A brief review

Jin-quan Yu

Academic Career:

July 2007 to Present - The Scripps Research Institute
Full Professor since Aug 2010

Mar 2004 to Jun 2007 - Brandeis University
Assistant Professor

Oct 2003 to Feb 2004 - University of Cambridge
Royal Society Research Fellow

Oct 1990 to Sep 1994 - Guangzhou Institute of Chemistry
TA and RA

---Zhi Ren
2012-8-29

Jin-quan Yu

Education:

Harvard University - Cambridge, MA, USA
- Postdoctoral Fellow
  Supervisor: E. J. Corey **(3 papers)**
  February 2001 to May 2002

University of Cambridge - Cambridge, UK
- Junior Research Fellow (JRF) of St. John's College
  October 1999 to October 2003

University of Cambridge - Cambridge, UK
- Ph.D. in Chemistry
  Supervisor: Jonathan B. Spencer **(21 papers)**
  October 1994 to September 1999

Guangzhou Institute of Chemistry - Guangzhou, China
- M.Sc. in Chemistry
  Supervisor: S.-D. Xiao **(2 papers)**
  September 1988 to July 1990

Shanghai Institute of Organic Chemistry - Shanghai, China
- Coursework for M.Sc. degree
  September 1987 to July 1988

East China Normal University - Shanghai, China
- B.Sc. in Chemistry
  Top 5% on national examination for admission to SIOC
  September 1982 to July 1987

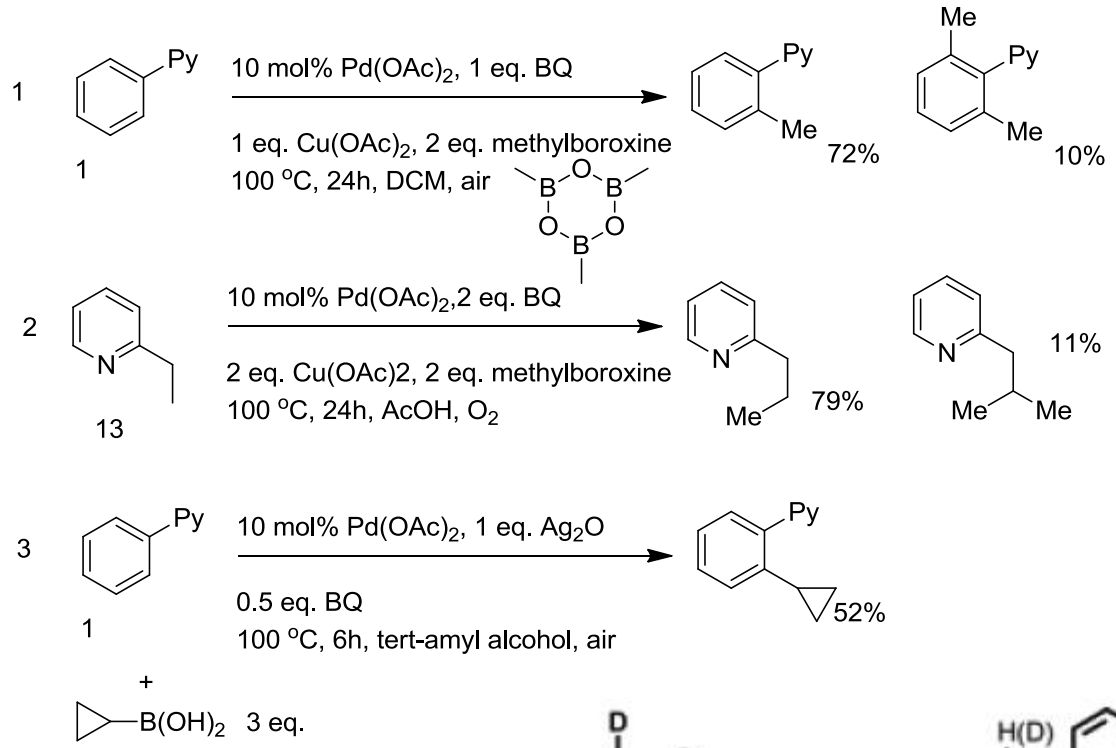
Outline

- 1. C-C bond formation
- 2. C-N bond formation
- 3. C-O bond formation
- 4. C-Halide bond formation
- 5. Other

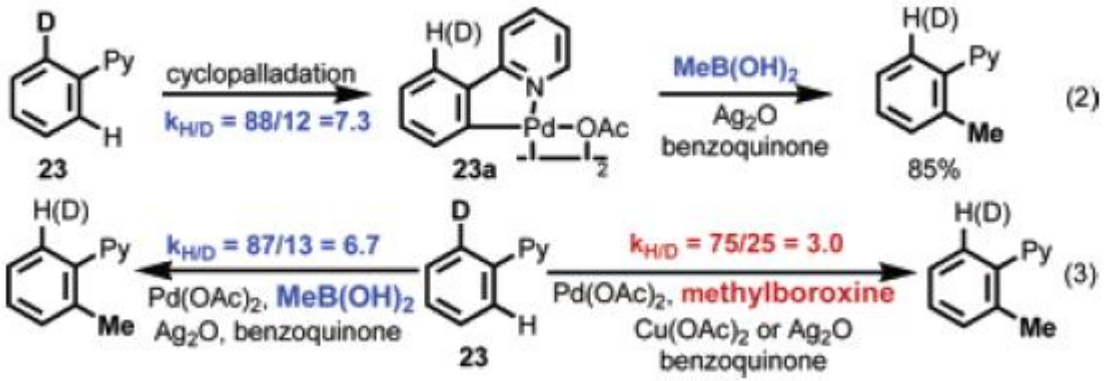
1.C-C bond formation

- 1-1. Pyridine as Directing Group=DG (2006-10, 1 pub.)
- 1-2. Oxazoline as DG (2006, 1 pub.)
- 1-3. Carboxylic acid as DG (2007-08, 2010-11, 3+2 pub.)
- 1-4. CONHX as DG (2008-11, 7 pub.)
- 1-5. No DG (2009-10, 3 pub.)
- 1-6. NHCOX as DG (2010, 1 pub.)
- 1-7. Remote DG (2012, 1 pub.)

1-1 Pyridine as DG



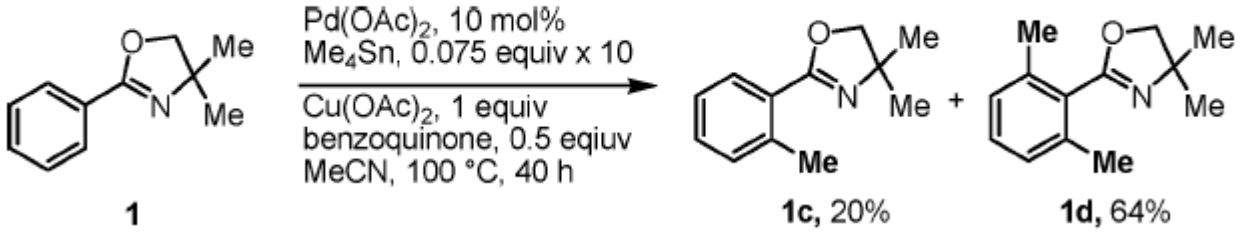
23 examples in total



J. AM. CHEM. SOC. 2006, *128*, 12634−12635 10.1021/ja0646747

1-2 Oxazoline as DG

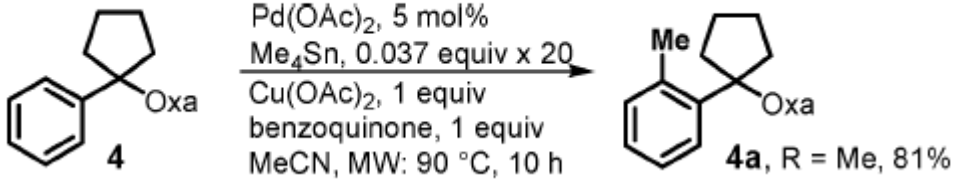
Scheme 2. Catalytic Methylation of Aryl C−H Bonds



1 **1c,** 20% **1d,** 64%

Every 3h per batch
19 examples

Scheme 5. Methylation Assisted by Microwave Irradiation



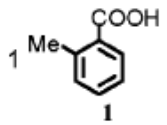
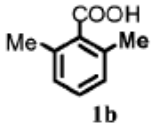
4 **4a**, R = Me, 81%

Every 0.5h per batch

J. AM. CHEM. SOC. 2006, *128*, 78−79 **10.1021/ja0570943**

1-3 Carboxylic acid as DG

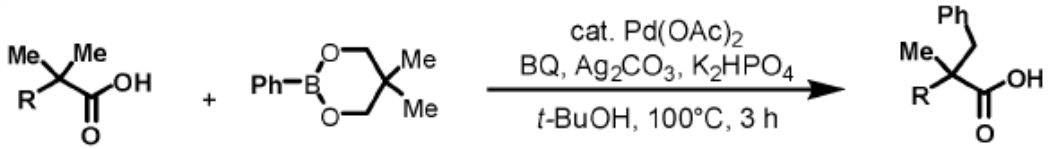
Ortho Methylation and Arylation of Benzoic Acids[a]

entry	substrate	product	yield(%)
1			75[b]
	1	1b	

6 examples

[a] Conditions: 10 mol % $Pd(OAc)_2$, 0.5 equiv of benzoquinone, 1 equiv of Ag_2CO_3, 1.5 equiv of K_2HPO_4, 2 equiv of $MeB(OH)_2$ or 1 equiv of **2**, *tert*-BuOH, 120 °C, 3 h.

β-Arylation of Aliphatic Acids Using Ph−B(OR)$_2$[a]

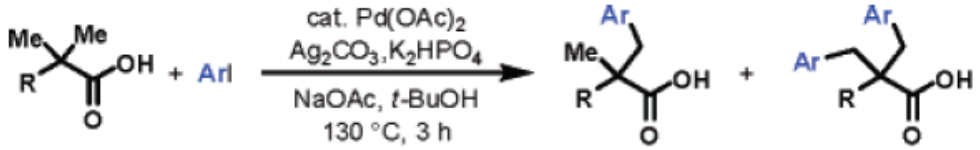


6 R = Me

6 examples

[a] Conditions: 10 mol % $Pd(OAc)_2$, 1 equiv of **2**, 0.5 equiv of benzoquinone, 1 equiv of Ag_2CO_3 and 1.5 equiv of K_2HPO_4. [b] Yields of their methyl esters. Less than 2% diarylated products were observed in **6**−**10**.

β-Arylation of Aliphatic Acids Using ArI[a]



7a **7b**

8 examples

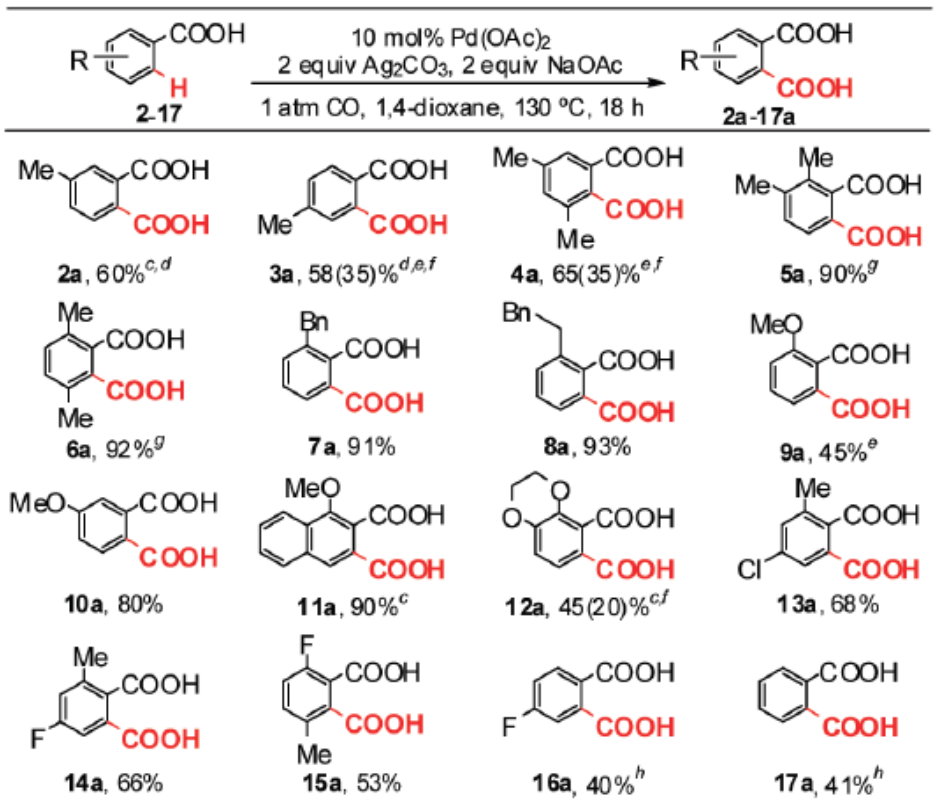
entry	product	yield
2	R = Et, Ar = Ph **7a**/**7b**, 4:1	72

[a] Conditions: 10 mol % $Pd(OAc)_2$, 2 equiv of aryl iodide, 2 equiv of Ag_2CO_3, 1 equiv of K_2HPO_4, and 2 equiv of NaOAc.

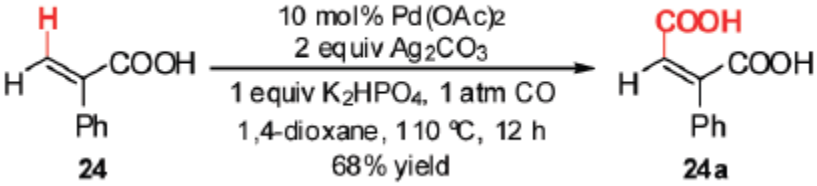
J. AM. CHEM. SOC. 2007, *129*, 3510−3511
10.1021/ja0701614

1-3 Carboxylic acid as DG

Table 2. Carboxylation of Benzoic Acid and Its Derivatives[a,b]



[a] Run using 10 mol % $Pd(OAc)_2$, 2 equiv of Ag_2CO_3, 2 equiv of NaOAc, 1 atm of CO, dioxane, 130 °C, 18 h. [b] Isolated yields. [c] Run in 30 h. [d] **2a** and **3a** are the same products obtained from ortho and para toluic acids **2** and **3**, respectively. [e] Run at 150 °C, 30 h. [f] NaOAc was replaced with K_2HPO_4. NMR yields in presence of NaOAc are given in parenthesis. [g] Run with 1 equiv of K_2HPO_4 added. [h] Run at 150 °C, 48 h.



EDG>EWG

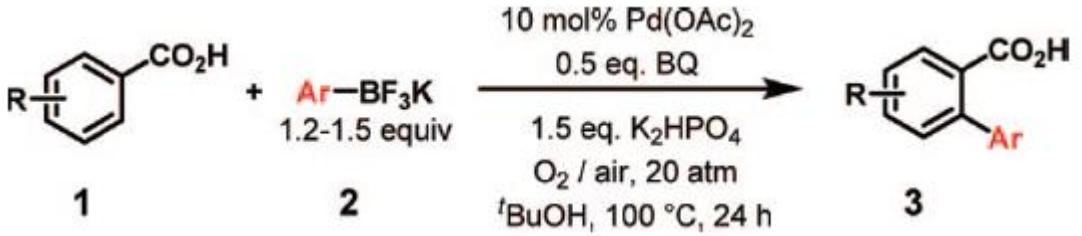
Electrophilic palladation pathway

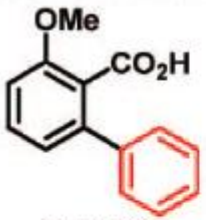
9 more examples

J. AM. CHEM. SOC. 2008, *130*, 14082–14083

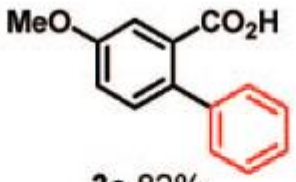
10.1021/ja8063827

1-3 Carboxylic acid as DG

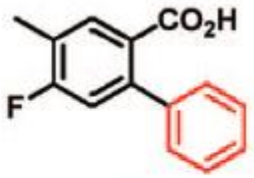




3d 45%



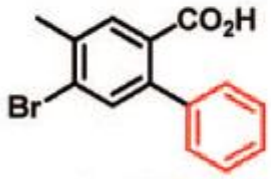
3e 82%
58% (1 atm O_2, 72 h)



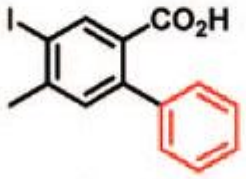
3f 91%

Excellent regioselectivity

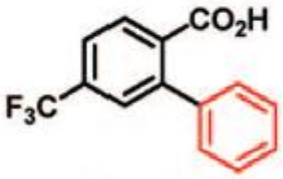
27 more examples



3g 85%



3h 36%



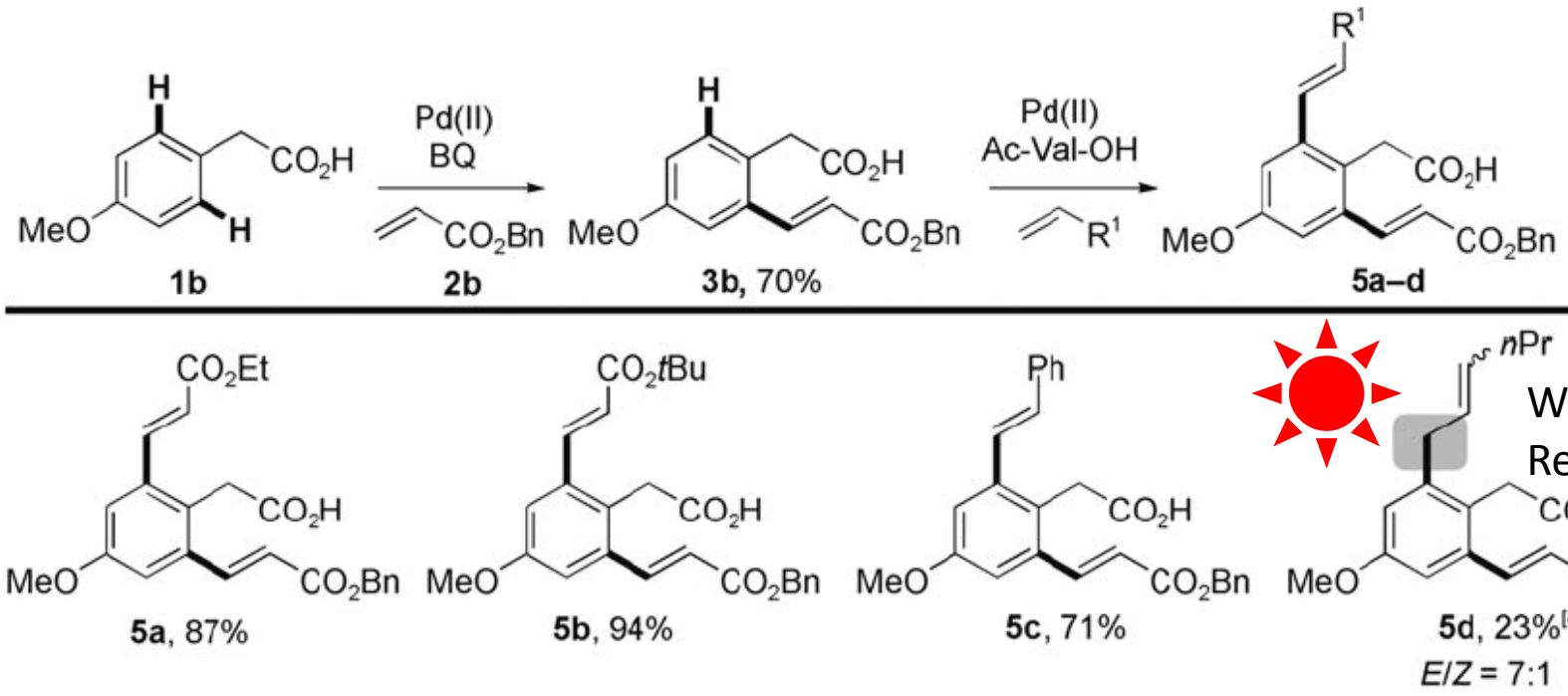
3i 83%

the presence of Ag^+ oxidant results in a complete loss of the reactivity.

J. AM. CHEM. SOC. 2008, *130*, 17676–17677

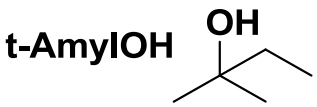
10.1021/ja806681z

1-3 Carboxylic acid as DG



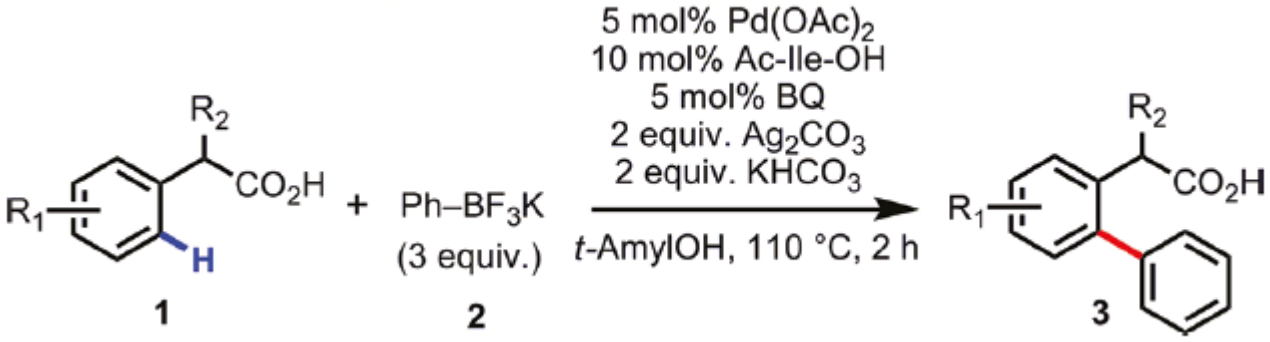
Why?
Related to Q3

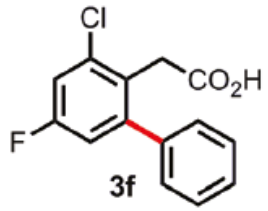
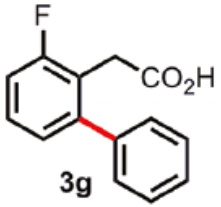
Scheme 6. Sequential olefination. Reaction conditions (1st step): **2b** (2 equiv), $Pd(OAc)_2$ (5 mol%), BQ (5 mol%), $KHCO_3$ (2 equiv), *t*AmylOH, 90°C, 1 atm O_2, 48 h. Reaction conditions (2nd step): olefin (2 equiv), $Pd(OAc)_2$ (5 mol%), Ac-Val-OH (10 mol%), $KHCO_3$ (2 equiv), *t*AmylOH, 90°C, 1 atm O_2, 6 h. Reported yields are for the isolated products. [a] Used 1-hexene (**2f**; 1 equiv).

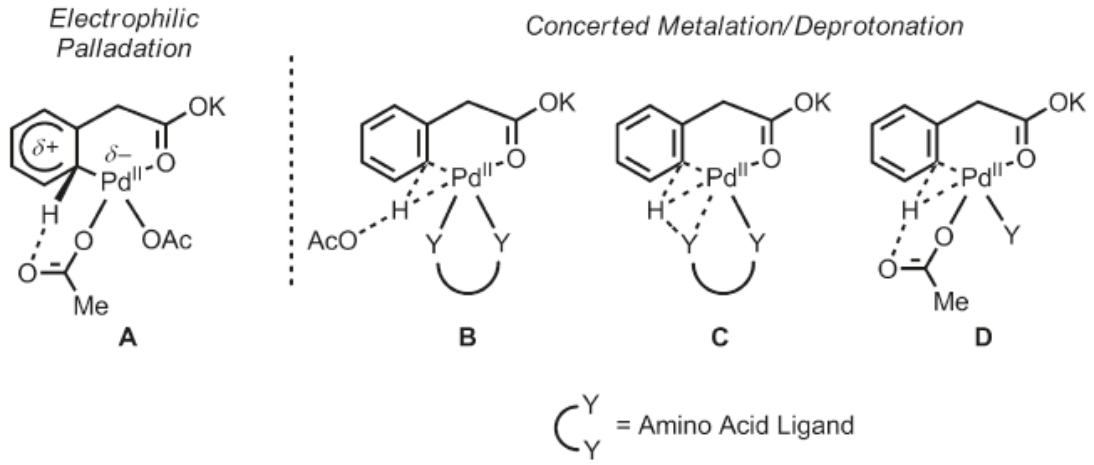


Angew. Chem. Int. Ed. **2010**, *49*, 6169–6173
DOI: 10.1002/anie.201002077

1-3 Carboxvlic acid as DG



Product	Ligand	% Conv.
 3f	---	5
	Ac-Ile-OH	>99 (98)
 3g	---	20
	Ac-Ile-OH	97 (96)



21 more substrates

dx.doi.org/10.1021/ja203978r | J. Am. Chem. Soc. 2011, 133, 18183–18193

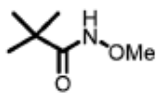
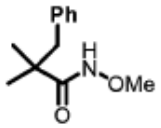
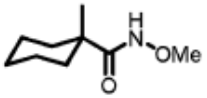
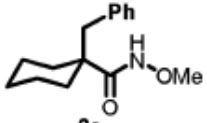
reaction rate: Ac-Ile-OH > Ac-Val-OH > Boc-Val-OH

≈ Boc-Ile-OH (1)

dx.doi.org/10.1021/ja207634t | J. Am. Chem. Soc. 2012, 134, 4600–4606

1-4 CONHX as DG

Table 1. *β*-Arylation of *O*-Methyl Hydroxamic Acids[a]

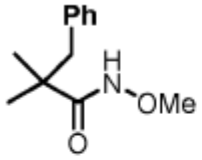
entry	substrate	product	isolated yield (%)
1	 **1**	 **1a**	85[b]
2	 **2**	 **2a**	94

[a] Reaction conditions: *O*-methyl hydroxamic acid (0.5 mmol), arylboronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), Ag_2O (1 mmol), benzoquinone (BQ, 0.25 mmol), K_2CO_3 (1 mmol), *t*-BuOH (3 mL), 70 °C, 18 h. Reactions were carried out in a Teflon cap-sealed tube. [b] *t*-BuOH:DMF = 4:1 as solvent.

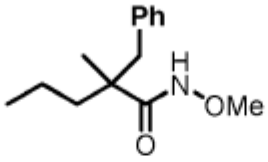
Bulky solvent to prevent homocoupling and beta-hydride elimination

8 more examples

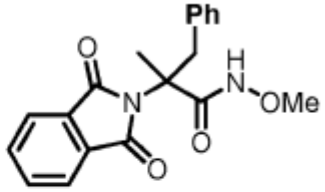
Table 3. C−H Activation/C−C Coupling Using Air as the Oxidant[a]



1a, 65[b], 75, 81[c]



3a, 86



4a, 73

O_2 instead of Ag_2O

6 more examples

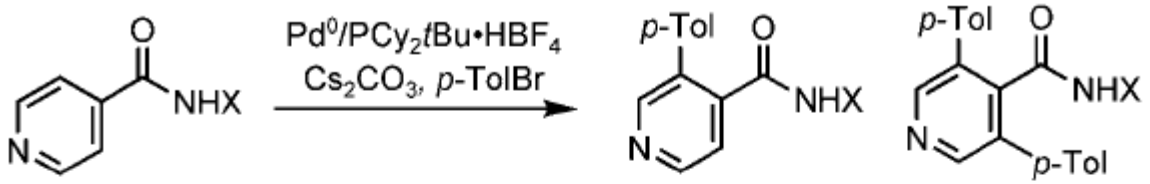
[a] Reaction conditions: *O*-methyl hydroxamic acid (0.5 mmol), boronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), K_2CO_3 (1 mmol), benzoquinone (BQ, 0.25 mmol), 20 atm air and 20 atm N_2, 80 °C, 48 h. Solvent for arylation: *t*-BuOH (3 mL). Solvent for alkylation: 2,2,5,5-tetramethylTHF (3 mL). Reactions were carried out in a high pressure vessel. [b] 20 atm air. [c] 20 atm air and 60 atm N_2.

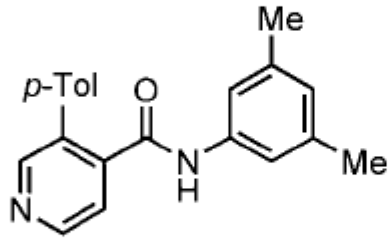
J. AM. CHEM. SOC. 2008, *130*, 7190–7191

10.1021/ja801355s

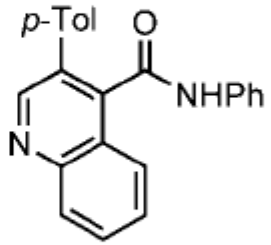
1-4 CONHX as DG

Arylation of nicotinic and isonicotinic derivatives.





5 a 86% mono
trace di



7 a 89%

15 more examples

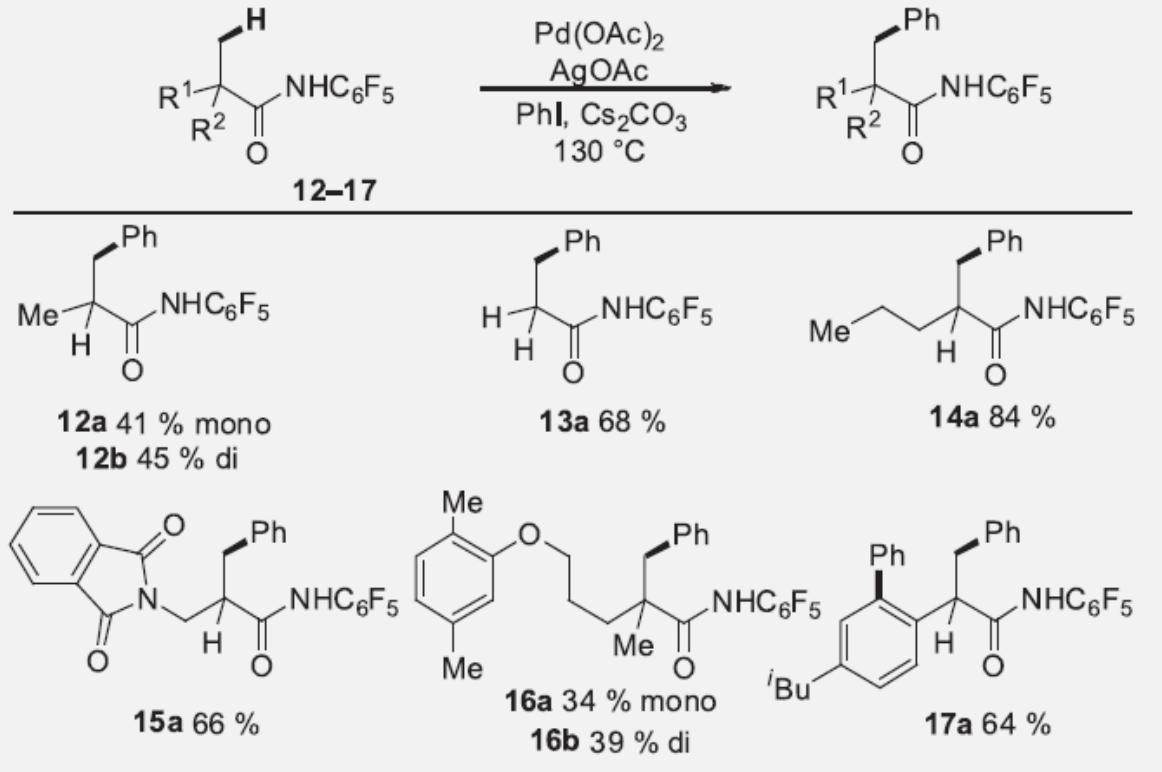
[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 10 mol% $PCy_2tBu{\cdot}HBF_4$, 3.0 equiv of Cs_2CO_3, 1.5 equiv of aryl bromide, 100 mg 3 Å M.S., 1 mL toluene, 130°C, N_2, 48 h. [b] Yield of isolated product.

Angew. Chem. Int. Ed. **2010**, *49*, 1275–1277

DOI: 10.1002/anie.200906104

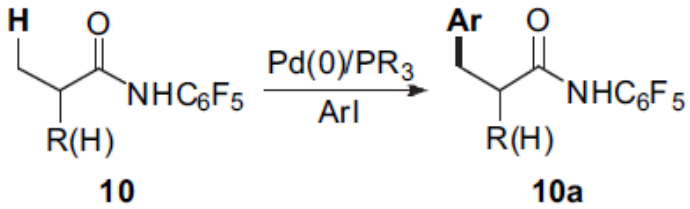
1-4 CONHX as DG

Table 3
Arylation of *N*-phenylpivalamides[a,b]



[a] Reaction conditions: 0.2 mmol substrate, 10 mol % $Pd(OAc)_2$, 4 equiv AgOAc, 1.2 equiv Cs_2CO_3, 0.5 mL iodobenzene, 130 °C, 3 h, air.

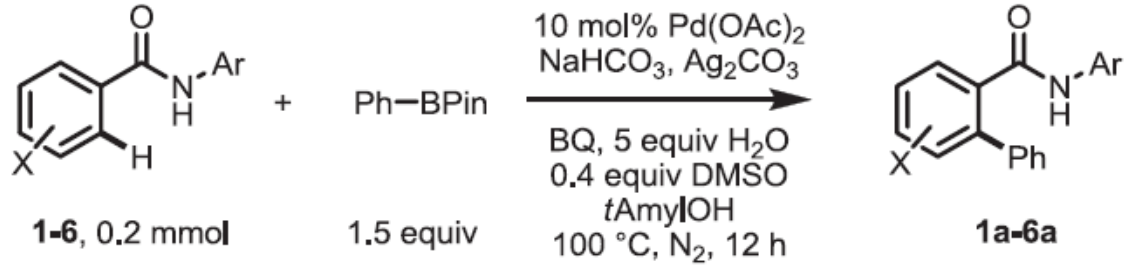
Using ArI instead of Boronic acid



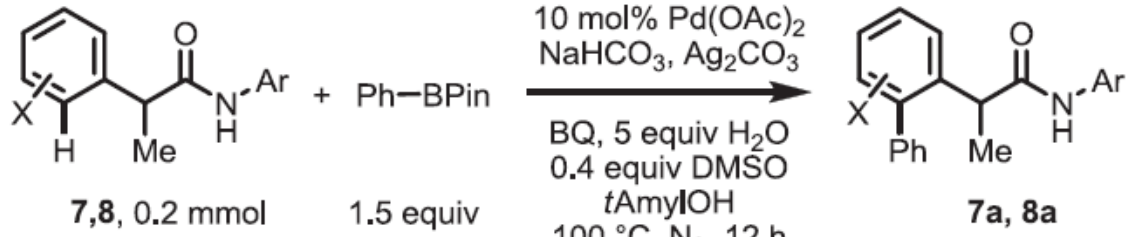
Pd:0➔II also can work

M. Wasa, J.-Q. Yu / Tetrahedron 66 (2010) 4811–4815
doi:10.1016/j.tet.2010.03.111

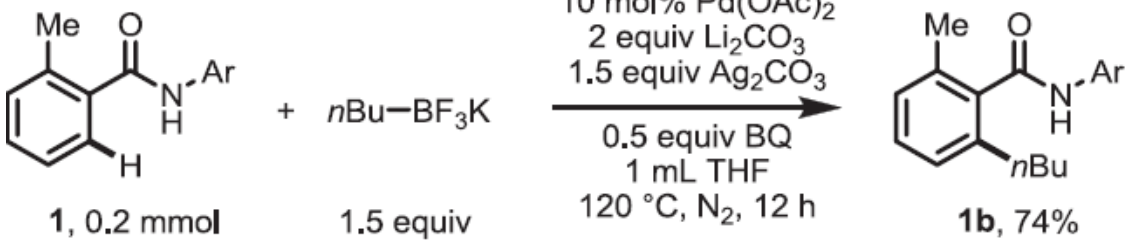
1-4 CONHX as DG



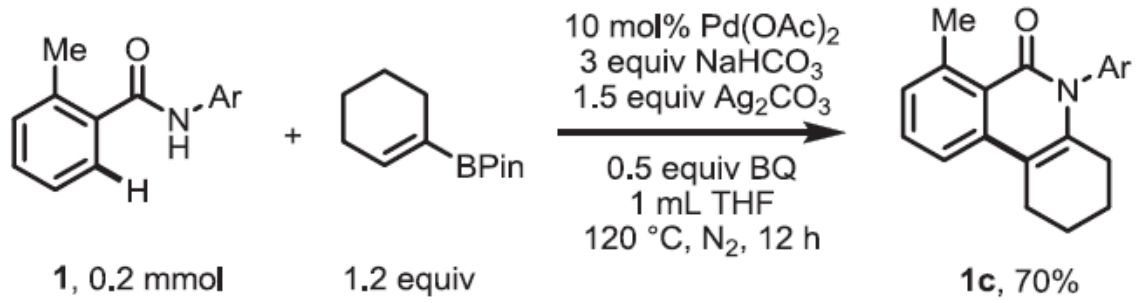
DMSO stabilizes the Pd(0)



10 examples in total



BQ is crucial for R.E. and Reoxidation.

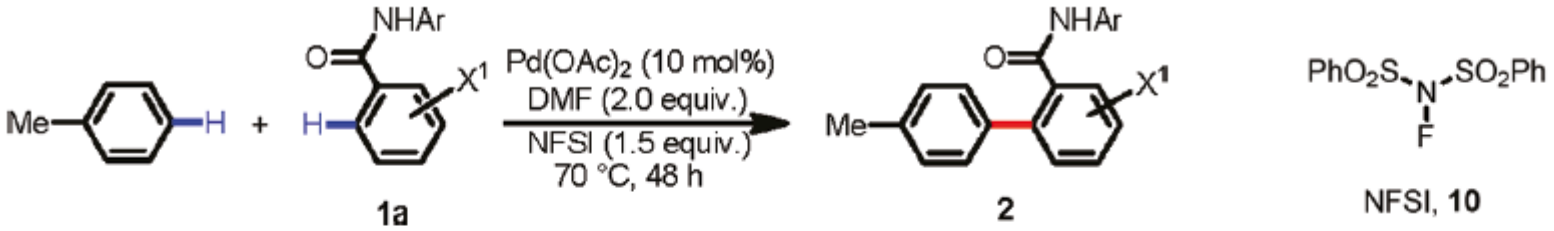


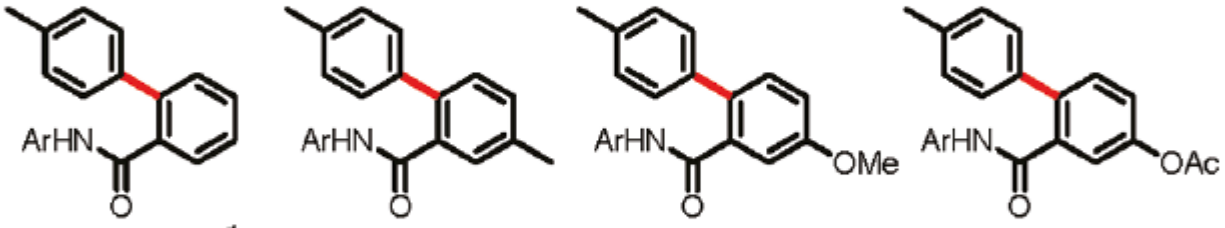
Chem. Lett. **2011**, *40*, 1004–1006

doi:10.1246/cl.2011.1004

1-4 CONHX as DG

Scope of Benzamides[a,b,c]





2b, 73% (17/1)[d] **2c**, 77% (20/1) **2d**, 82% (15/1) **2e**, 80% (29/1)

20 examples in total

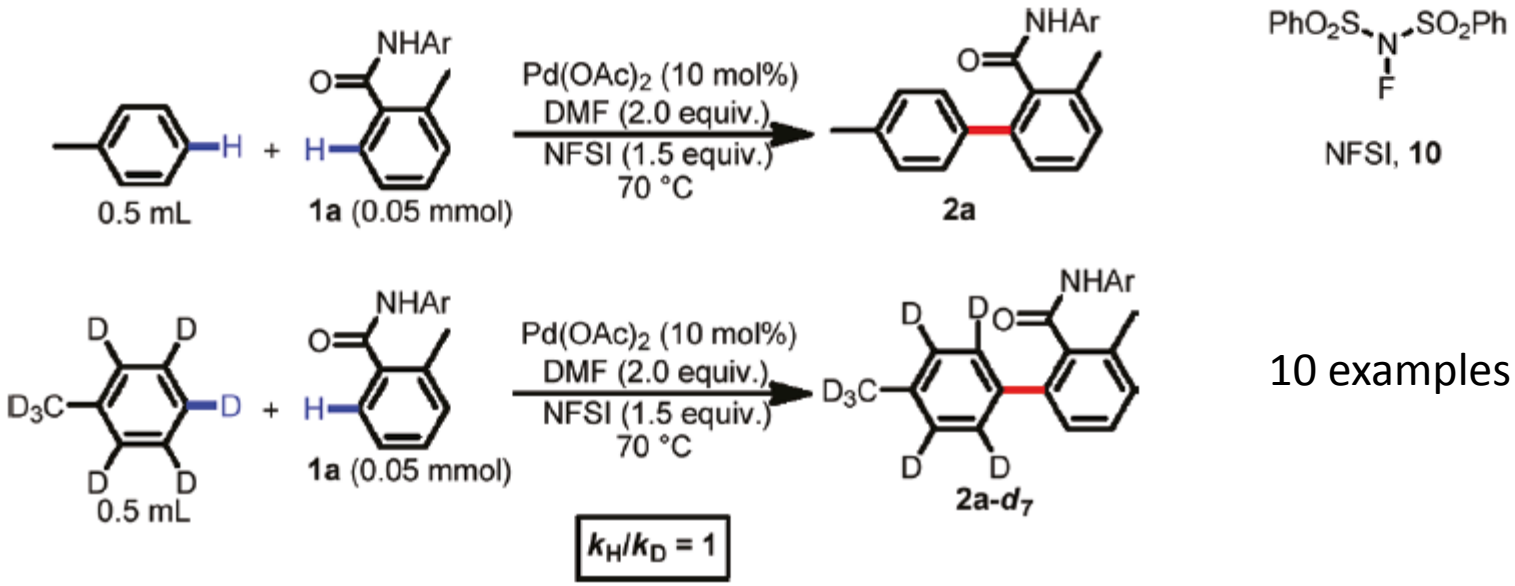
[ArPd(IV)F] species

Might be the reason of para-selective

[a] Unless otherwise noted, the reaction conditions were as follows: amide **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1.5 equiv), DMF (2.0 equiv), toluene (2 mL), 70 °C, 48 h. [b] Isolated yields are given. [c] Regioselectivity determined by GC analysis (*para*/*meta*, no *ortho*-product was observed) is shown in parentheses. [d] 90 °C, 24 h. [e] 80 °C, 36 h. [f] 100 °C, 24 h. [g] 15 mol % $Pd(OAc)_2$.

dx.doi.org/10.1021/ja206572w | *J. Am. Chem. Soc.* 2011, 133, 13864–13867

1-4 CONHX as DG



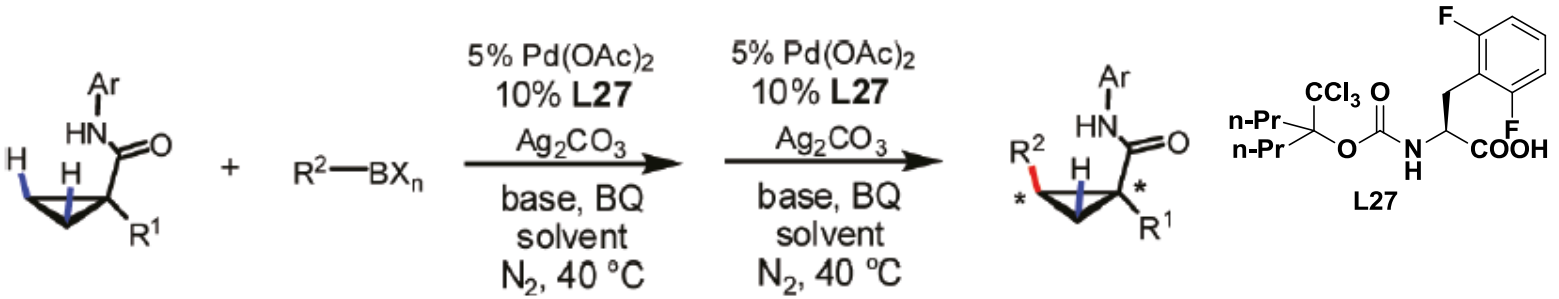
10 examples in total

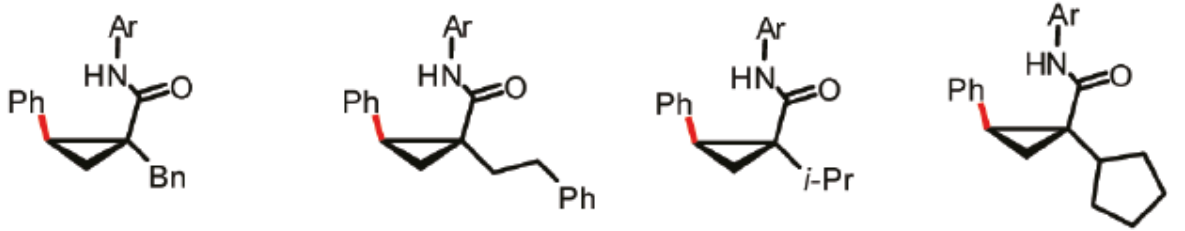
Figure 2. Kinetic isotope effect.

dx.doi.org/10.1021/ja206572w | *J. Am. Chem. Soc.* 2011, 133, 13864–13867

1-4 CONHX as DG

Table 5. Asymmetric Cyclopropane C–H Functionalization[a,b]





4a, 80% yield
92% ee

5a, 72% yield
88% ee

6a, 57% yield
92% ee

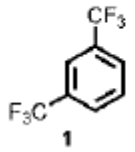
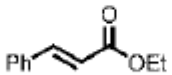
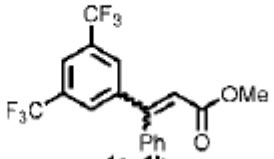
7a, 66% yield
87% ee

19 examples in total

[a] Conditions: (first batch) 0.1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 1.0 equiv of Ph–BPin, 0.75 equiv of Ag_2CO_3, 2.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 3 equiv of H_2O, 0.5 mL of *t*-Amyl-OH, 40 °C, N_2, 6 h; (second batch) 5 mol % $Pd(OAc)_2$, 10 mol % ligand, 0.5 equiv of Ph–BPin, 0.75 equiv of Ag_2CO_3, 1.0 equiv of $NaHCO_3$, 0.25 equiv of BQ, 1 equiv of H_2O, 0.2 mL of *t*-Amyl-OH, 40 °C, N_2, 6 h.

dx.doi.org/10.1021/ja207607s | *J. Am. Chem. Soc.* 2011, 133, 19598–19601

1-5 No DG

Entry	Arene	Alkene	Product	Time (h)	Yield (%)[a]
1[b]	 1		 1a, 1b	36	74 (E/Z = 85/15)

[a] Unless otherwise noted, the reactions were carried out with 0.6 mmol of alkene, 10 mol% $Pd(OAc)_2$ (0.06 mmol), 20 mol% **L3** (0.12 mmol), 1.0 equiv of Ac_2O, 1 atm of O_2 in 2 mL (20−30 equiv) of arene at 90 °C. The isomer ratios were determined by GC. All the standard *para* and *meta* compounds were prepared *via* Heck coupling of the corresponding aryl halides and alkenes.

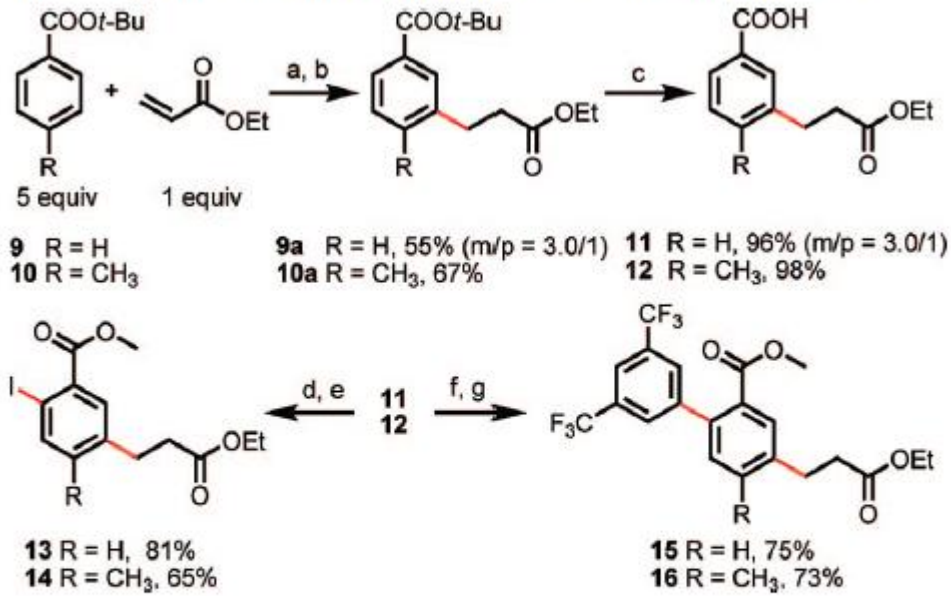
14 examples in total

J. AM. CHEM. SOC. 2009, *131*, 5072–5074

10.1021/ja900327e

1-5 No DG

Scheme 2. Synthesis of Tri- and Tetrasubstituted Arenes[a]



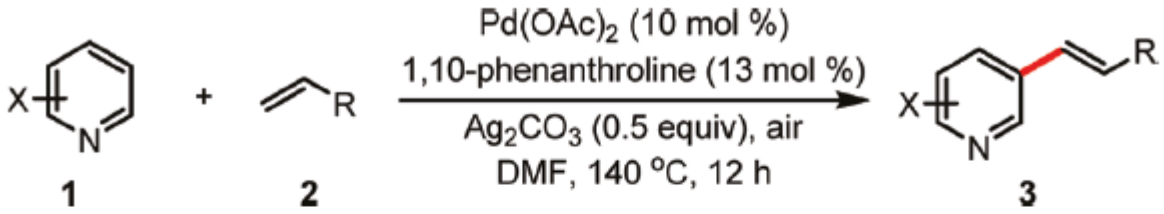
[a] (a) $Pd(OAc)_2$ (10 mol%), **L3** (20 mol%), Ac_2O (1.5 equiv), EtOAc, 90 °C; (b) H_2, Pd/C, EtOAc; (c) TFA, DCM; (d) $PhI(OAc)_2$ (1.0 equiv), I_2 (1.0 equiv), $Pd(OAc)_2$ (10 mol%), Bu_4NI (1.0 equiv), DCE, 80 °C; (e) CH_2N_2; (f) $Pd(OAc)_2$ (10 mol%), ArI (3.0 equiv), AgOAc (1.5 equiv), AcOH (5.0 equiv), 120 °C; (g) CH_2N_2.

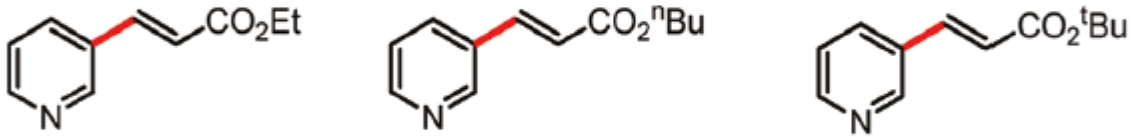
J. AM. CHEM. SOC. 2009, *131*, 5072–5074

10.1021/ja900327e

1-5 No DG

Table 2. Pd-Catalyzed Olefination of Pyridine Derivatives [a,b,c]





3a, 73% [12/1/1] **3b**, 63% [8/1/1] **3c**, 67% [11/1/1]

[a] Reaction conditions: **1a** (8.0 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ligand (13 mol %), and Ag_2CO_3 (0.25 mmol) in DMF (1 mL). [b] Isolated yield of C-3 product. [c] Ratio of C-3/C-2/C-4 was determined by ^1H NMR. [d] Bathophenanthroline (13 mol %), 24 h. [e] 3.0 and 1.5 mmol of pyridine substurate were used respectively.

21 examples in total

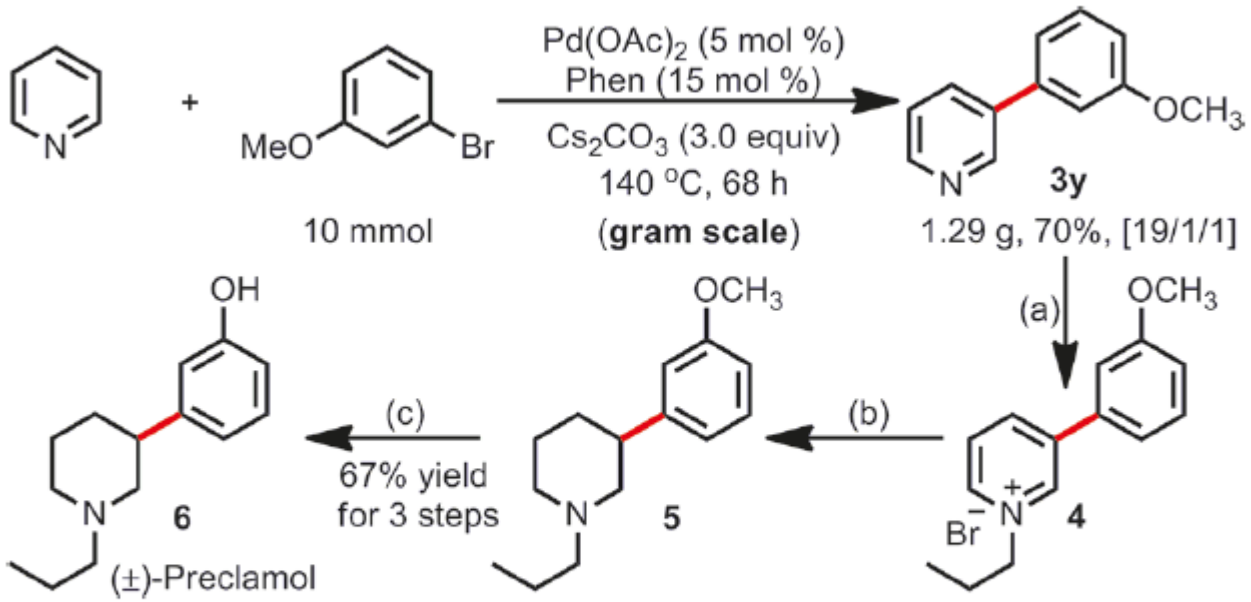
16 eq. of **1**
The olefin is the limiting reagent.

KIE=4.0
So it is not a Friedel-Crafts rxn.

dx.doi.org/10.1021/ja2021075 | *J. Am. Chem. Soc.* 2011, 133, 6964–6967

1-5 No DG

Scheme 1. Synthesis of (±)-Preclamol[a]



[a] Reagents and conditions: (a) 1-bromopropane, CH_3CN, 110 °C; (b) PtO_2, MeOH, H_2 (60 psi), room temperature; (c) HBr in HOAc (33%), reflux.

24 examples in total

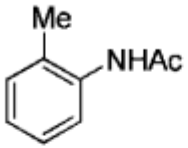
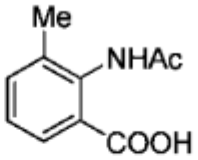
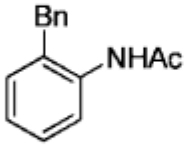
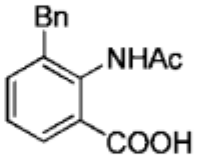
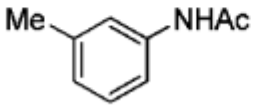
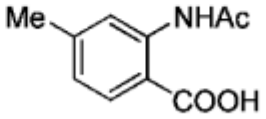
6 eq. of pyridine
The olefin is the limiting reagent.

KIE=4.2
C-H activation may via Concert metalation

dx.doi.org/10.1021/ja209510q | *J. Am. Chem. Soc.* 2011, 133, 19090–19093

1-6. NHCOX as DG

Ortho-Carboxylation of Anilides via C−H Activation[a,b]

Entry	Substrate	Product	% Yield
1	 **2**	 **2a**	60
2	 **3**	 **3a**	53[c]
3	 **4**	 **4a**	94

[a] 10 mol % $Pd(OAc)_2$, 0.5 equiv of *p*-TsOH·H_2O, 1 equiv of benzoquinone, 1 atm of CO, HOAc/dioxane (2:1). [b] Isolated yields. [c] Dioxane was used as a solvent.

20 examples in total

TsO- is crucial
Reason see next slide

J. AM. CHEM. SOC. 2010, *132*, 686–693

10.1021/ja9077705

1-6. NHCOX as DG

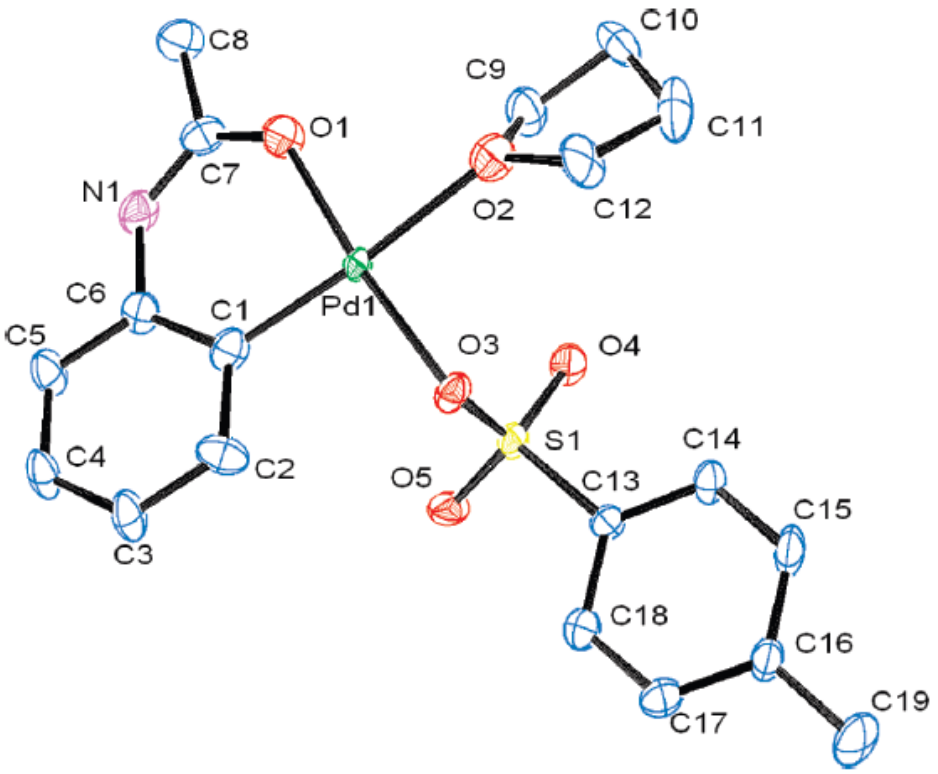


Figure 1. Crystal structure of **1c**.

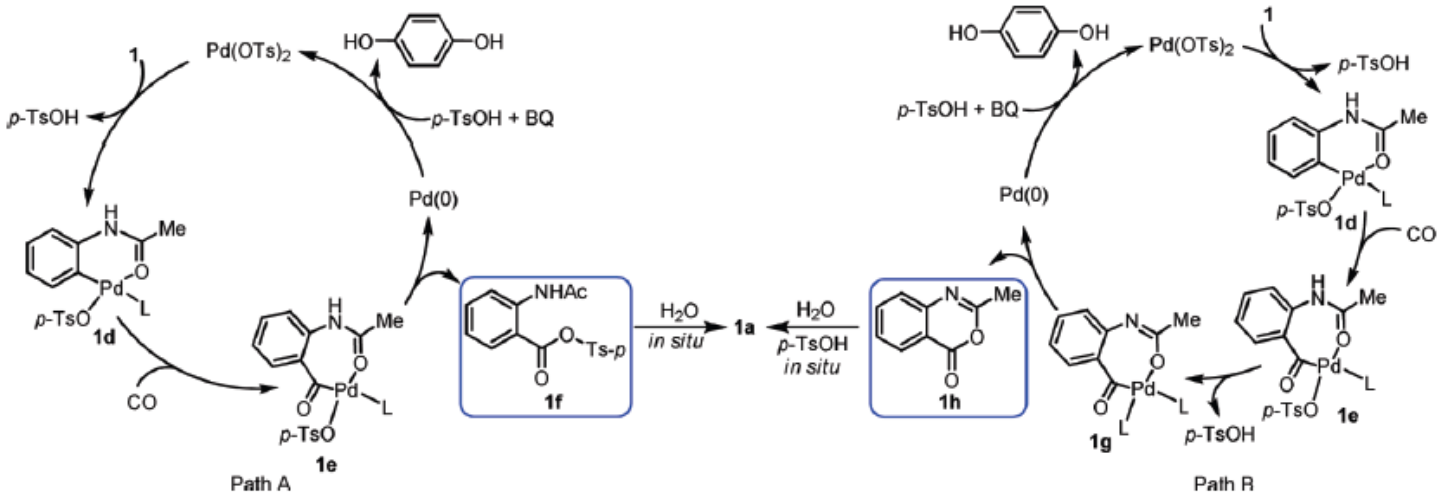
Allow CO to attach to Pd

J. AM. CHEM. SOC. 2010, *132*, 686–693

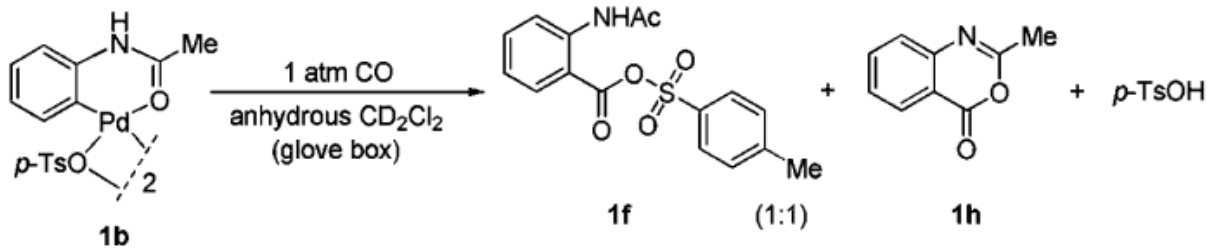
10.1021/ja9077705

1-6. NHCOX as DG

Scheme 8. Dual-Reaction Pathways of Catalytic Carboxylation in the Presence of H_2O



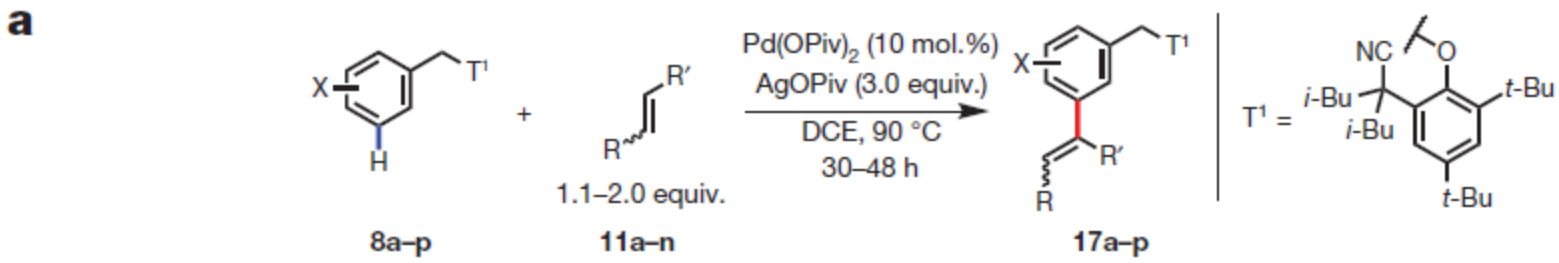
Scheme 9. Stoichiometric Reaction of Palladacycle **1b** with CO under Anhydrous Conditions

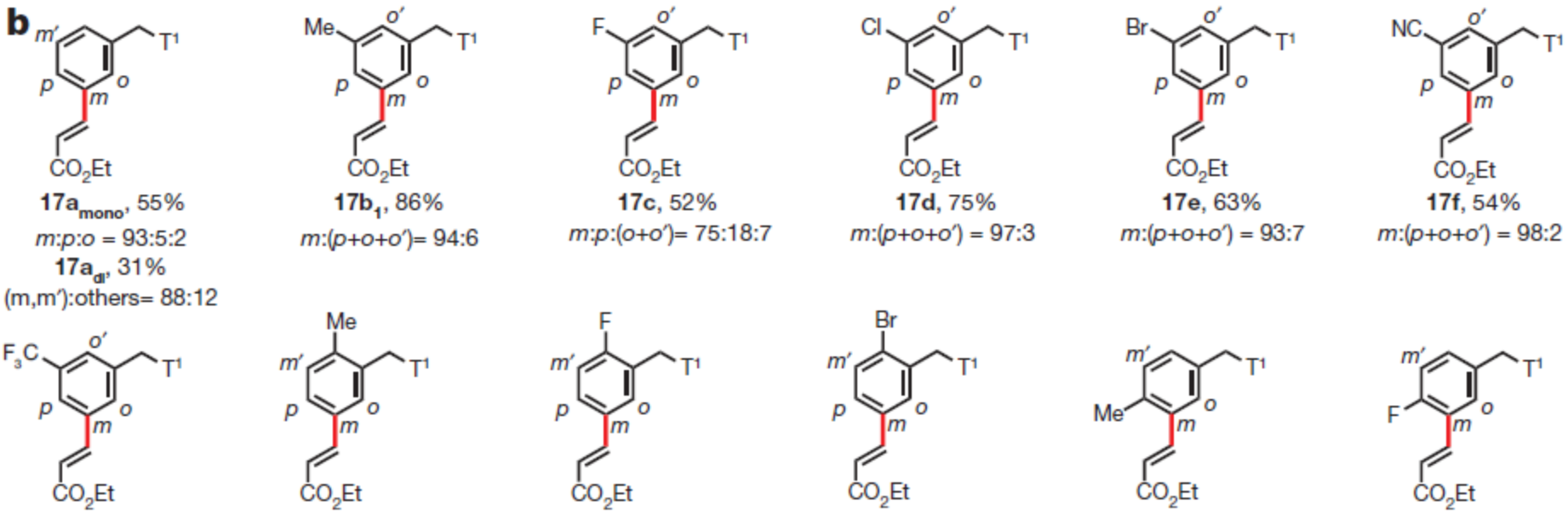


J. AM. CHEM. SOC. 2010, *132*, 686–693

10.1021/ja9077705

1-7. Remote DG

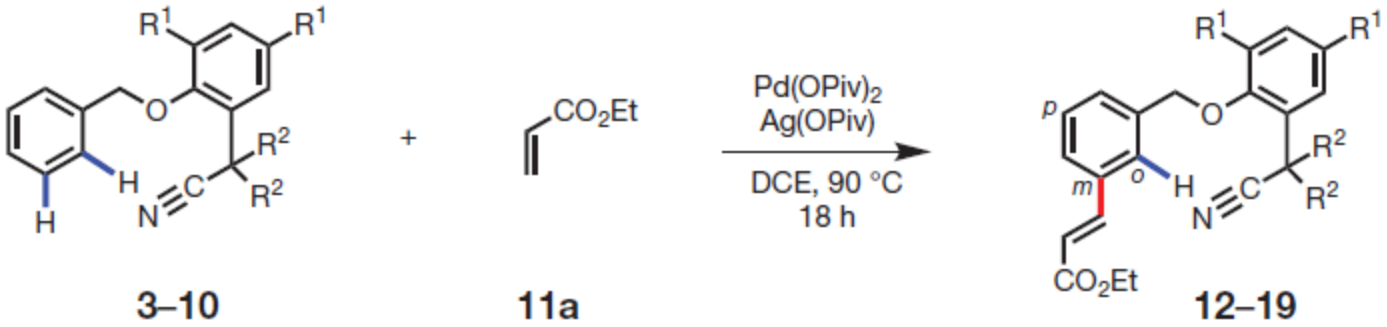




doi:10.1038/nature11158

1-7. Remote DG

Table 1 | Optimization of template

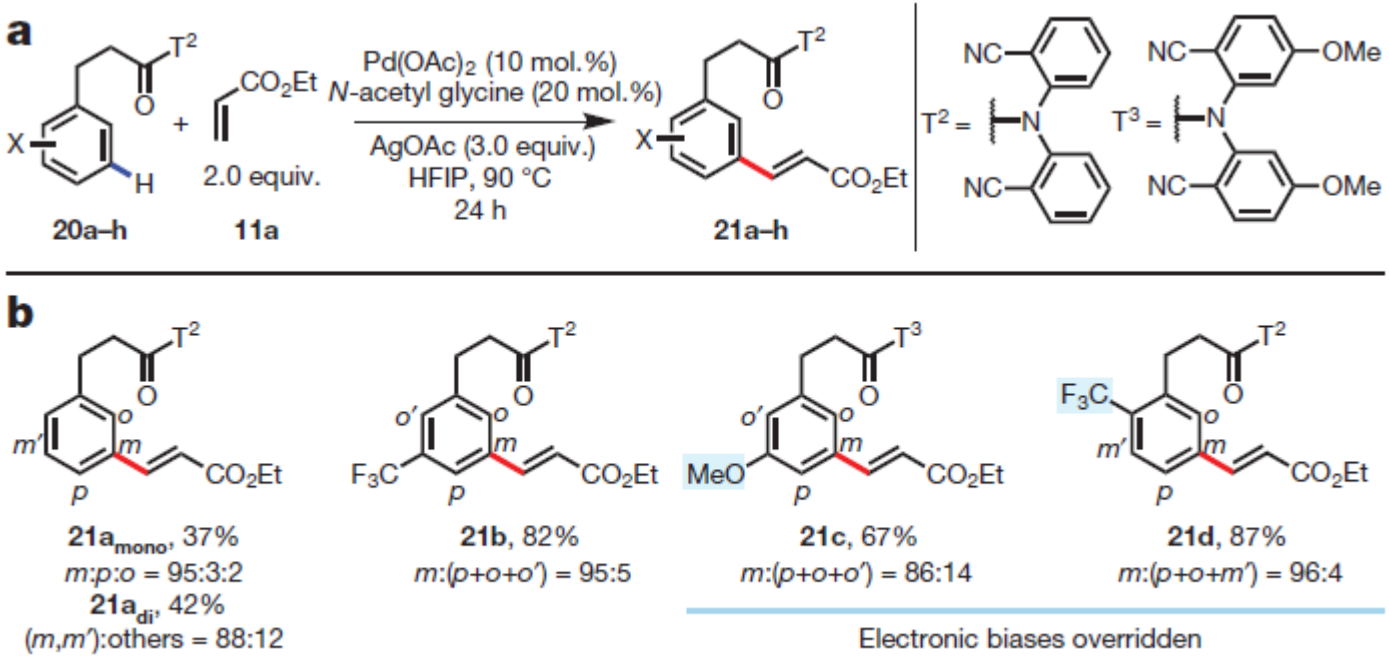


3–10 **11a** **12–19**

Entry	Substrate	R^1	R^2	Yield (%) (mono)	Yield (%) (di)	Selectivity (*meta*:*para*:*ortho*)
1	**3**	*tert*-butyl	H	Trace	0	—
2	**3**	*tert*-butyl	H	4	0	56:26:18
3	**3**	*tert*-butyl	H	15	0	59:33:8
4	**4**	*tert*-butyl	Methyl	60	17	91:7:2
5	**5**	*tert*-butyl	Ethyl	52	16	93:6:1
6	**6**	*tert*-butyl	$-(CH_2)_4-$	50	11	88:7:5
7	**7**	*tert*-butyl	$-(CH_2)_5-$	51	15	91:5:4
8	**8a**	*tert*-butyl	Isobutyl	63	20	95:4:1
9	**9**	H	Isobutyl	—	—	—
10	**10**	Methyl	Isobutyl	39	10	91:8:1

doi:10.1038/nature11158

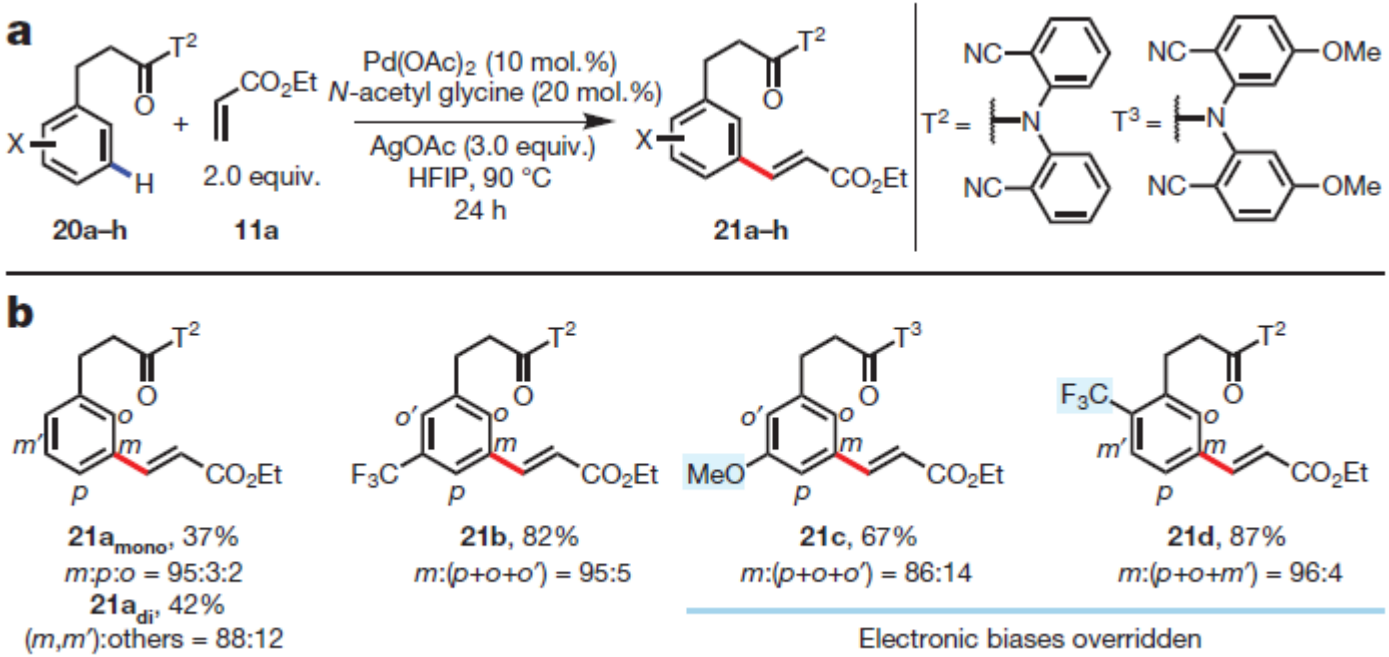
1-7. Remote DG



T2 is more easier to remove.
Good functional groups tolerence.
38 examples in total.

518 | NATURE | VOL 486 | 28 JUNE 2012
doi:10.1038/nature11158

1-7. Remote DG



T2 is more easier to remove.
Good functional groups tolerence.
38 examples in total.

518 | NATURE | VOL 486 | 28 JUNE 2012
doi:10.1038/nature11158

Summary

- 1. Good directing group is the most important
- 2. Many types of reactants as coupling partner

Boronic acid, Halides, CO, Olefins…

- 3. Two different mechanism are purposed.

2.C-N bond formation

- 2-1. Intramolecular C-N bond formation

----Cyclization reaction

From 2008-09, 3 publications.

- 2-2. Intermolecular C-N bond formation

From 2011, 1 publication.

In contrast, achieving the Pd-catalyzed C−H amination reaction represents a distinct challenge and has been met with a number of difficulties, as can be anticipated from the many tremendous hurdles encountered in the development of the Buchwald−Hartwig amination reaction.[2]

2.C-N bond formation

- Let’s tell the story from the beginning…

2-1. Intramolecular C-N

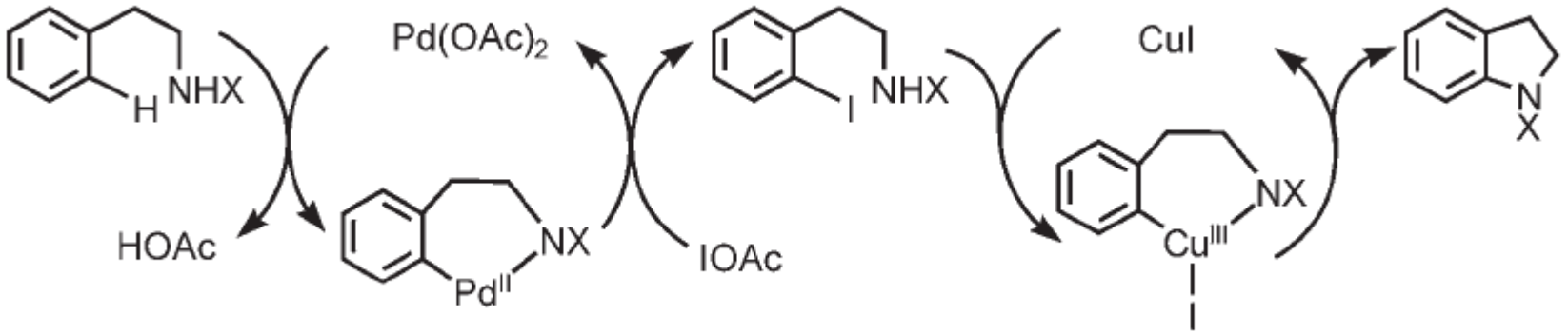
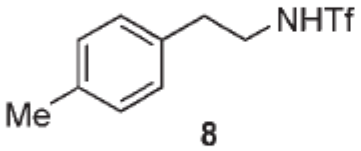
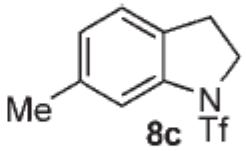


Table 3: One-pot intramolecular amination catalyzed by $Pd(OAc)_2$ and CuI.[a]

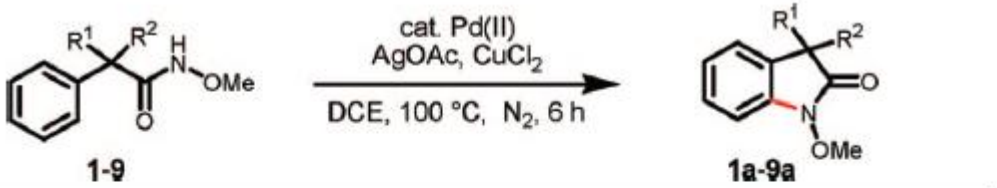
Entry	Substrate	Product	Yield [%]
1	 8	 8c	59[b]

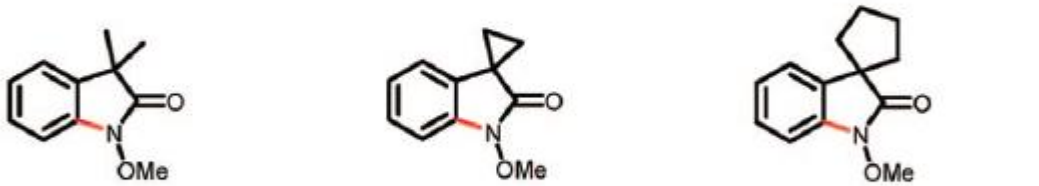
[a] Reaction conditions: 10 mol% $Pd(OAc)_2$, 2 equiv $C_6H_5I(OAc)_2$, 2 equiv I_2, 1 equiv Cs_2CO_3, 1 equiv CuI, DMF, 130 °C, 96 h. [b] 5-Iodoindolines were isolated in 7—10% yield . [c] 0.5 equiv CuI.

Only 7 examples are synthesized in this way

Angew. Chem. Int. Ed. **2008**, *47*, 6452–6455
DOI: 10.1002/anie.200802187

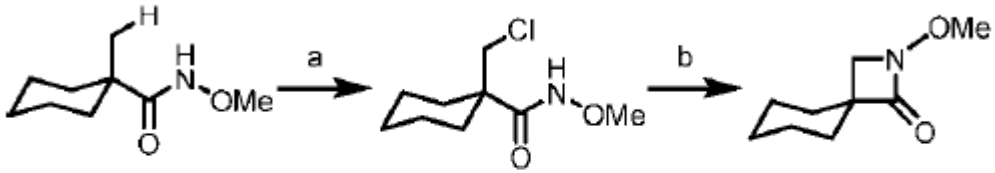
2-1. Intramolecular C-N





[a] Conditions: 0.5 mmol of substrate, 10 mol% $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, 10 mL of dichloroethane, N_2, 100 °C, 6 h.

Scheme 1. One-Pot Synthesis of β-Lactams[a]



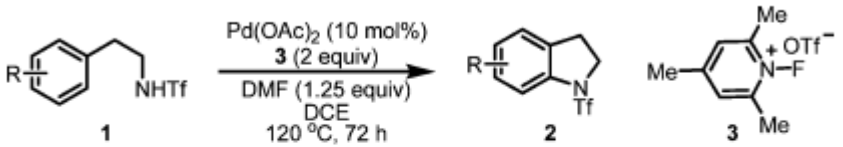
[a] Reaction conditions: (1) 0.5 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, DCE, 100 °C, N_2, 10 h. (2) 4 equiv of CsF, 0.18 equiv of benzyltriethyl ammonium chloride, 100 °C, 12 h.

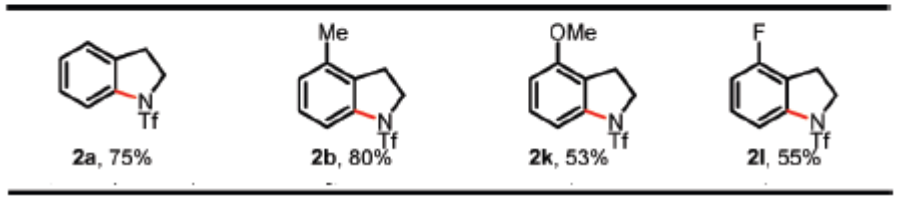
18 examples in total.

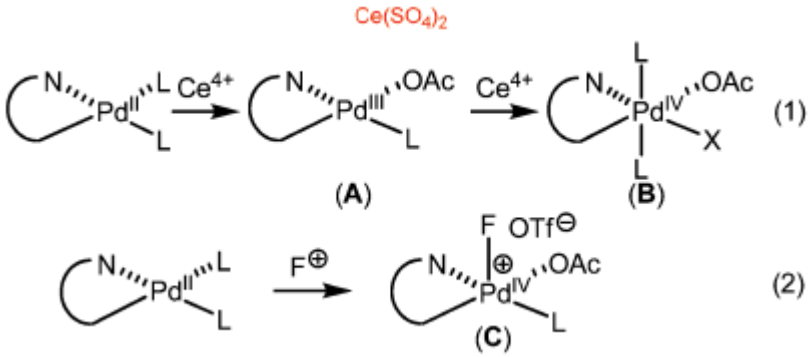
J. AM. CHEM. SOC. ■ VOL. 130, NO. 43, 2008
10.1021/ja807129e

2-1. Intramolecular C-N

Table 2. Pd-Catalyzed Amination Using F^+ As an Oxidant







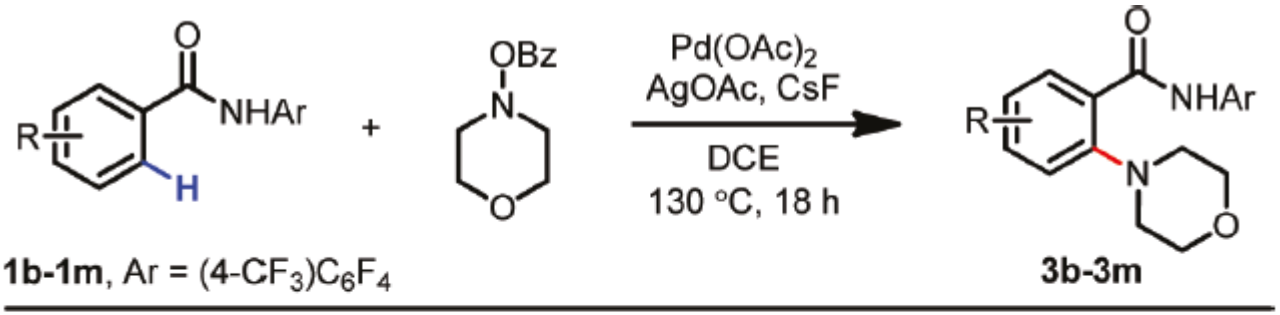
24 examples in this procedure.

$Ce(SO_4)_2$ was the first oxidant that shows good reactivity. 9 examples. But the acetoxylation product also gave 35% yield.

J. AM. CHEM. SOC. 2009, *131*, 10806–10807

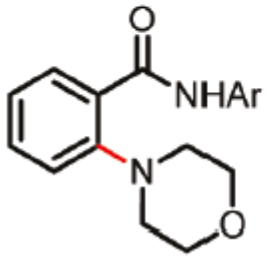
10.1021/ja904709b

2-2. Intermolecular C-N

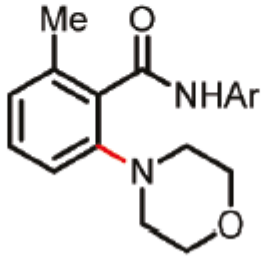


1b-1m, Ar = (4-CF_3)C_6F_4

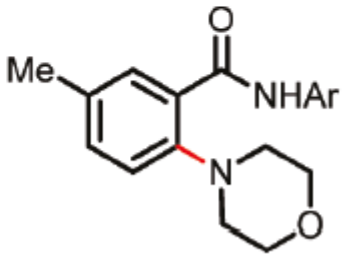
3b-3m



3b, 85%



3c, 89%



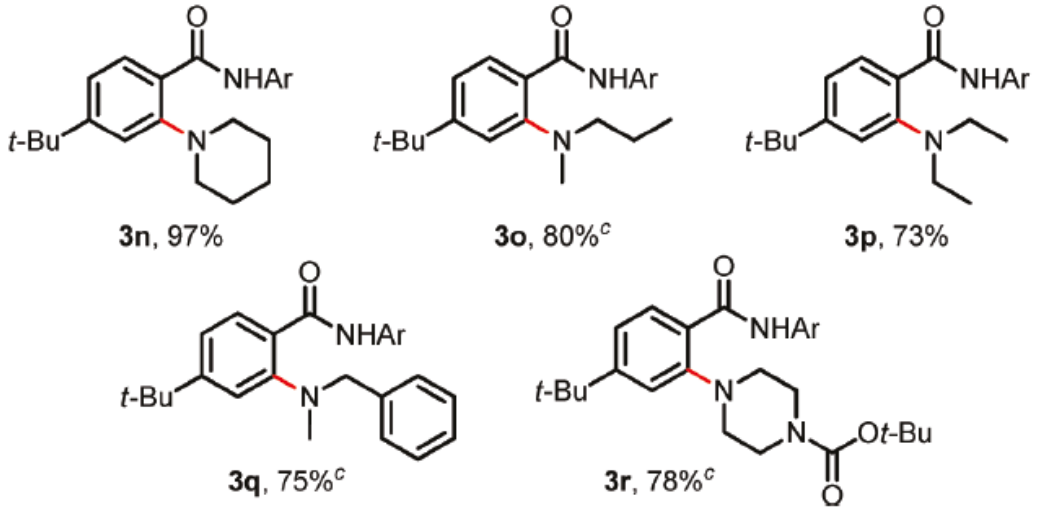
3d, 82%

[a] Reaction conditions: benzamide substrate **1** (0.2 mmol), *O*-benzoyl hydroxylmorpholine (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), CsF (0.4 mmol), DCE (1 mL), 130 °C, 18 h. [b] Isolated yield.

12 examples using this
amine partner.
Does other amines work?

dx.doi.org/10.1021/ja202563w | *J. Am. Chem. Soc.* 2011, 133, 7652–7655

2-2. Intermolecular C-N



[a] Reaction conditions: **1a** (0.2 mmol), *O*-benzoyl hydroxylamine (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), CsF (0.4 mmol), DCE (1 mL), 130 °C, 18 h. [b] Isolated yield. [c] α,α,α-Trifluorotoluene was used as a solvent.

12 examples using this amine partner.
Does other amines work?

dx.doi.org/10.1021/ja202563w | *J. Am. Chem. Soc.* 2011, 133, 7652–7655

2-2. Intermolecular C-N

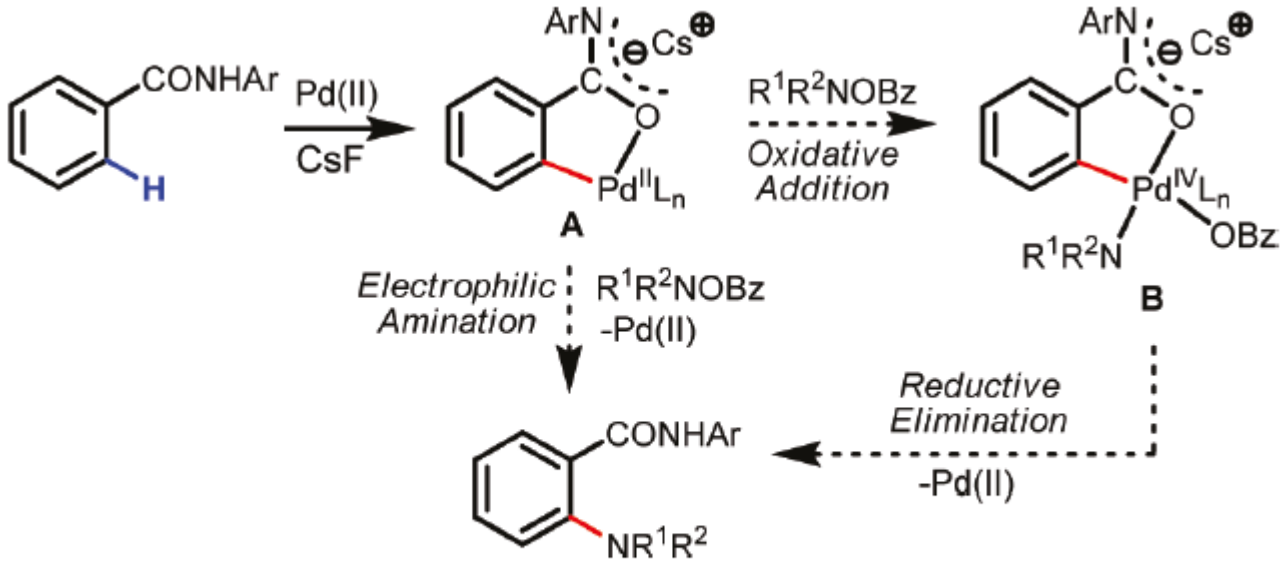


Figure 2. Possible reaction pathways with Pd(II) catalyst.

I think F also play an important role here.

dx.doi.org/10.1021/ja202563w | *J. Am. Chem. Soc.* 2011, 133, 7652–7655

Future

- 1. sp^3 C-N bond
- 2. practical approach --- no Ag, or expensive F

3.C-O bond formation

- 3-1. C-OAc as Product

from 2005-10, 3 publications.

- 3-2. C-OH as Product

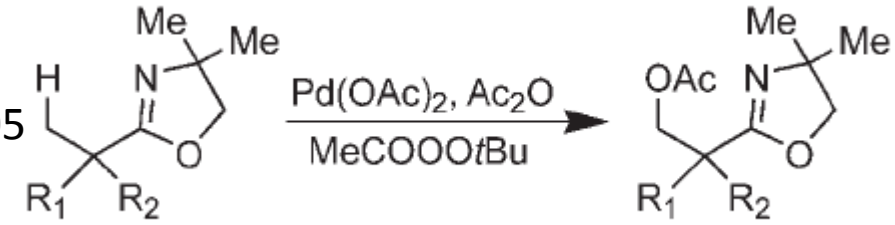
2009, 1 publication.

- 3-3. Cyclization reaction

2010, 1 publication.

3-1. C-OAc as Product

2005



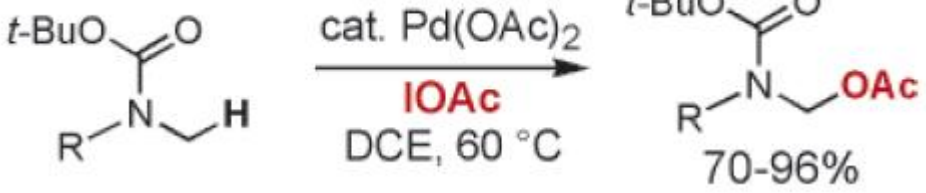
(1)

Angew. Chem. Int. Ed. **2005**, *44*, 7420–7424

DOI: 10.1002/anie.200502767

15 examples 50-90% yield

2006



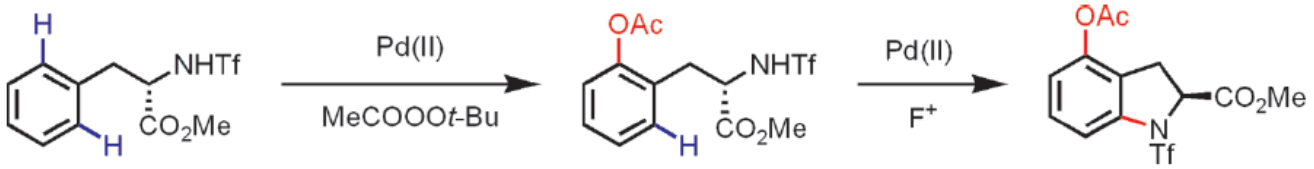
ORGANIC LETTERS

2006
Vol. 8, No. 15
3387–3390

10.1021/ol061384m

18 examples

2010



23 examples, 33-93% yield

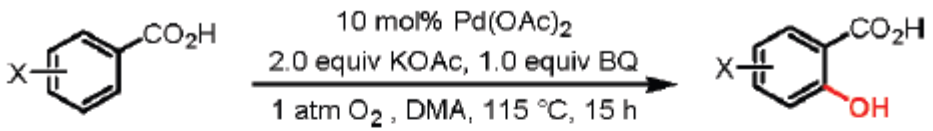
ORGANIC LETTERS

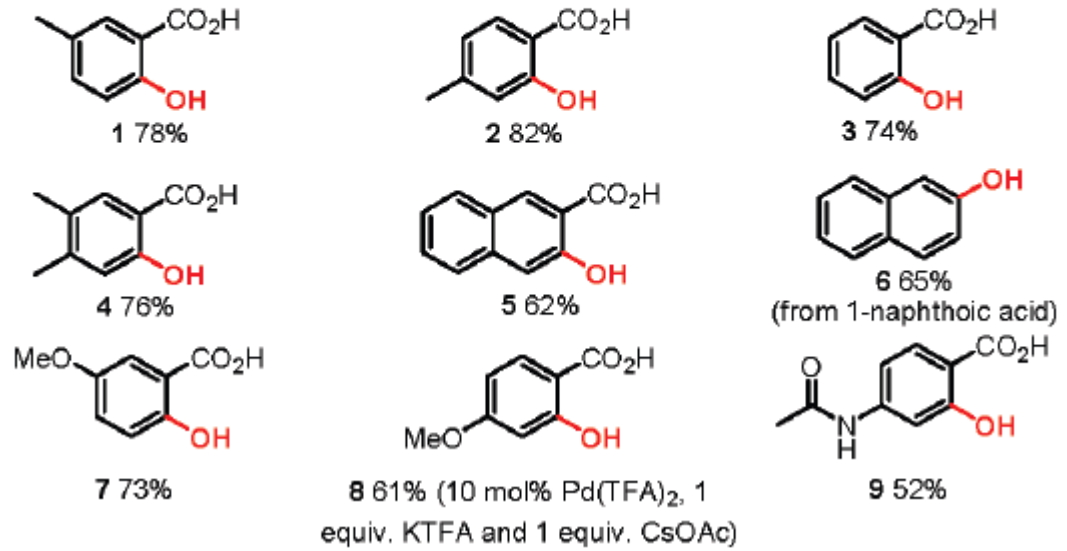
2010
Vol. 12, No. 11
2511–2513

10.1021/ol1007108

3-2. C-OH as Product

Table 2. Pd-Catalyzed *ortho*-Hydroxylation with O_2[a]



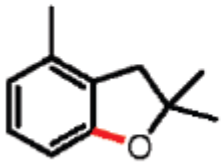


J. AM. CHEM. SOC. 2009, *131*, 14654–14655

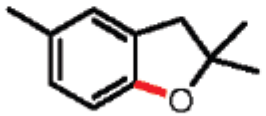
10.1021/ja907198n

3-3. Cyclization reaction

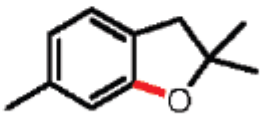
Table 2. Pd(II)-Catalyzed C−H Activation/C−O Cyclization[a,b]



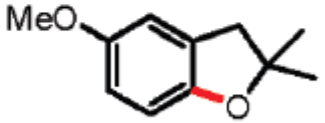
2b, 88%



2c, 83%



2d, 85%



2e, 76%[c]

[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), $PhI(OAc)_2$ (0.3 mmol, 1.5 equiv), Li_2CO_3 (0.3 mmol, 1.5 equiv), C_6F_6 (2 mL), 100 °C, 36 h. [b] Isolated yields are reported. [c] Na_2HPO_4 was used instead of Li_2CO_3. [d] Using 10 mol % $Pd(OAc)_2$.

23 examples in total. 42-91% yield.

J. AM. CHEM. SOC. 2010, *132*, 12203–12205

10.1021/ja105366u

4. C-Halide bond formation

- 4-1. C-I Bond formation

From 2005-10, 4+3 (application) Publications.

- 4-2. C-Cl Bond formation

2006 1 Publication.

- 4-3. C-F Bond formation

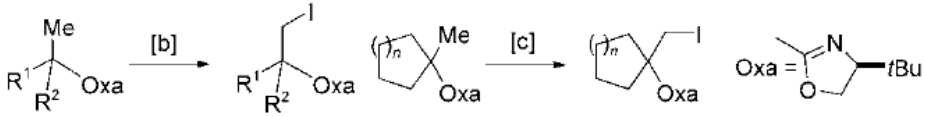
From 2009-2011, 2 Publications.

- 4-4. C-CF_3 Bond formation

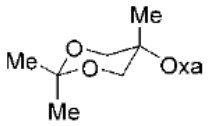
From 2010-12, 2 Publications.

4-1. C-I Bond formation

Table 1: Monoiodination of methyl groups catalyzed by $Pd(OAc)_2$.[a]



5a–7a **5b–7b** **8a–10a** **8b–10b**

Entry		Substrate	Yield [%]
1	**5a**	$R^1 = R^2 = Me$	92
2	**6a**	$R^1 = Me$; $R^2 = Et$	91[d]
3	**7a**	$R^1 = R^2 = Et$	88[e]
4	**8a**	$n = 1$	90[e]
5	**9a**	$n = 2$	97[e]
6	**10a**	$n = 3$	81
7	**11a**		67[f]
8	**12a**		98
9	**13a**		32

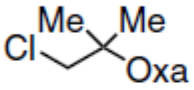
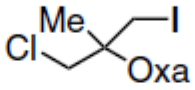
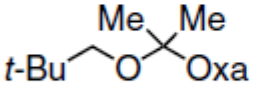
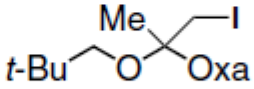
[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48–72 h. [b] Entries 1–3. [c] Entries 4–6. [d] 63:37 d.r. (NMR spectroscopy). [e] PdI_2 precipitated at 36–48 h, $PhI(OAc)_2$ (1 equiv) was added, and stirring continued for another 48 h. [f] $PhI(OAc)_2$ (2 equiv), 50 °C, 48 h.

4 more examples with d.r. selectivity

Angew. Chem. **2005**, *117*, 2150–2153
DOI: 10.1002/ange.200462884

4-1. C-I Bond formation

Table 1. Diastereoselective iodination[a]

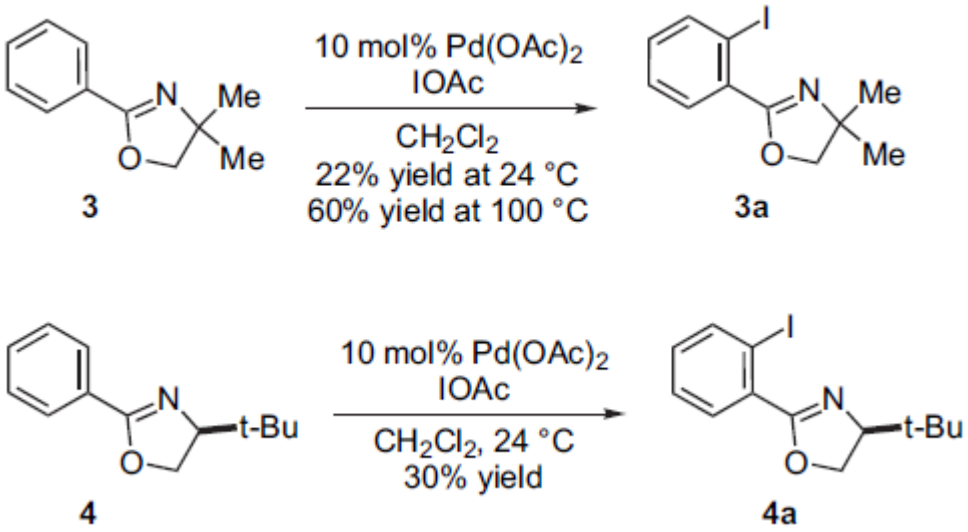
Entry	Substrate	Product	Yield (%)	de (%)
1	 **16**	 **16a**	60[b]	35
2	 **17**	 **17a**	41[c]	55

[a] Oxa = (*S*)-4-*tert*-Butyloxazoline-2-. Reaction conditions: $Pd(OAc)_2$ (10 mol %) I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2.
[b] 65 °C, $PhI(OAc)_2$ (1 equiv) was added after 12 h, and stirring continued for another 24 h.

18 examples in total. 41-83% yield.

Tetrahedron: *Asymmetry* 16 (2005) 3502–3505
doi:10.1016/j.tetasy.2005.08.049

4-1. C-I Bond formation



17 examples in total. 29-95% yield.

Tetrahedron: *Asymmetry* 16 (2005) 3502–3505
doi:10.1016/j.tetasy.2005.08.049

4-1. C-I Bond formation

1, X = H
2, X = Na

3, 5%
3, 85%

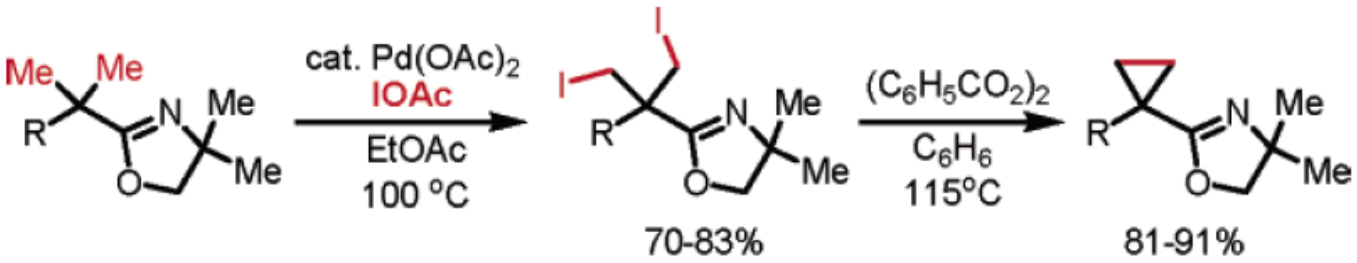
DMF can promote this reaction. Use the following condition for 14 examples, with 65-85% yield.

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), IOAc (3 equiv (entries 3–6, 9, and 12) or 2 equiv (entries 8, 10, 11, 13, 14)), DMF, 100 °C, 36 h.

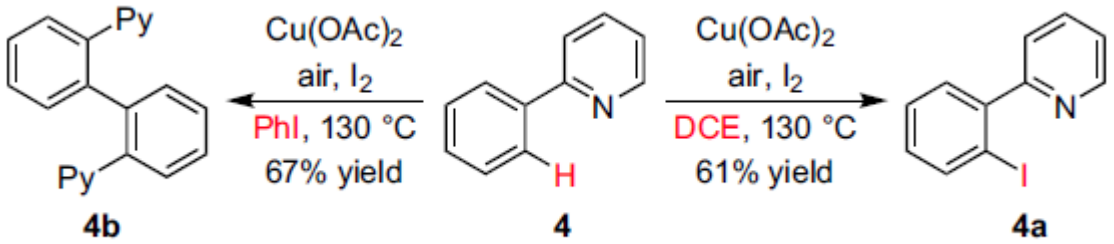
Angew. Chem. Int. Ed. **2008**, *47*, 5215–5219
DOI: 10.1002/anie.200705613

4-1. C-I Bond formation

- Application



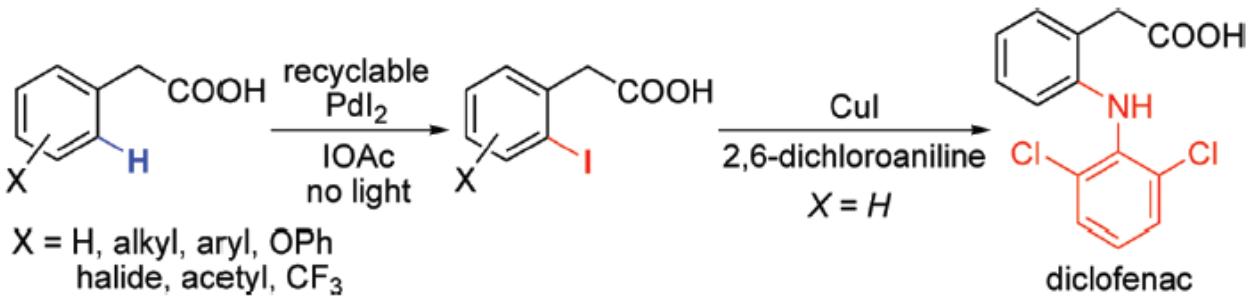
ORGANIC LETTERS
2006
Vol. 8, No. 25
5685−5688



Tetrahedron 65 (2009) 3085–3089

7 examples, from 24-88% yield

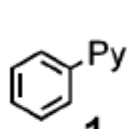
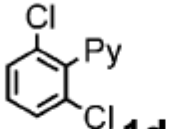
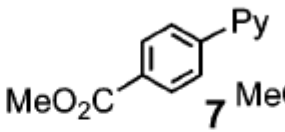
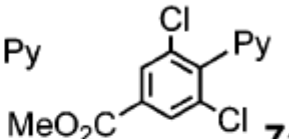
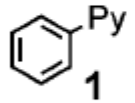
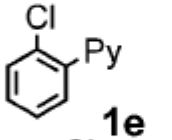
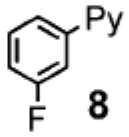
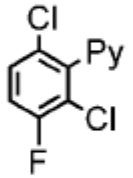
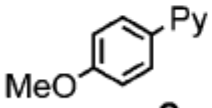
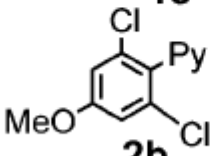
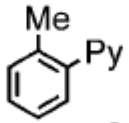
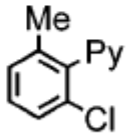
Scheme 2. Cu(II)-catalyzed C–H functionalization.



ORGANIC LETTERS
2010
Vol. 12, No. 14
3140−3143

4-2. C-Cl Bond formation

Table 1. Cu(II)-Catalyzed Chlorination of Aryl C−H Bonds[a]

entry	substrate	product	yield	entry	substrate	product	yield
1	 **1**	 **1d**	92%	8	 **7**	 **7a**	81%
2	 **1**	 **1e**	63%[b]	9	 **8**	 **8a**	91%
3	 **2**	 **2b**	93%	10	 **9**	 **9a**	92%

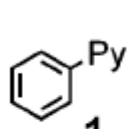
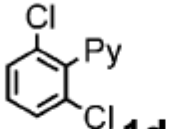
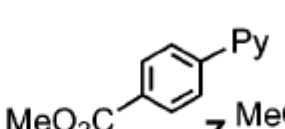
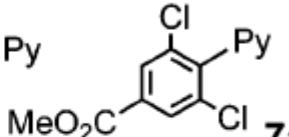
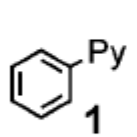
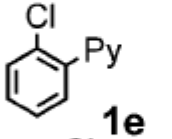
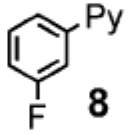
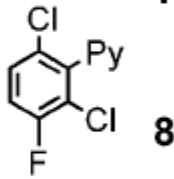
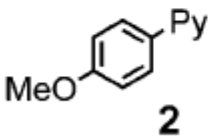
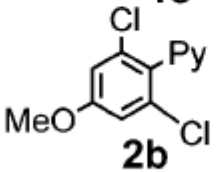
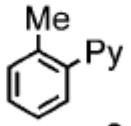
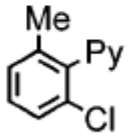
[a] With 20 mol % of $CuCl_2$, $Cl_2CHCHCl_2$, O_2 (1 atm), 130 °C, 24 h.
[b] At 100 °C; 23% dichlorinated product was also obtained.

14 examples
20-92% yield

J. AM. CHEM. SOC. 2006, *128*, 6790−6791
10.1021/ja061715q

4-2. C-Cl Bond formation

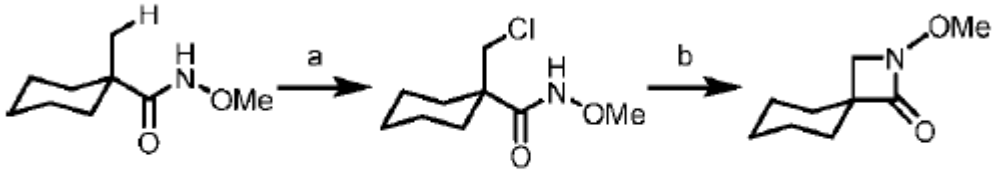
Table 1. Cu(II)-Catalyzed Chlorination of Aryl C−H Bonds[a]

entry	substrate	product	yield	entry	substrate	product	yield
1	 **1**	 **1d**	92%	8	 **7**	 **7a**	81%
2	 **1**	 **1e**	63%[b]	9	 **8**	 **8a**	91%
3	 **2**	 **2b**	93%	10	 **9**	 **9a**	92%

[a] With 20 mol % of $CuCl_2$, $Cl_2CHCHCl_2$, O_2 (1 atm), 130 °C, 24 h.
[b] At 100 °C; 23% dichlorinated product was also obtained.

14 examples
20-92% yield

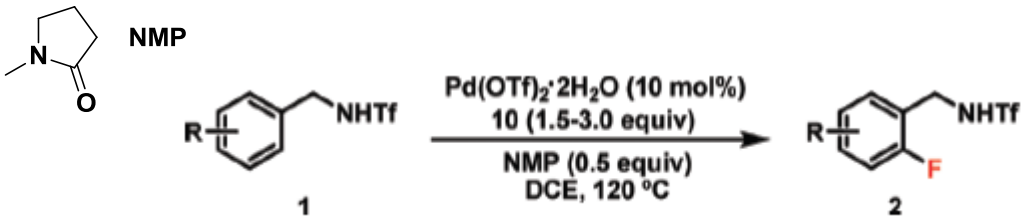
Scheme 1. One-Pot Synthesis of β-Lactams[a]



20 **20a** **20b**, 68%

[a] Reaction conditions: (1) 0.5 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, DCE, 100 °C, N_2, 10 h. (2) 4 equiv of CsF, 0.18 equiv of benzyltriethyl ammonium chloride, 100 °C, 12 h.

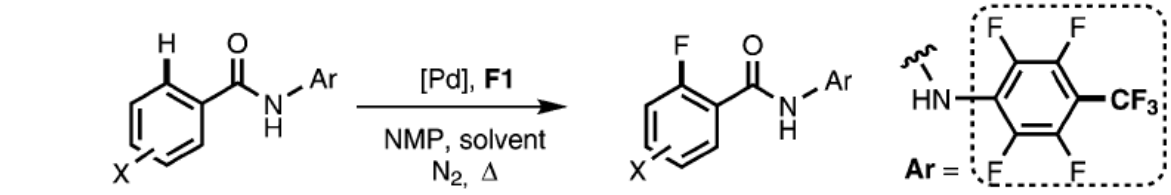
4-3. C-F Bond formation

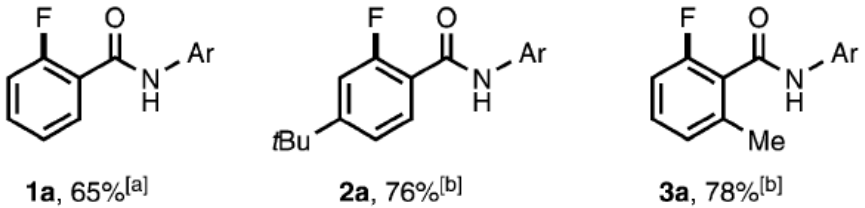


Finally, the detailed role of NMP remains to be elucidated. Investigations have led Vigalok to propose that oxidation of L_2PdArI by the F^+ source via an S_N2-type mechanism gives a cationic pentacoordinated $L_2Pd(IV)ArIF$ complex.[8]

J. AM. CHEM. SOC. ■ VOL. 131, NO. 22, 2009
10.1021/ja901352k

17 examples, 41-88% yield



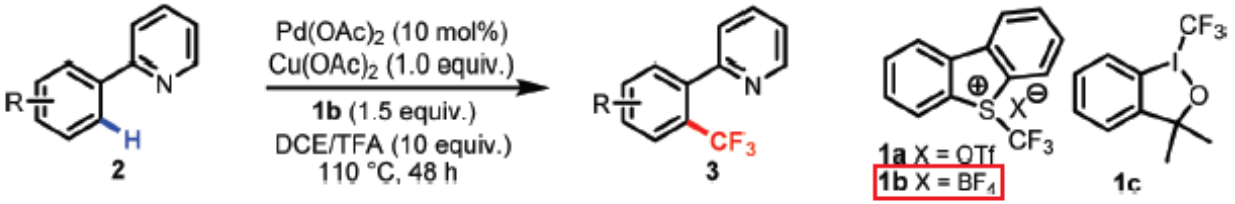


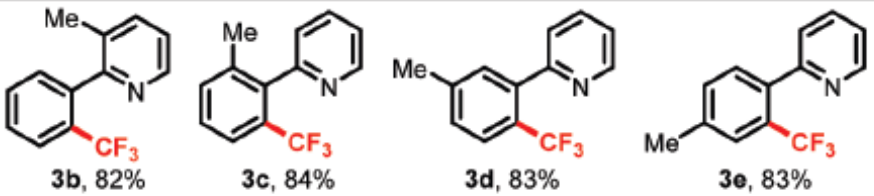
20 examples in total, 36-88% yield

Scheme 4. Monofluorination of benzamides. Unless otherwise specified the reaction conditions used were: 0.1 mmol of substrate, 10 mol% of $[Pd(OTf)_2(MeCN)_4]$, 20 mol% of NMP, 1.5 equiv of *N*-fluoro-2,4,6-trimethylpyridinium triflate (**F1**), 2 mL of MeCN, 120 °C, N_2, 24 h. The yield is of the isolated products. [a] The reaction was carried out for 8–12 h. [b] The reaction was carried out for 2–3 h.

Angew. Chem. Int. Ed. **2011**, *50*, 9081–9084
DOI: 10.1002/anie.201102985

4-4. C-CF_3 Bond formation

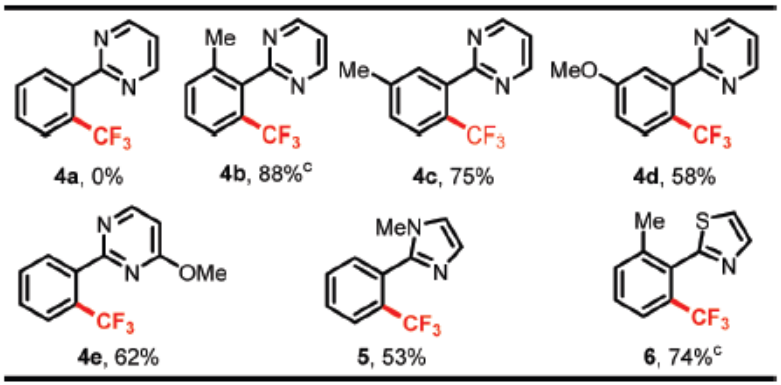




13 examples, 33-88% yield

[a] Unless otherwise noted, the reaction conditions were as follows: substrate (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), $Cu(OAc)_2$ (0.2 mmol, 1.0 equiv), **1b** (0.3 mmol, 1.5 equiv), TFA (2.0 mmol, 10 equiv), DCE (1 mL), 110 °C, 48 h. [b] Isolated yield. [c] $Pd(OAc)_2$ (15 mol %) was used. [d] $Pd(OAc)_2$ (20 mol %) was used.

Table 3. C−H Trifluoromethylation Using Diverse Heterocyclic Directing Groups[a,b]

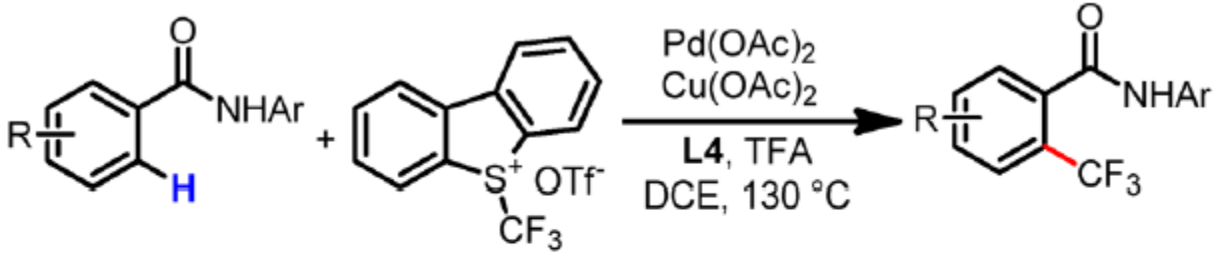


J. AM. CHEM. SOC. 2010, *132*, 3648–3649

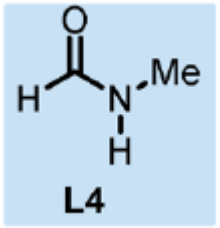
10.1021/ja909522s

4-4. C-CF_3 Bond formation

Table 2. Pd-Catalyzed Ortho Trifluoromethylation[a,b]

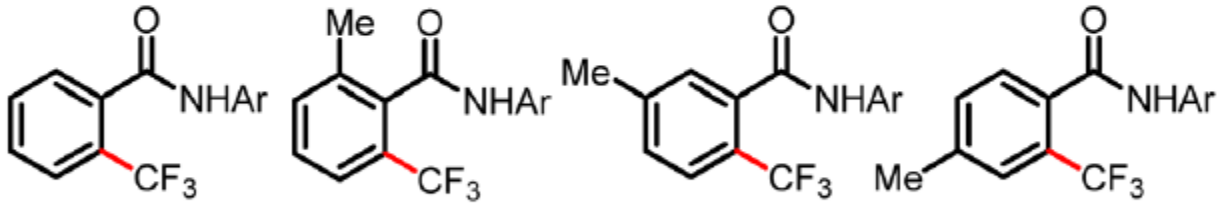


1a-1s, Ar = $(4\text{-}CF_3)C_6F_4$ **2a** **3a-3s**



L4

19 examples, 32-94% yield



3a, 79% **3b**, 84% **3c**, 94% **3d**, 53%

[a]Conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (0.2 mmol), TFA (1 mmol), **L4** (1.5 mmol), DCE (3 mL), 130 °C, 24 h. [b]Isolated yields are shown. [c]**2a** (0.2 mmol) for 48 h.

dx.doi.org/10.1021/ja305259n | *J. Am. Chem. Soc.* 2012, 134, 11948−11951

5. Other

- 5-1. Ligand development

3 publications, one science. Very important, related to many JACS publications.

- 5-2. Cyclization reaction: 5 publications.
- 5-3. C-B Bond and C-P Bond (not C-H) Formation

1 publication for each

- 5-3. Mechanism related: 6 publications.

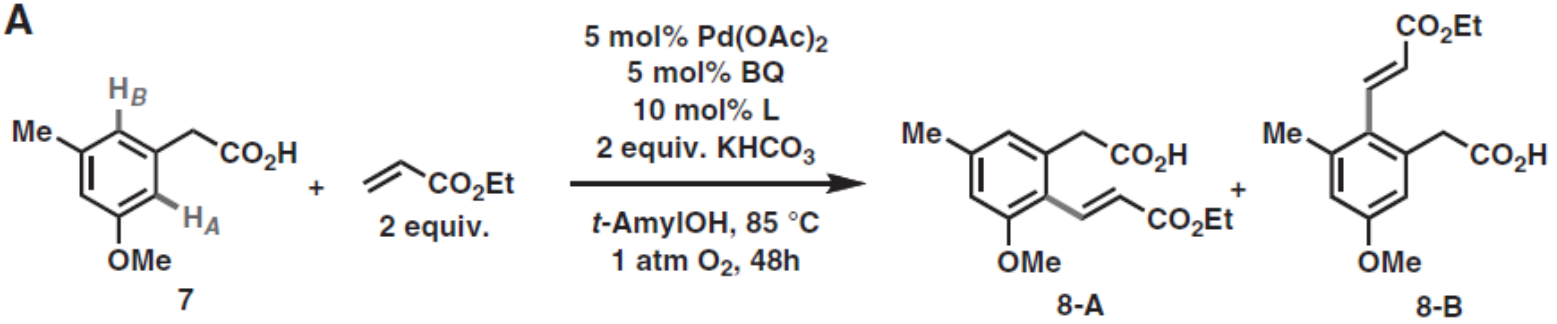
2 computational, 2 kinetic, 1 Pd complex, 1 model study.

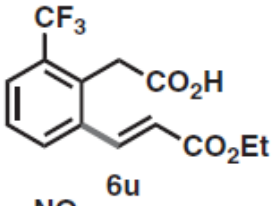
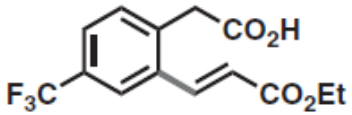
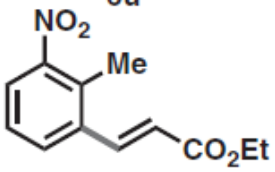
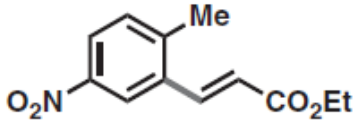
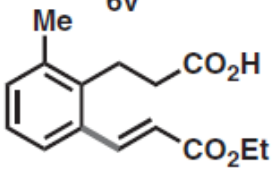
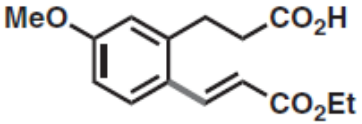
- 5-4. Application: 2 publications.
- 5-5. Other works: 3-4 publications.

Science **327**, 315 (2010);
DOI: 10.1126/science.1182512

5-1. Ligand

A



Product	Ligand	Yield (%)*	Product	Ligand	Yield (%)*
 6u	---	12	 6w	---	13
	Boc-Val-OH	90		Boc-Ile-OH	85‡
 6v	---	0	 6x	---	0
	Boc-Val-OH	50†		Boc-Val-OH	57§
 18a	---	8	 18b	---	22
	Boc-Val-OH	60		PG_1-Leu-OH‖	75¶

*Isolated Yield. †2-Nitrophenylacetic acid was used as substrate; the product was completely decarboxylated under the reaction conditions: 10 mol% $Pd(OAc)_2$, 10 mol% BQ, 20 mol% Boc-Val-OH. ‡Mono:Di = 2:1. §4-Nitrophenylacetic acid was used as substrate; decarboxylated:non-decarboxylated = 2:1. ‖PG_1 = (–)-Menthyl(O_2C). ¶Mono:Di = 3:1.

Science **327**, 315 (2010);
DOI: 10.1126/science.1182512

5-1. Ligand

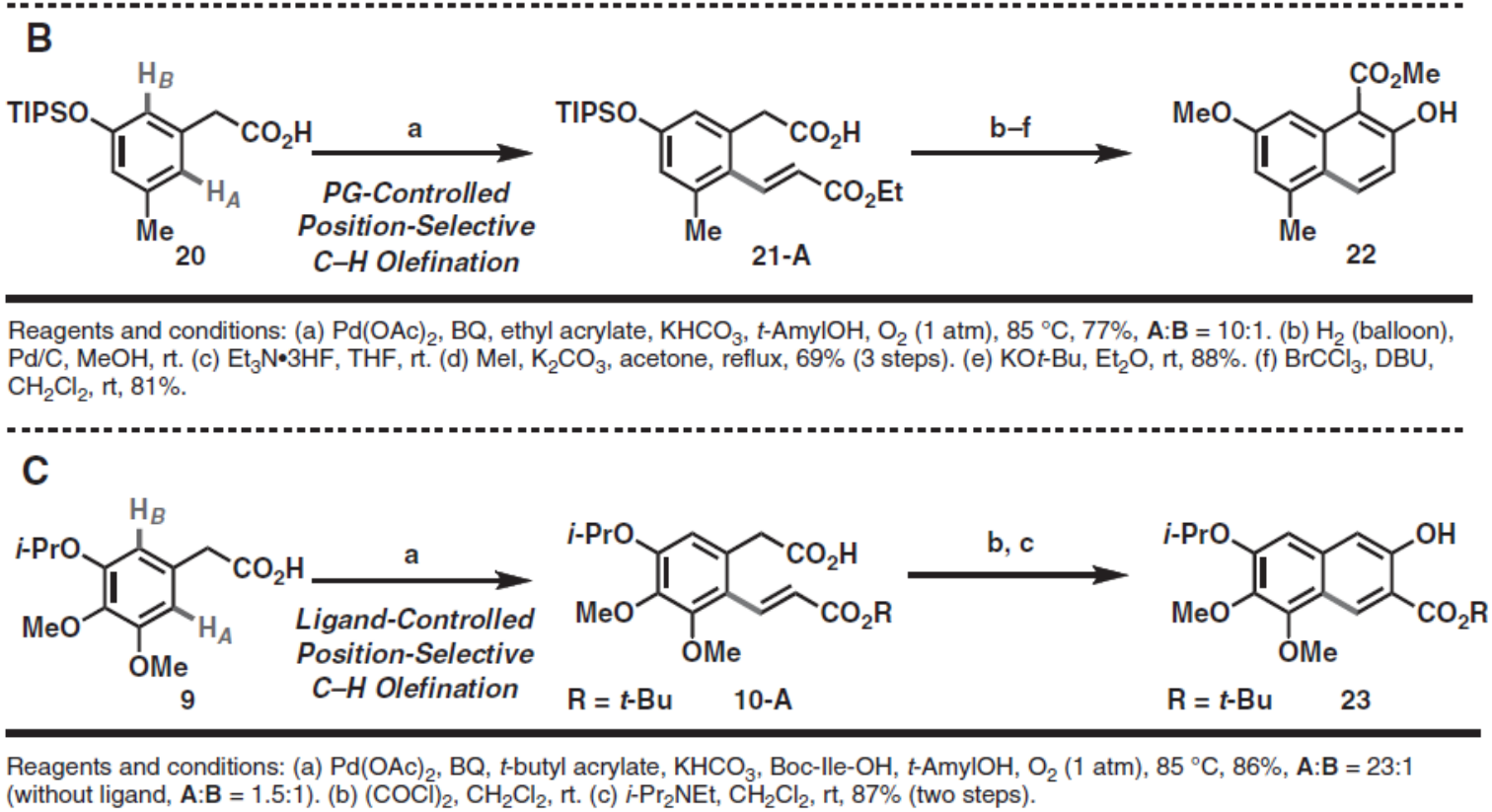
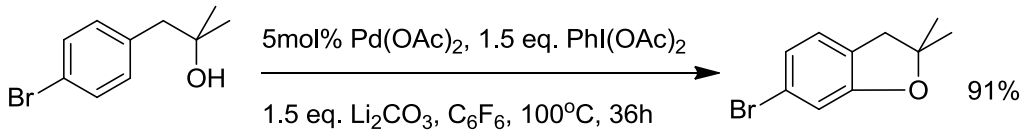
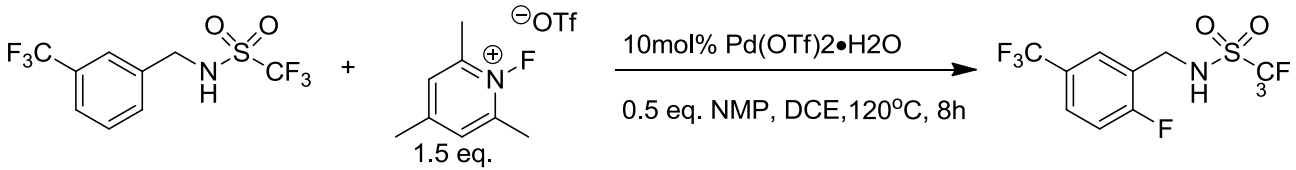


Fig. 4. (**A**) Synthesis of 7,8-dimethoxytetalin-2-one. (**B**) Synthesis of the naphthoic acid component of neocarzinostatin (**1**). (**C**) Synthesis of the naphthoic acid component of kedarcidin (**3**).

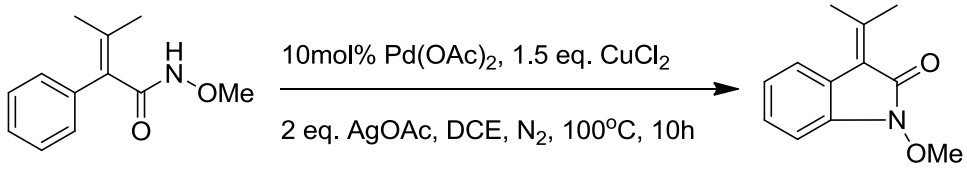
Thanks!

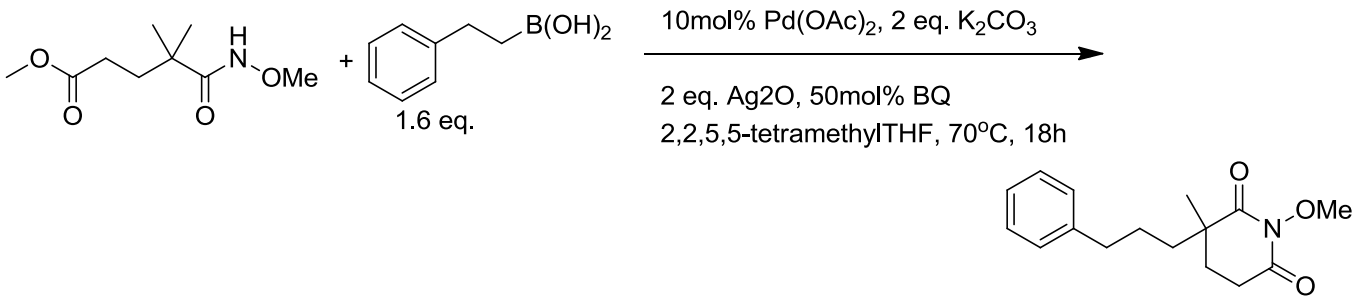
Q1. Predict the Product



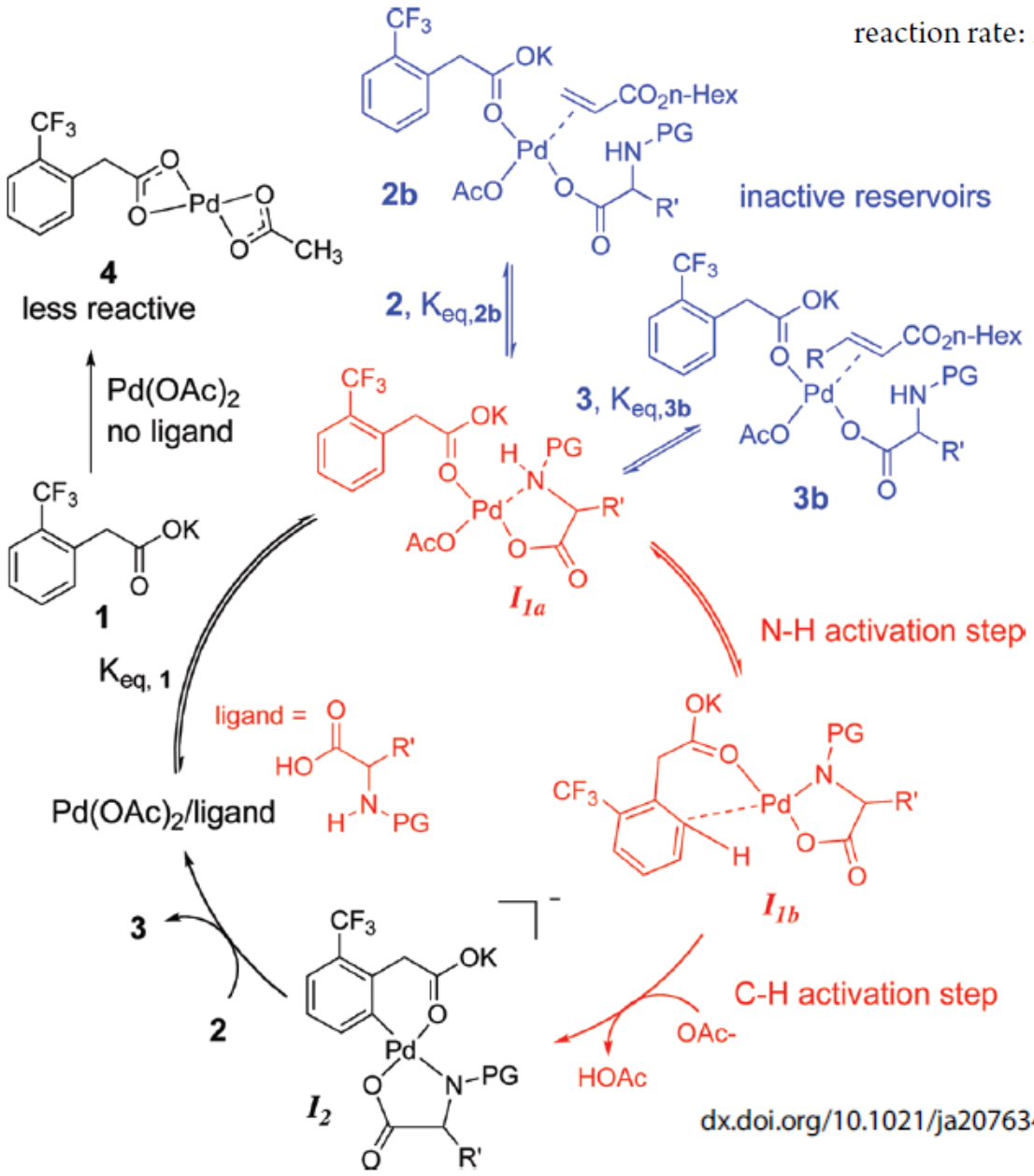


Q2. Predict the Product





Scheme 4. Proposed Reaction Mechanism Highlighting Dual Rate-Determining Steps and Off-Cycle Catalyst Reservoirs



Kinetic

dx.doi.org/10.1021/ja207634t | *J. Am. Chem. Soc.* 2012, 134, 4600–4606