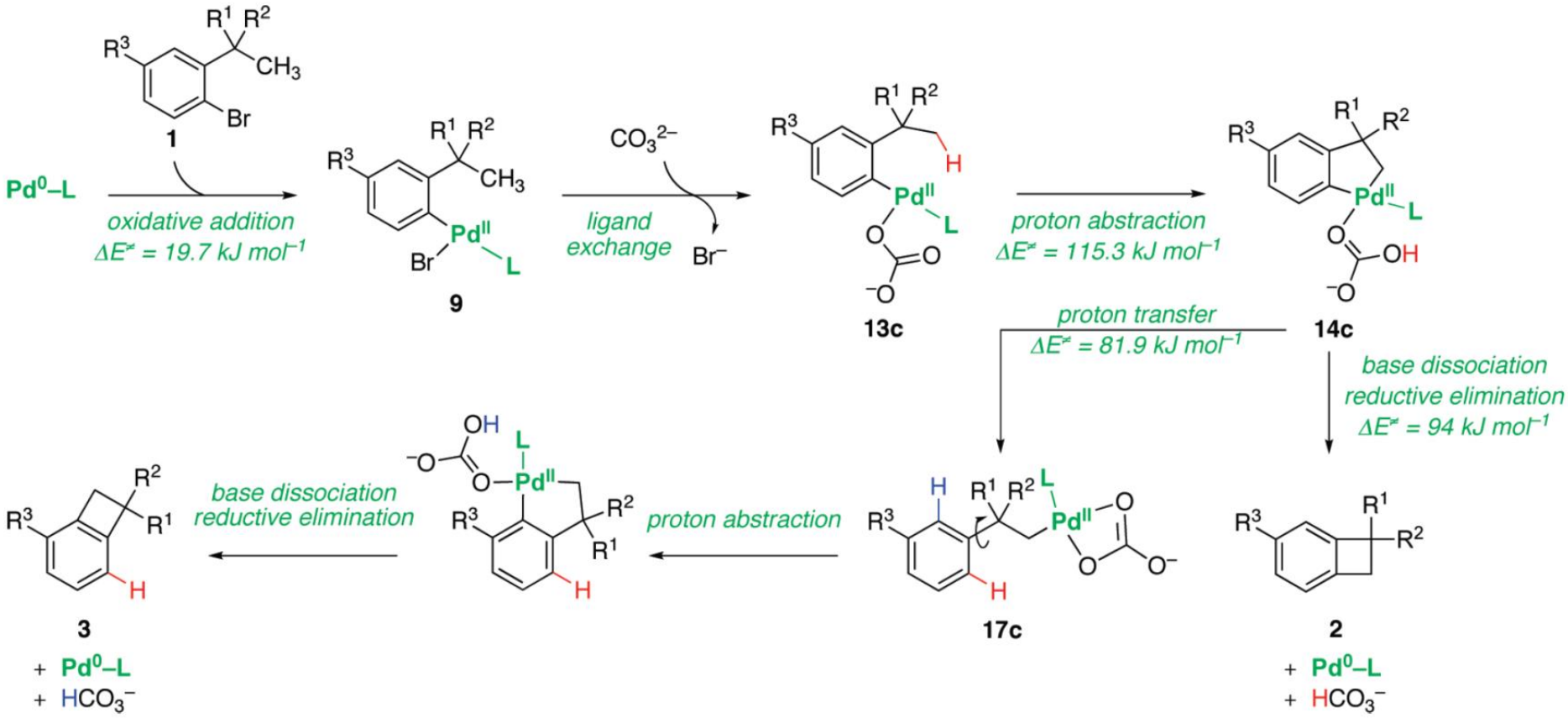
non-allylic sp3 C–H bonds:
Pd(II)/Pd(0) and Pd(II)/Pd(IV), *heteroatom DG* play crucial roles

tremendous challenge ahead

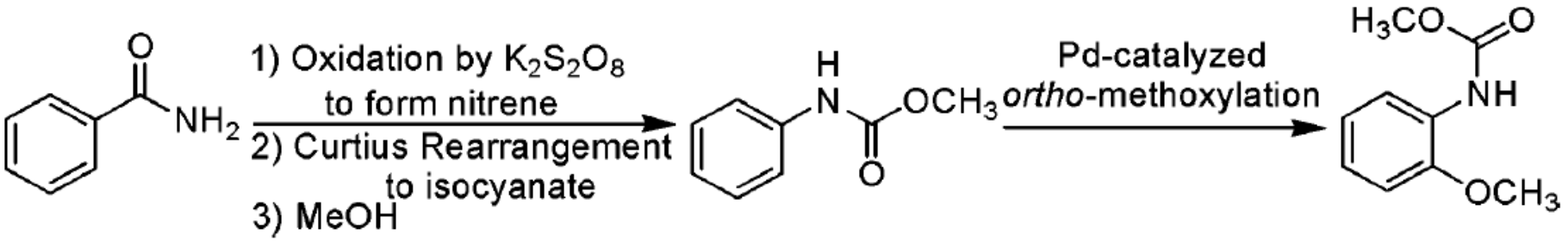
- *lower catalyst loadings*
- *milder conditions*
- *site-selectivity / broader C-H bonds scope*
- *useful enantioselectivity*

Thank You !

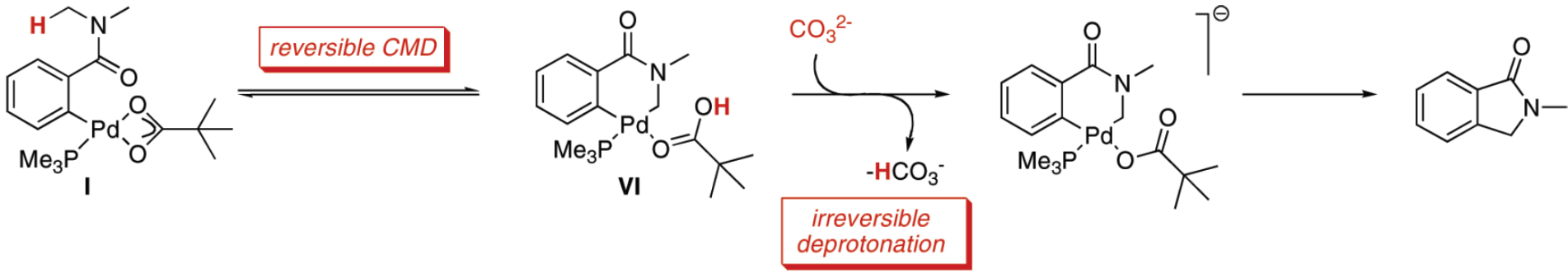
1)


1
Pd0–L
oxidative addition
ΔE≠ = 19.7 kJ mol–1
9
CO32–
ligand exchange
Br–
13c
proton abstraction
ΔE≠ = 115.3 kJ mol–1
14c
proton transfer
ΔE≠ = 81.9 kJ mol–1
base dissociation
reductive elimination
ΔE≠ = 94 kJ mol–1
2
+ Pd0–L
+ HCO3–
17c
proton abstraction
base dissociation
reductive elimination
3
+ Pd0–L
+ HCO3–

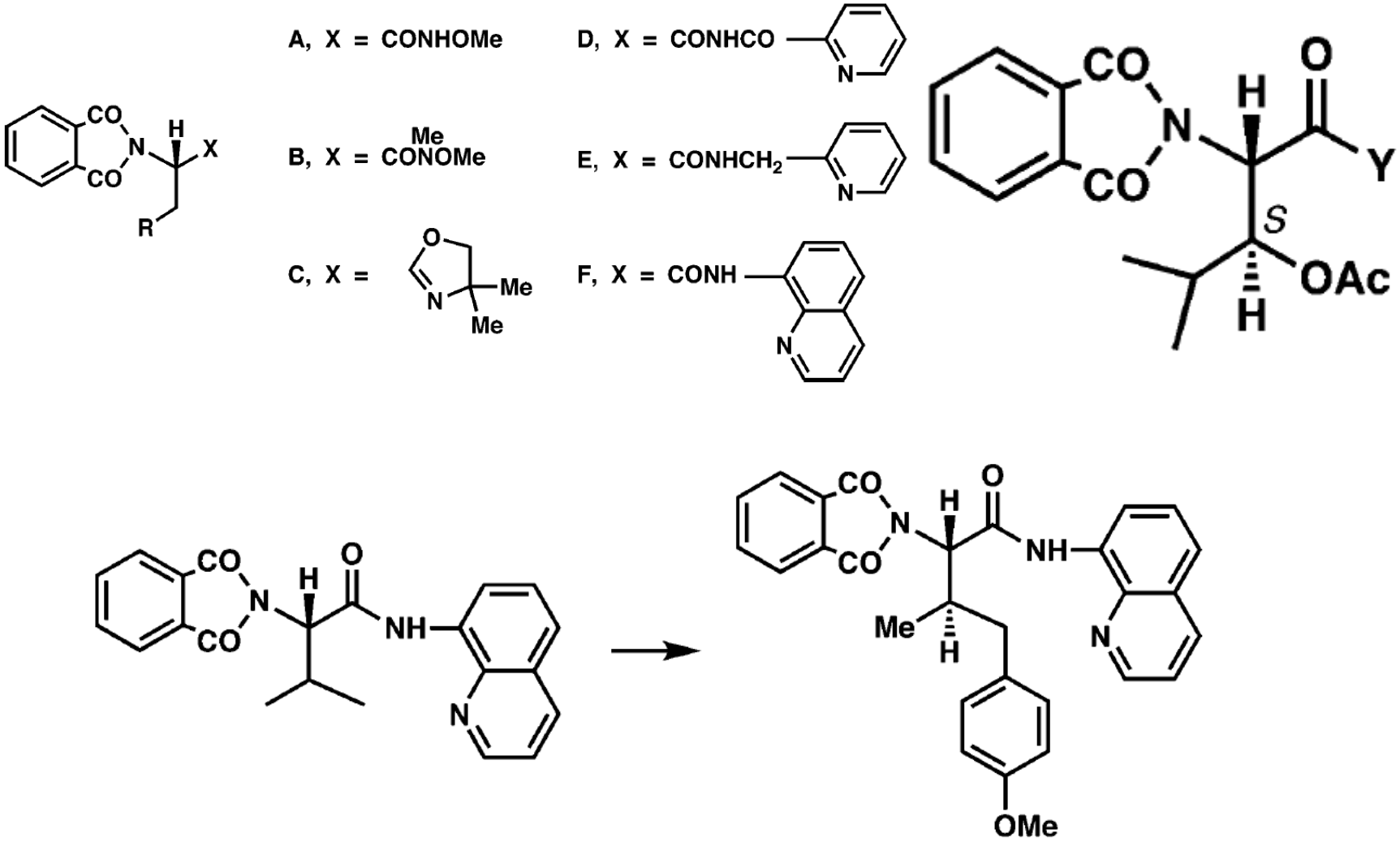
2)


1) Oxidation by $K_2S_2O_8$
to form nitrene
2) Curtius Rearrangement
to isocyanate
3) MeOH
Pd-catalyzed
ortho-methoxylation

3)


reversible CMD
I
VI
CO_3^{2-}
$-HCO_3^-$
irreversible
deprotonation

Common C–H activation: Direct C–C bond formation triggered by C-H cleavage



E. J. Corey, *Org. Lett.*, **2006**, *8*, 3391.