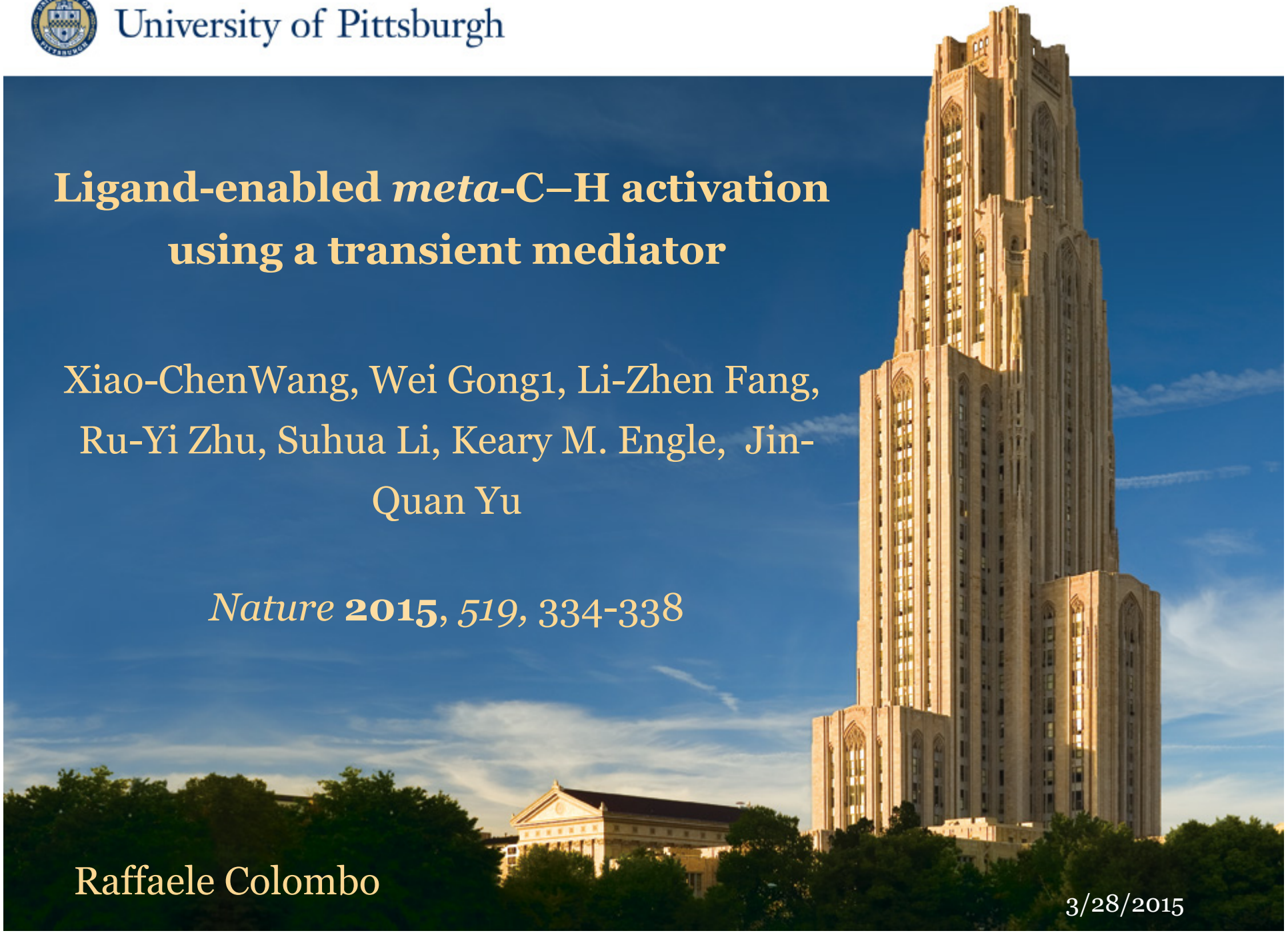
University of Pittsburgh

Ligand-enabled *meta*-C–H activation using a transient mediator

Xiao-ChenWang, Wei Gong1, Li-Zhen Fang, Ru-Yi Zhu, Suhua Li, Keary M. Engle, Jin-Quan Yu

Nature **2015**, *519*, 334-338



Raffaele Colombo

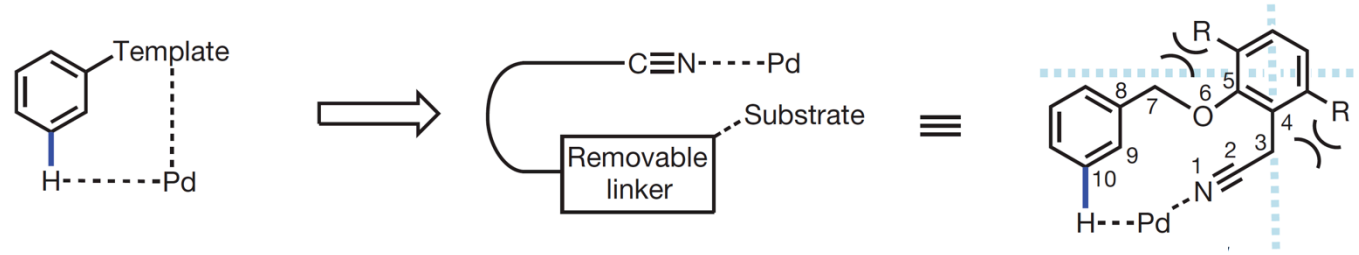
3/28/2015

meta C-H activation

- C–H activation methods are **limited to proximal C–H bonds**, which are spatially and geometrically accessible from the directing functional group
- **Site selectivity** in C–H functionalization reactions **is a significant challenge**, especially when the target C–H bond is distant from existing functional groups
- In 2012, Yu and coworkers reported a set of flexible, **U-shaped templates to direct meta-C–H activation**

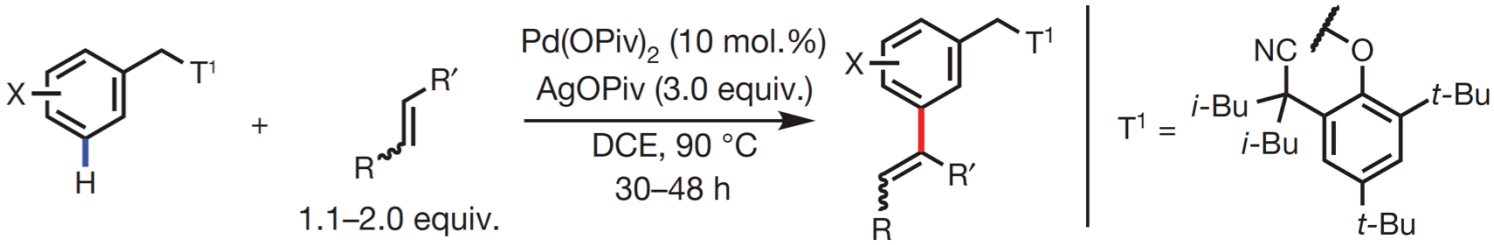
- The development of **more general and efficient approaches** to achieve meta-C–H activation remains an important goal!

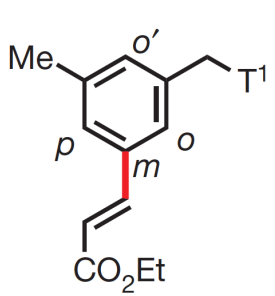
Yu's Template approach



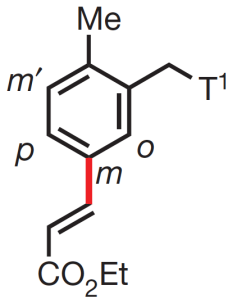
Cyclophane-like pre-transition state
≥12-membered ring

12-membered ring

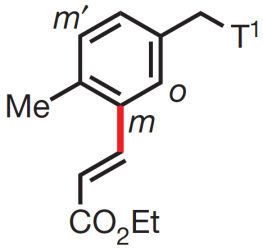




17b$_1$, 86%
m:(*p*+*o*+*o*′)= 94:6



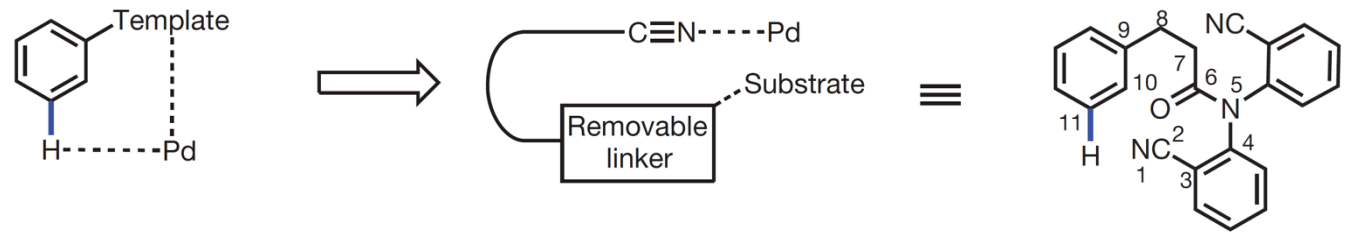
17h, 89%
m:(*p*+*o*+*m*′) = 91:9



17k$_{mono}$, 54%
m:*o* = 96:4
17k$_{di}$, 26%
(*m*,*m*′):others = 88:12

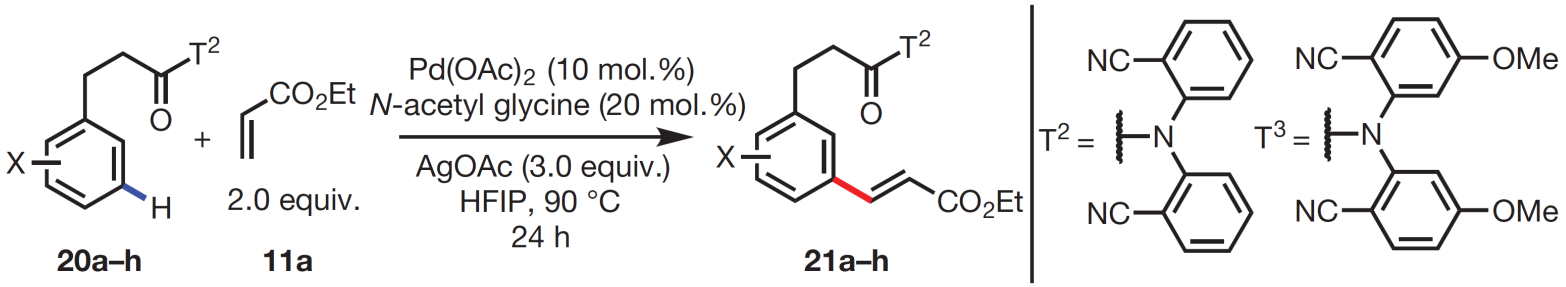
Yu et al.
Nature **2012**, *486*, 518

Yu's Template approach

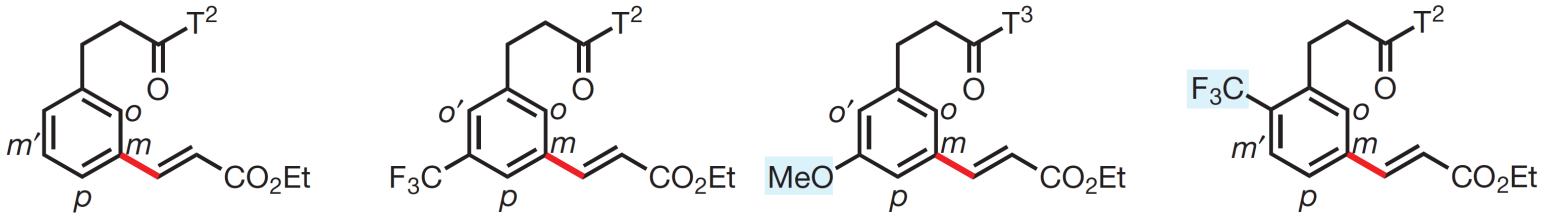


Cyclophane-like pre-transition state
≥12-membered ring

11-membered ring



20a–h **11a** **21a–h**



21a$_{mono}$, 37%
m:*p*:*o* = 95:3:2
21a$_{di}$, 42%
(*m*,*m*′):others = 88:12

21b, 82%
m:(*p*+*o*+*o*′) = 95:5

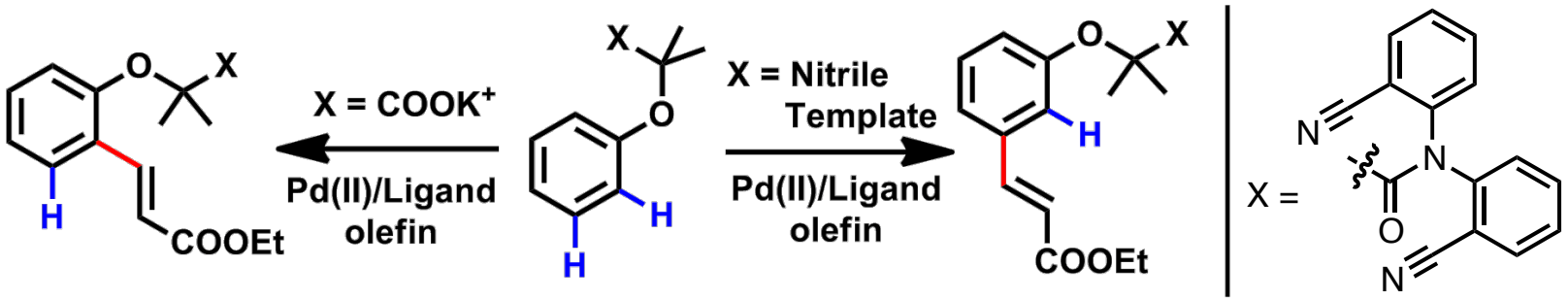
21c, 67%
m:(*p*+*o*+*o*′) = 86:14

21d, 87%
m:(*p*+*o*+*m*′) = 96:4

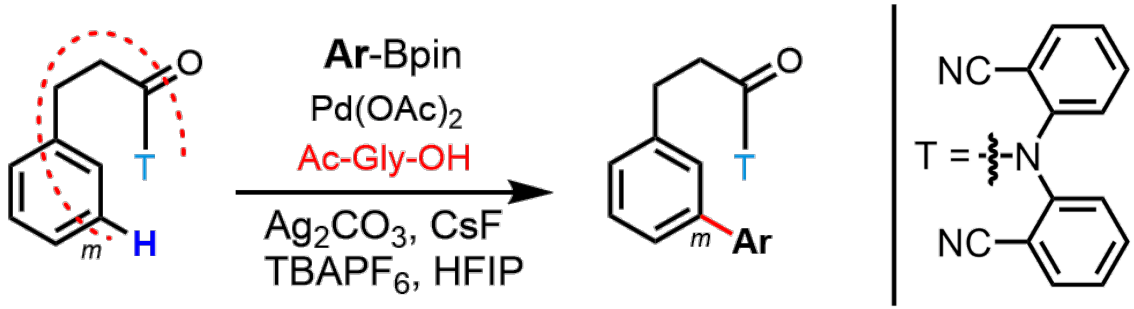
Electronic biases overridden

Yu et al. *Nature* **2012**, *486*, 518

Yu's Template approach

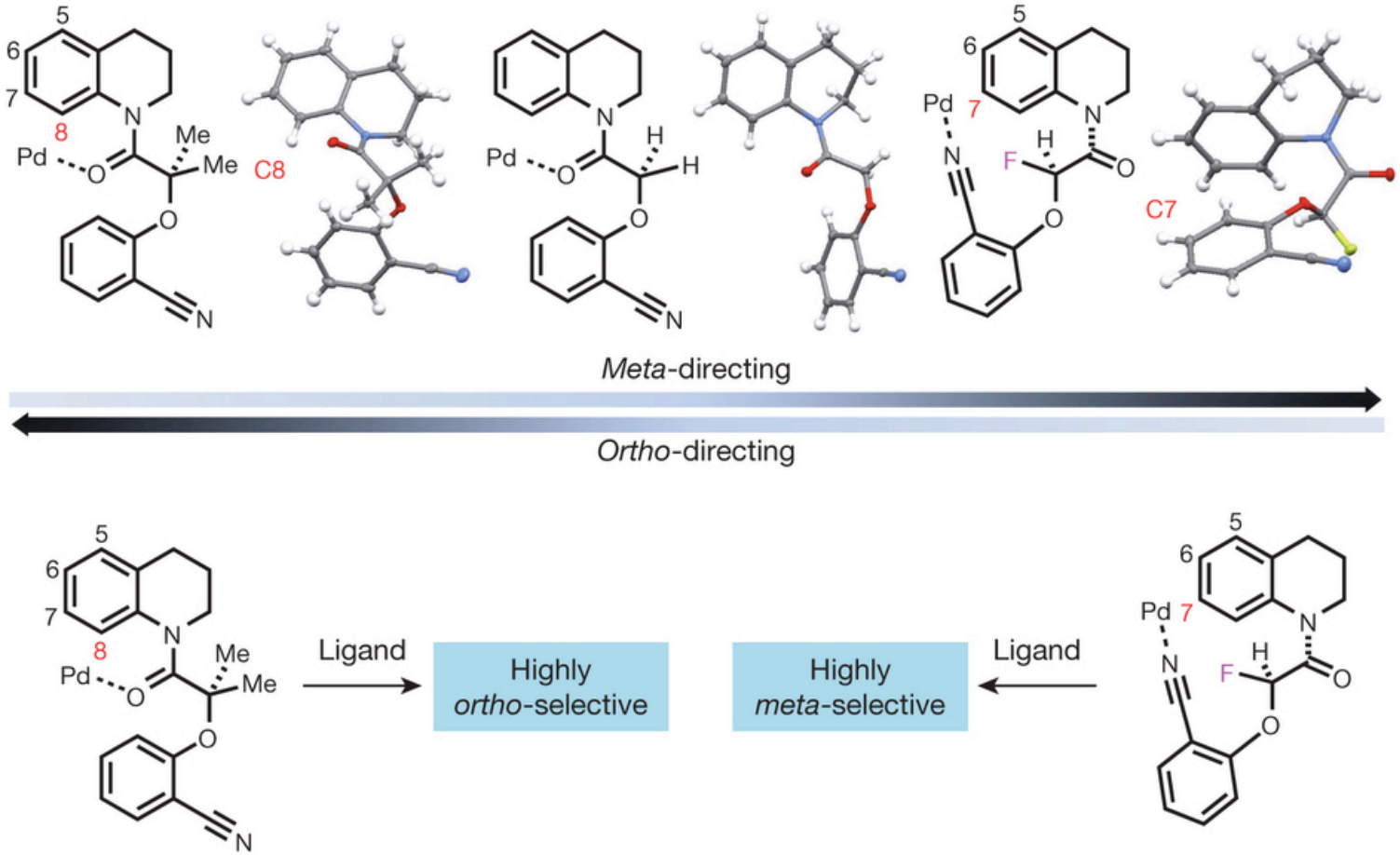


Yu et al. *J. Am. Chem. Soc.* **2013**, *135*, 7567



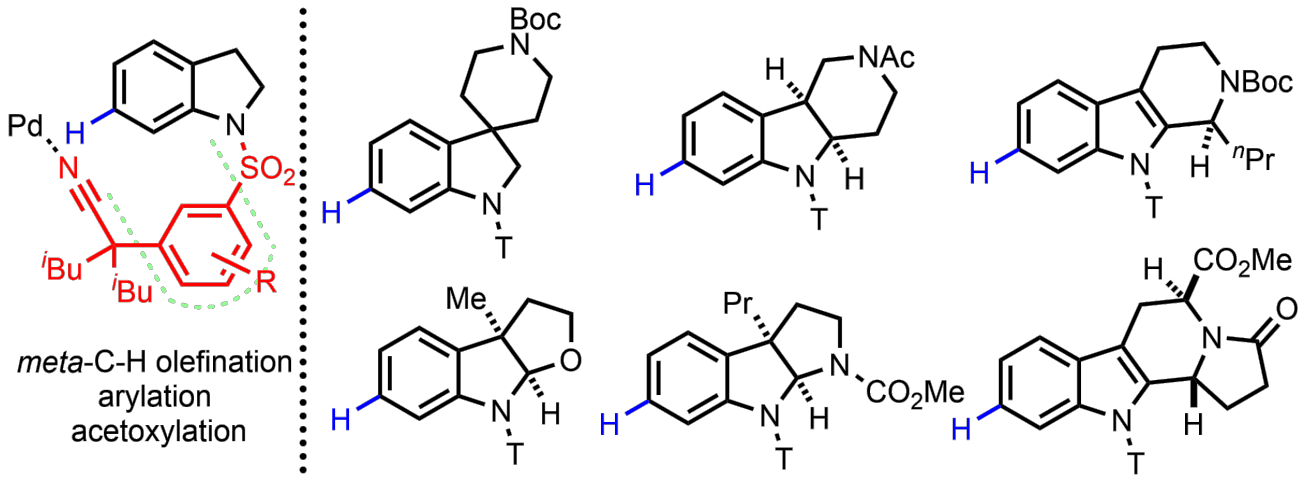
Yu et al. *J. Am. Chem. Soc.* **2013**, *135*, 18056

Yu's Template approach

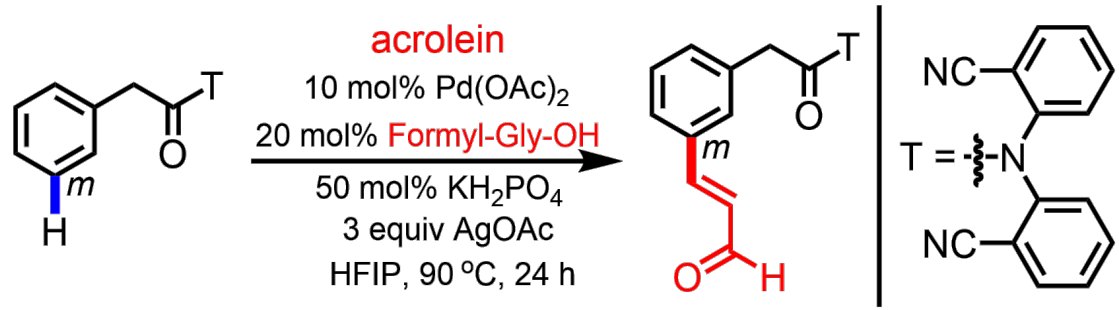


Yu et al. *Nature* **2014**, *507*, 215

Yu's Template approach

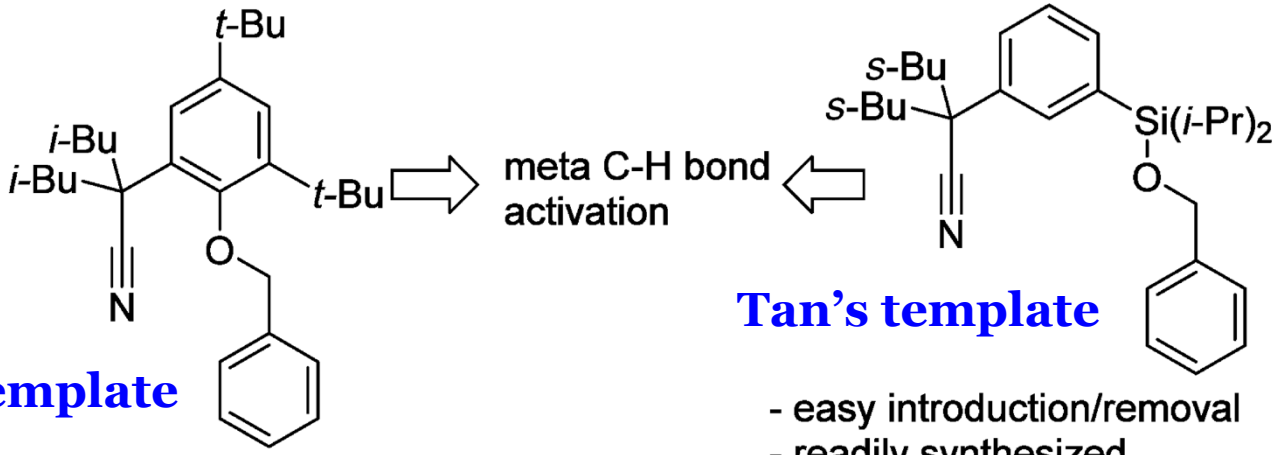


Yu et al. *J. Am. Chem. Soc.* **2014**, *136*, 10807



Yu et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 888

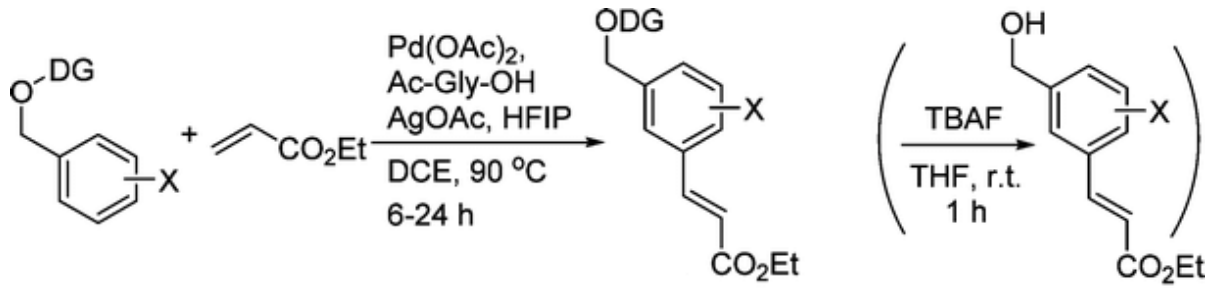
Tan's Template approach

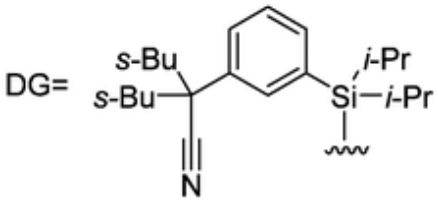


Yu's template

Tan's template

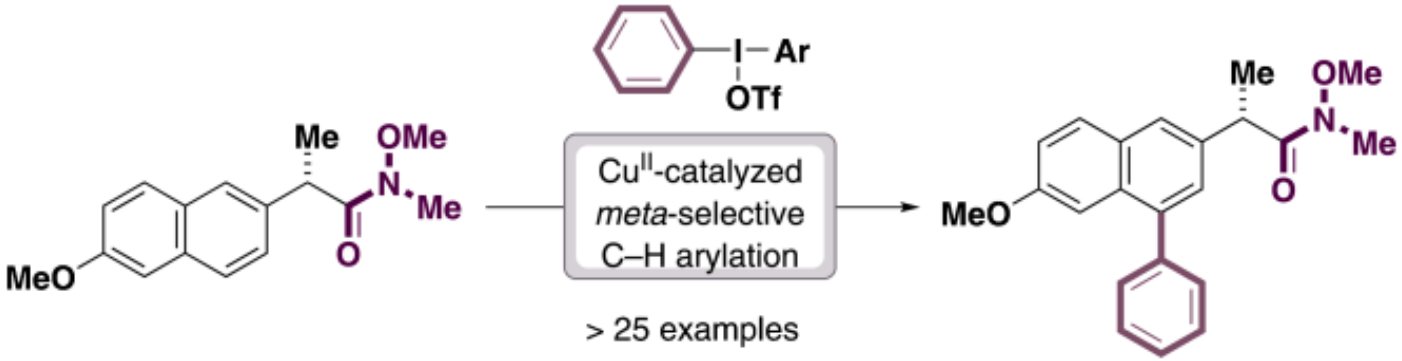
- easy introduction/removal
- readily synthesized
- reusable

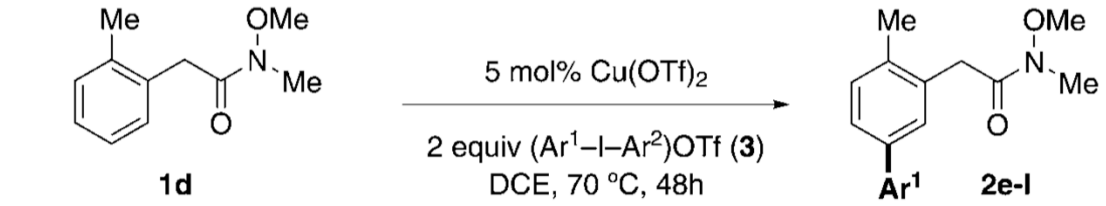


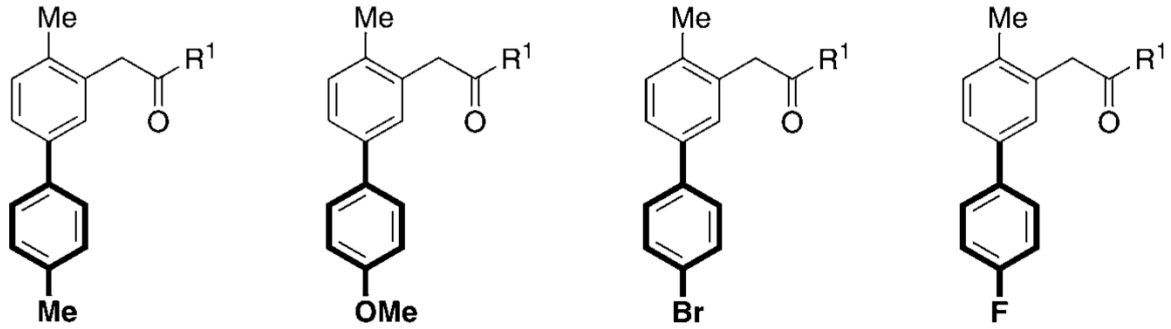


K. L. Tan et al. *J. Am. Chem. Soc.* **2013**, *135*, 18778

Gaunt Template approach



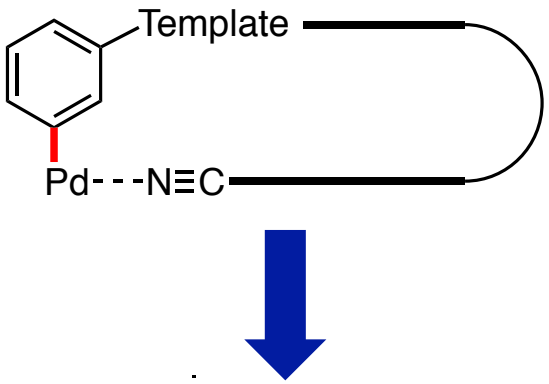




84 %, **2 e**[b] 52 %, **2 f**[b] 70 %, **2 g**[b] 78 %, **2 h**[c]

M. J. Gaunt et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 463

This work

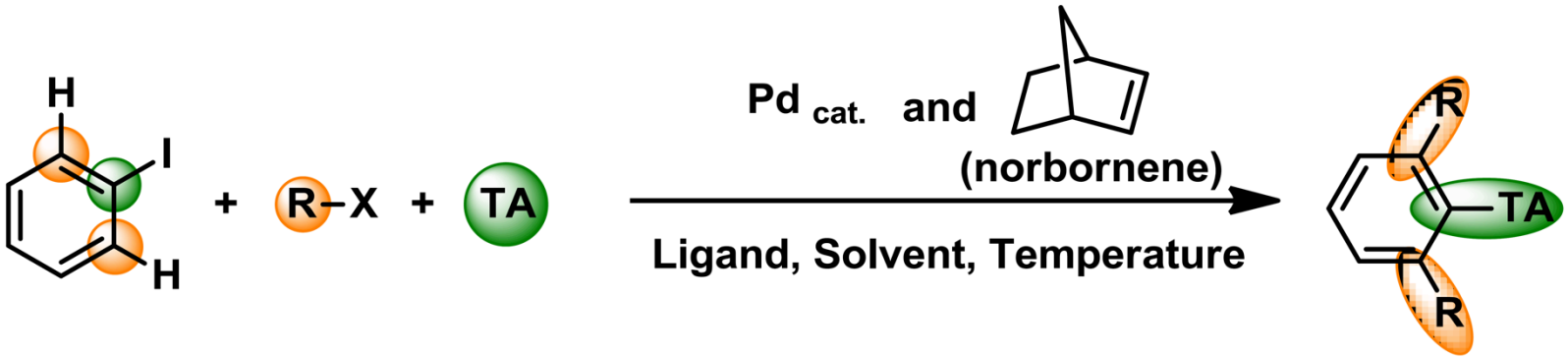


… inspired by Catellani reactions

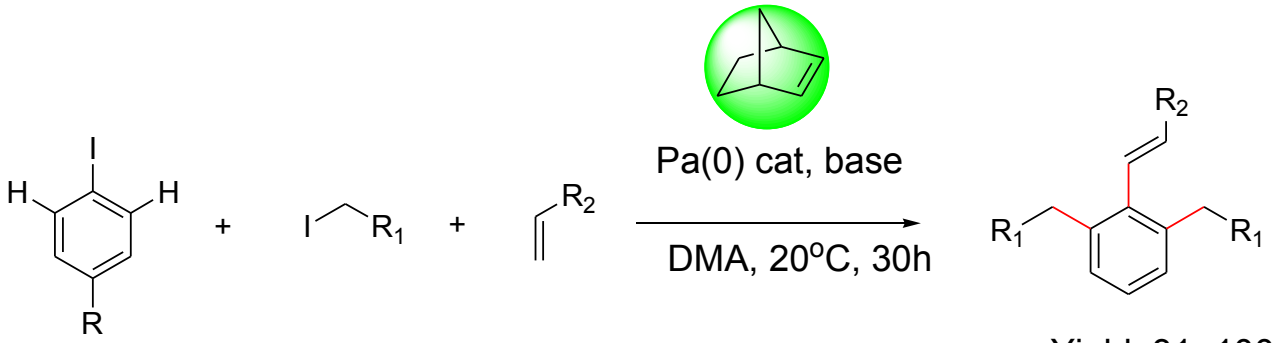
"We expect that this approach will enable many previously reported ortho-C–H activation reactions to be rendered highly meta-selective"

Yu *et al. Nature* **2015**, *519*, 334-338

Catellani Reaction



R = Alkyl, Aryl
X = I, Br, Cl
TA: Terminating Agent = Aryl, Alkenyl, H, CN

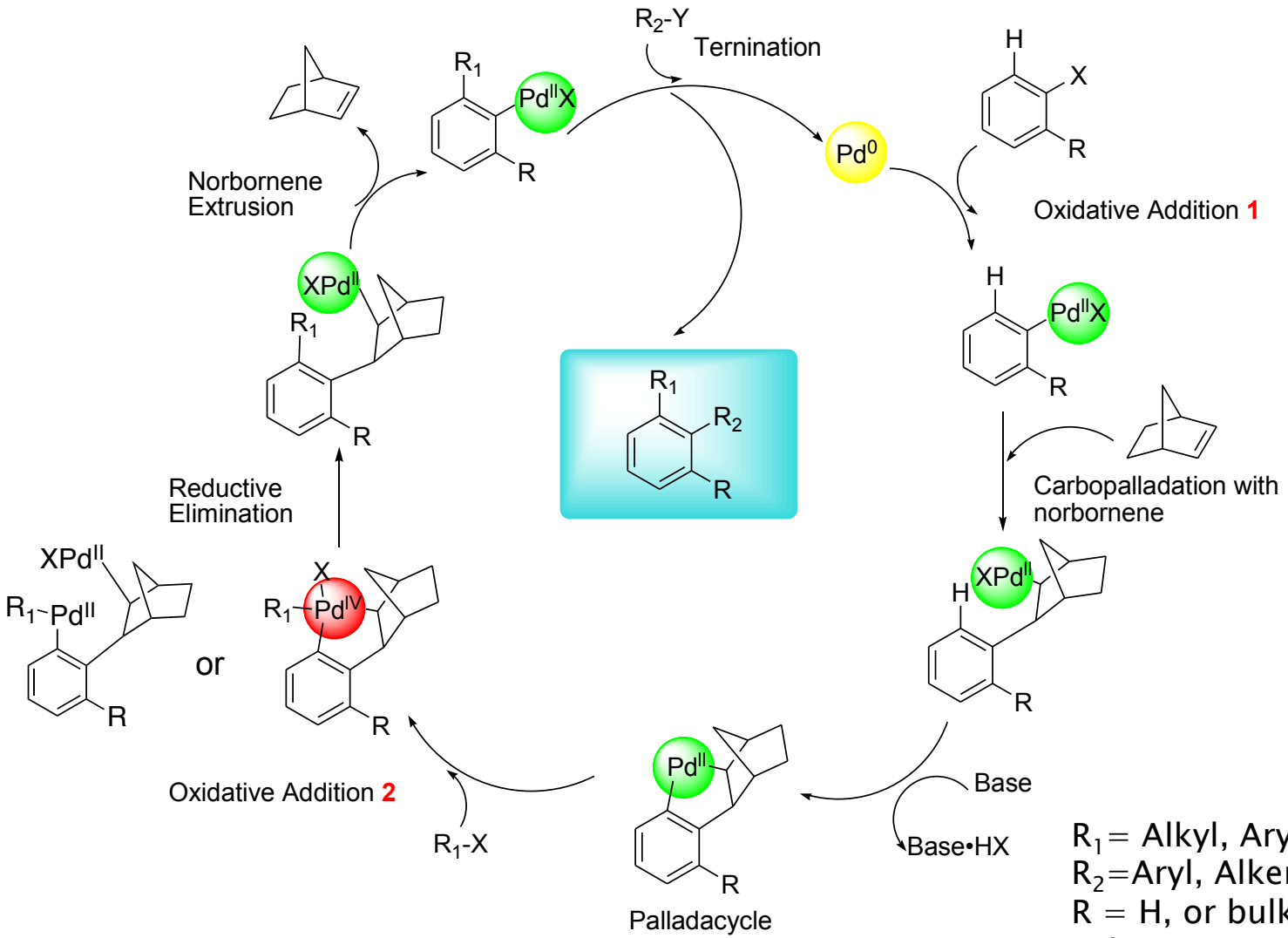


R=H, Me, CO_2Me
R1=n-Bu, $BnCH_2$,n-Oct
R2=CO_2Me, Ph, n-Hex

Yield: 31~100%
E type: 89~95%

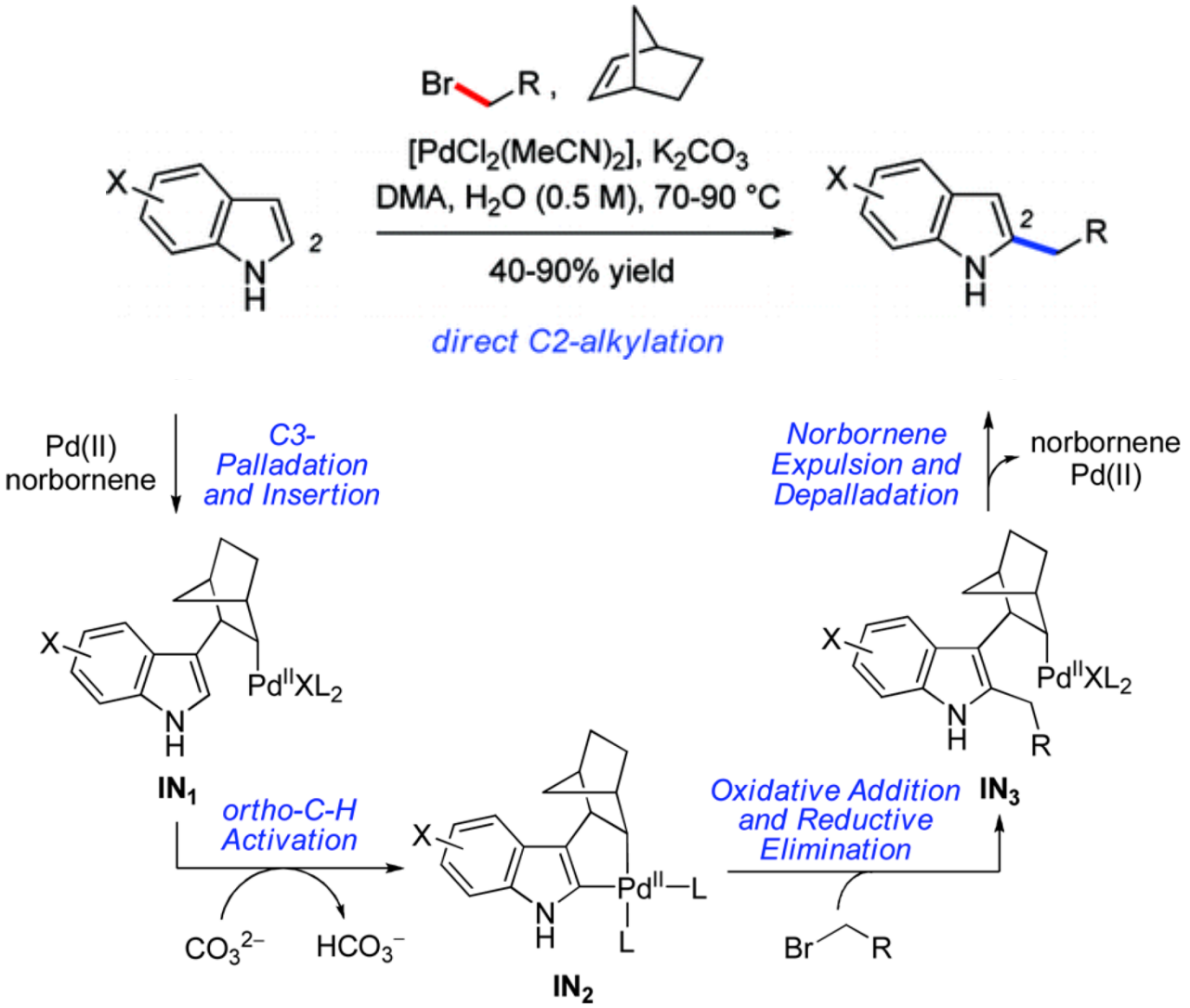
M. Catellani et al. *Angrew. Chem. Int. Ed.* **1997**, *36*, 119

Catellani Reaction



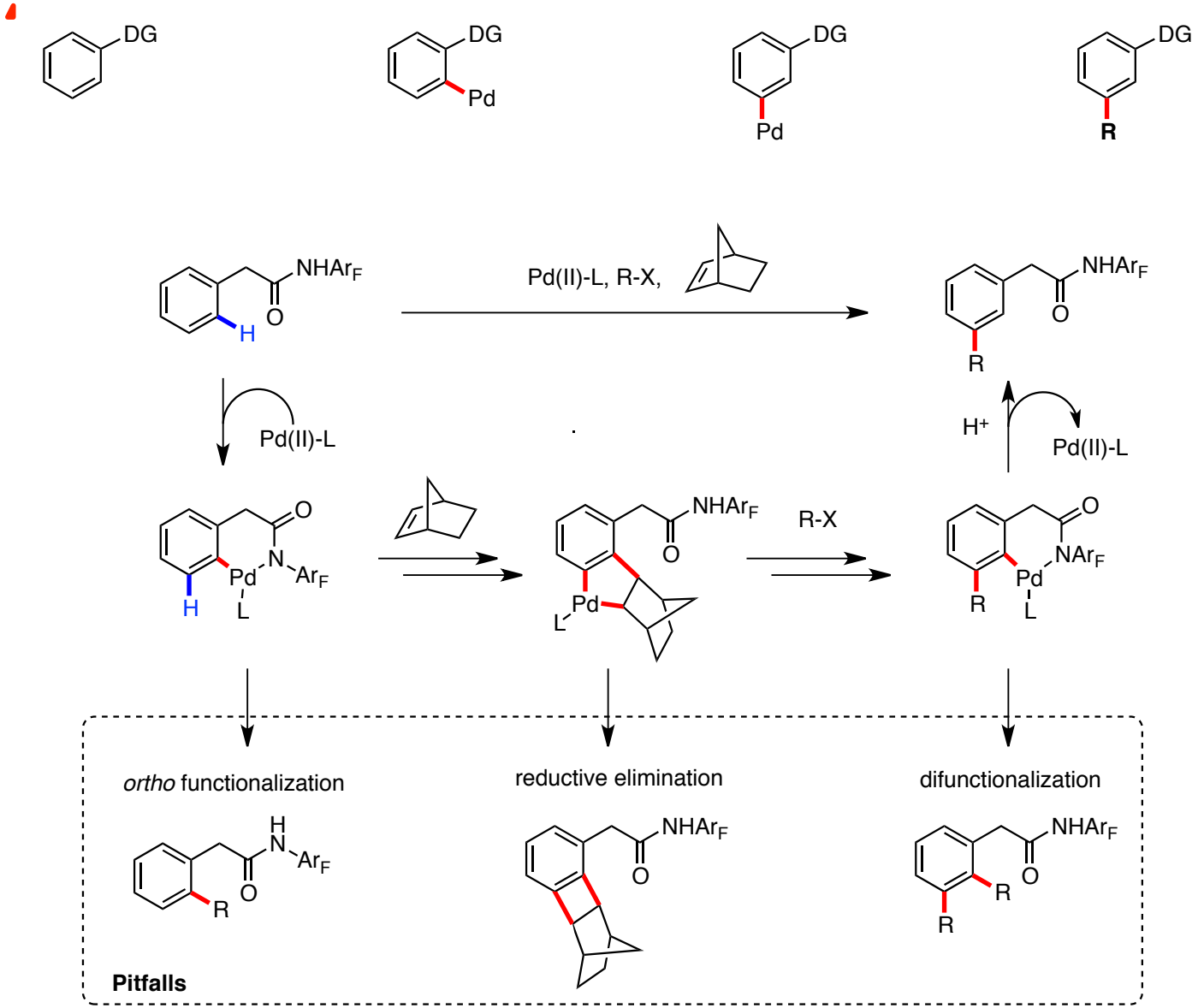
M. Catellani et al. *Angrew. Chem. Int. Ed.* **1997**, *36*, 119

Indole C-2 alkylation



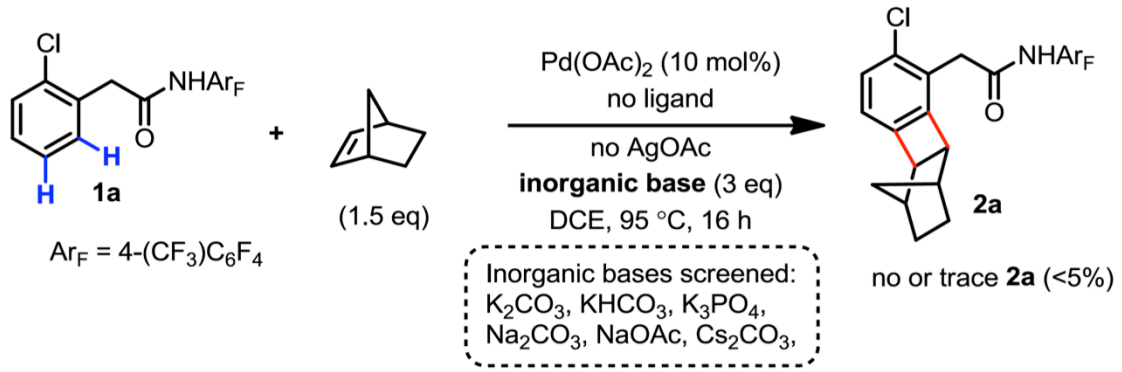
Bach *et al. J. Am. Chem. Soc.* **2011**, *133*, 12990

This work

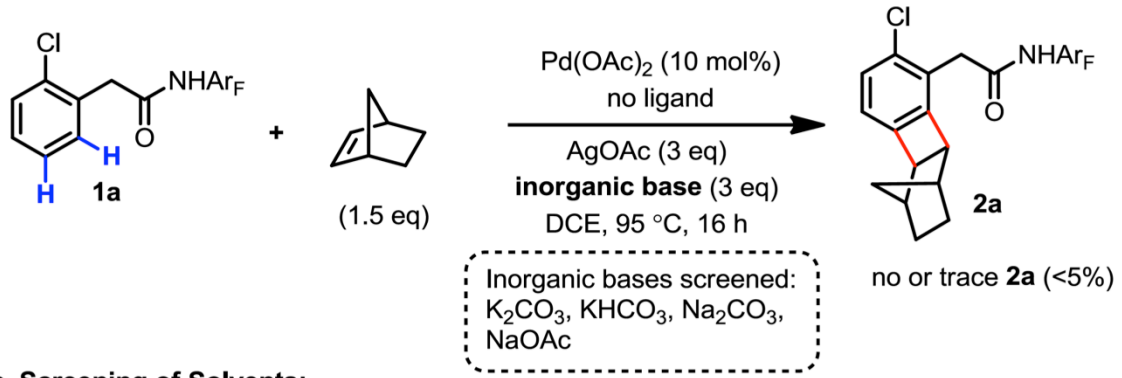

DG
DG
Pd
DG
Pd
DG
R
NHArF
O
H
Pd(II)-L, R-X,
NHArF
O
R
Pd(II)-L
H+
Pd(II)-L
O
N
ArF
Pd
H
L
NHArF
O
Pd
L
R-X
O
NArF
Pd
R
L
ortho functionalization
H
N
ArF
O
R
reductive elimination
NHArF
O
difunctionalization
NHArF
O
R
R
Pitfalls

Screening

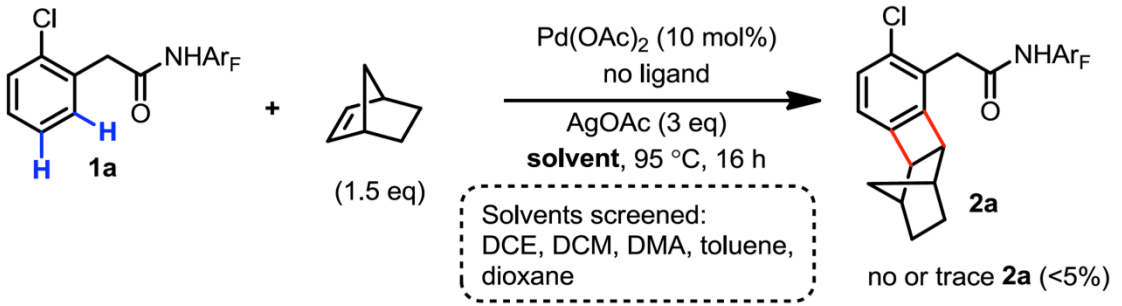
a. Screening of Inorganic Bases without AgOAc:



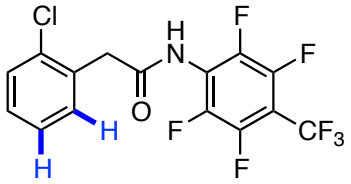
b. Screening of Inorganic Bases with AgOAc:



c. Screening of Solvents:

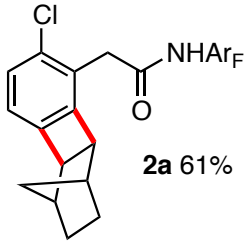


Screening



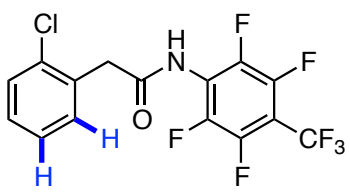
$Pd(OAc)_2$ (10 mol%)
Pyridine (20 mol%)

Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h



2a 61%

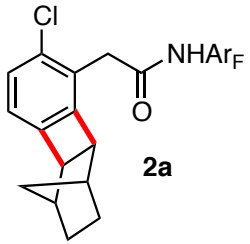
Screening



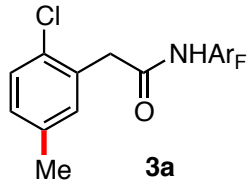
Me-I
(3 eq)

$Pd(OAc)_2$ (10 mol%)
Ligand (20 mol%)

Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h



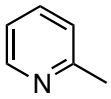
2a



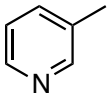
3a

No Ligand
No reaction

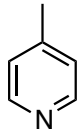
2a: 15%
3a: 15%



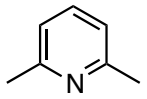
2a: 16%
3a: 29%



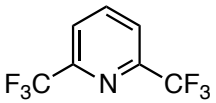
2a: 8%
3a: 13%



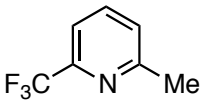
2a: 9%
3a: 17%



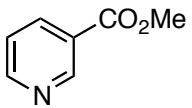
2a: 25%
3a: 37%



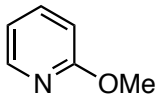
No reaction



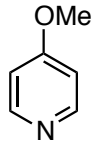
No reaction



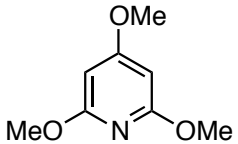
2a: 8%
3a: 9%



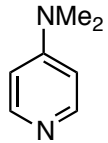
2a: 4%
3a: 12%



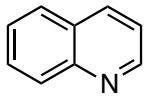
2a: 12%
3a: 15%



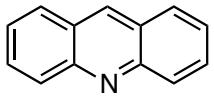
2a: 8%
3a: 23%



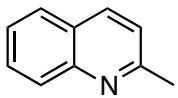
2a: 8%
3a: 32%



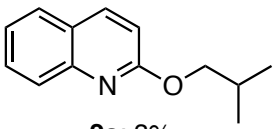
2a: 22%
3a: 30%



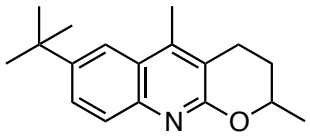
2a: 56%
3a: 28%



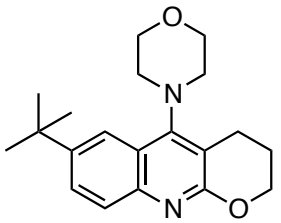
2a: 51%
3a: 28%



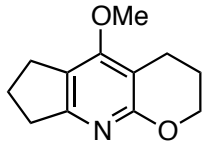
2a: 3%
3a: 13%



2a: 20%
3a: 80%

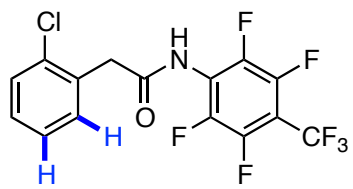


2a: 20%
3a: 80%



2a: 15%
3a: 85%
(80% isolated yield)

Screening

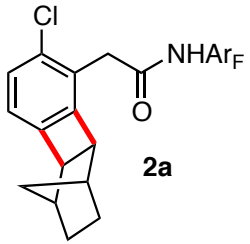


Me-I

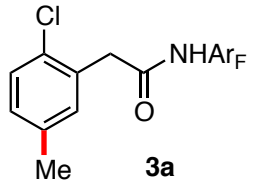
(3 eq)

$Pd(OAc)_2$ (10 mol%)
Ligand (20 mol%)

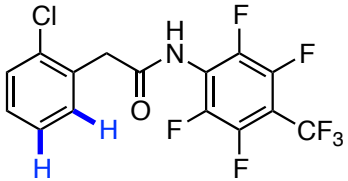
Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h

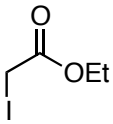


2a

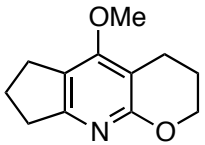


3a





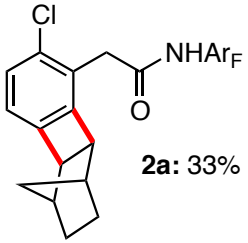
(3 eq.)



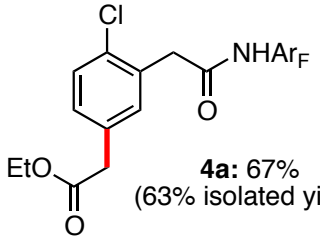
20 mol%

$Pd(OAc)_2$ (10 mol%)

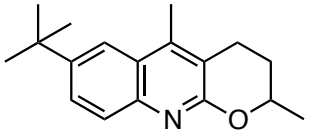
Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h



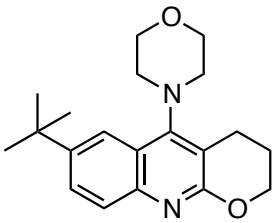
2a: 33%



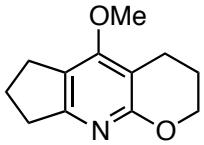
4a: 67%
(63% isolated yield)



2a: 20%
3a: 80%

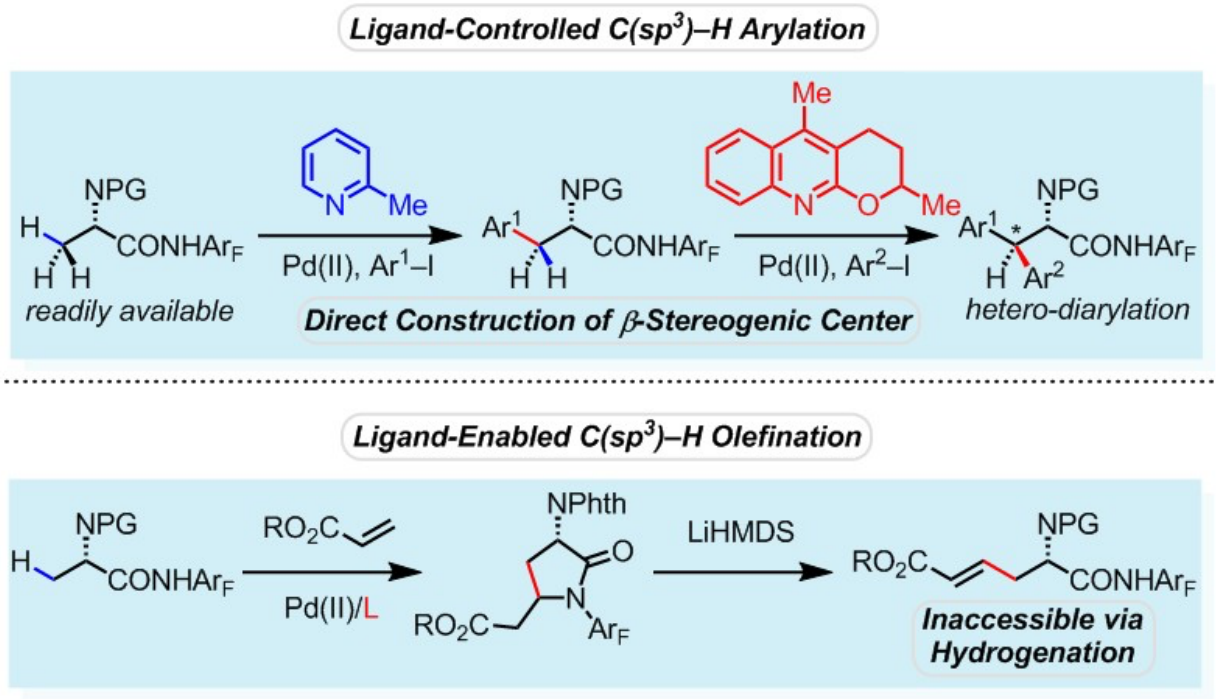


2a: 20%
3a: 80%

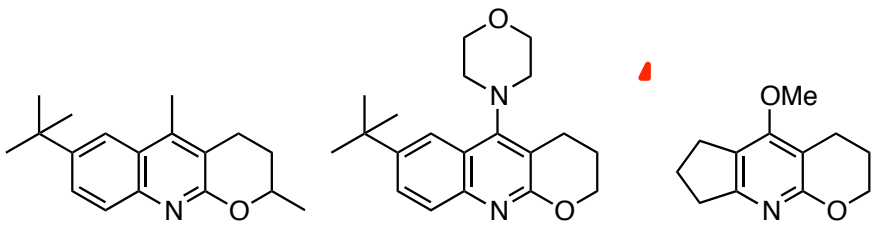


2a: 15%
3a: 85%
(80% isolated yield)

Screening



Yu et al. *Science* **2014**, *343*, 1216

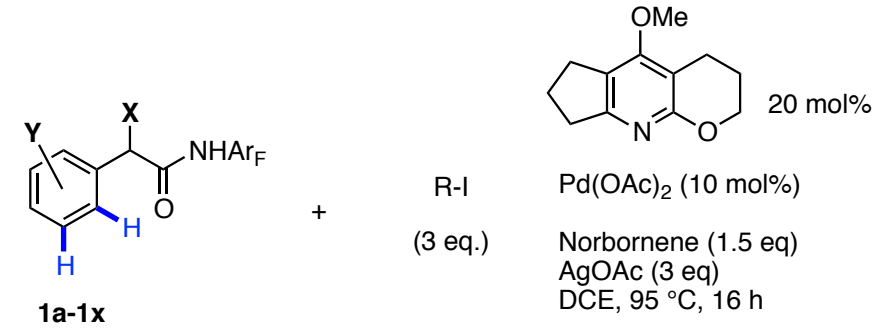


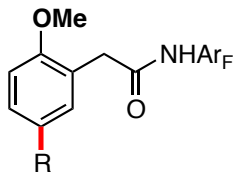
2a: 20%
3a: 80%

2a: 20%
3a: 80%

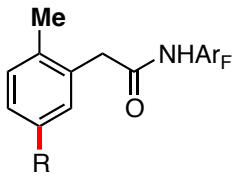
2a: 15%
3a: 85%
(80% isolated yield)

Reaction scope

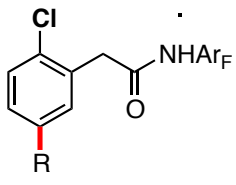




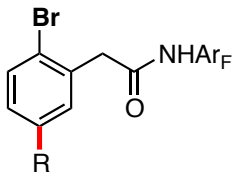
3a, 91%
4a, 73%



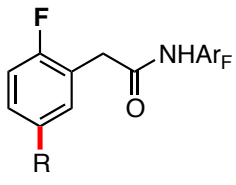
3b, 90%
4b, 84%



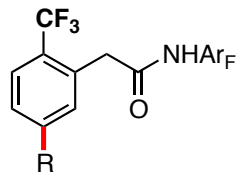
3c, 80%
4c, 63%



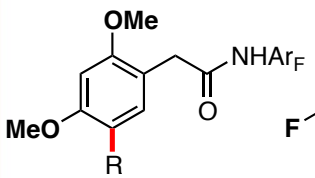
3d, 88%
4d, 81%



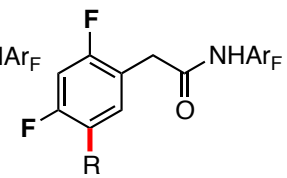
3e, 86%
4e, 68%



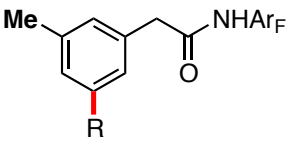
3f, 72%
4f, 75%



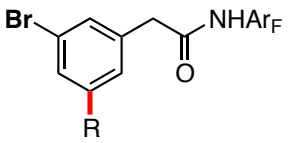
3f, 87%
4f, 82%



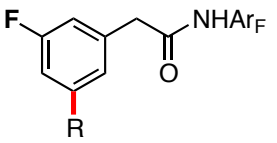
3g, 87%
4g, 82%



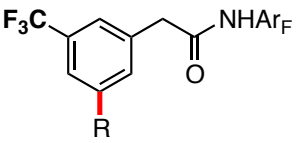
3h, 84%
4h, 32%



3i, 56%
4i, 47%

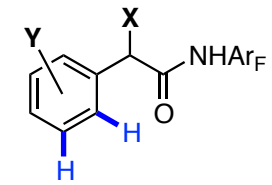


3l, 90%
4l, 86%



3m, 72%
4m, 51%

Reaction scope



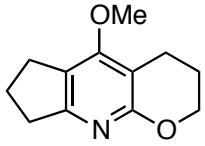
1a-1x

Ar_F = 4-(CF_3)C_6F_4

+

R-I

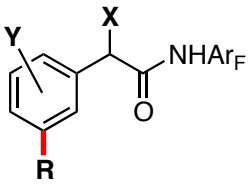
(3 eq.)



20 mol%

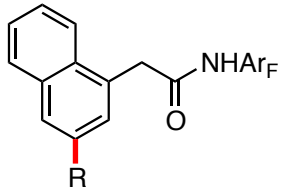
$Pd(OAc)_2$ (10 mol%)

Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h

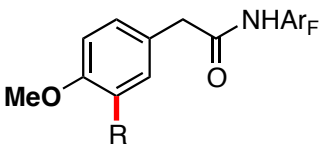


3a-3x (when R = Me)

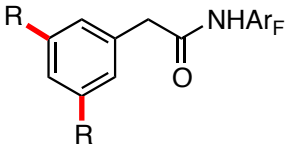
4a-4x (when R = CH_2CO_2Et)



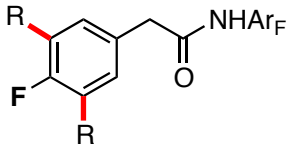
3n, 87%
4n, 82%



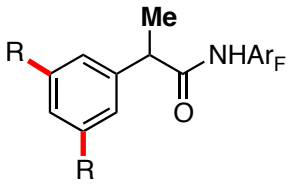
3o, <10%
4o, 68%



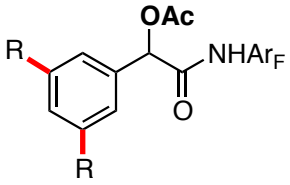
3p, 80%
4p, <10%



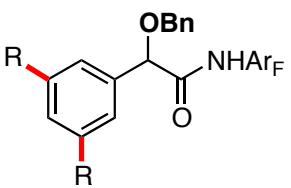
3q, 85%
4q, 59%



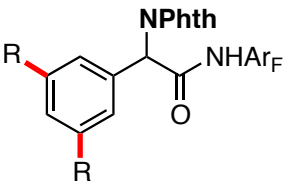
3r, 72%
4r, <10%



3s, 75%
4s, <10%

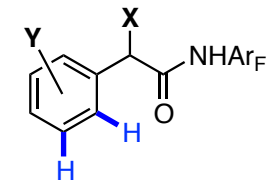


3t, 72%
4t, 52%



3u, 82%
4u, <10%

Reaction scope



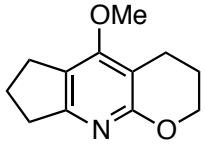
1a-1x

Ar_F = 4-(CF_3)C_6F_4

+

R-I

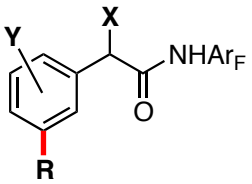
(3 eq.)



20 mol%

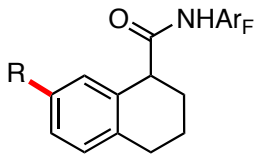
$Pd(OAc)_2$ (10 mol%)

Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h

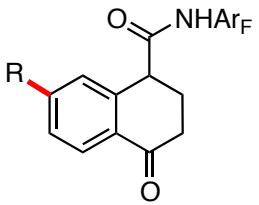


3a-3x (when R = Me)

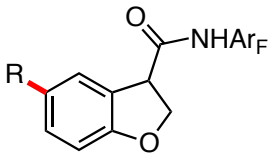
4a-4x (when R = CH_2CO_2Et



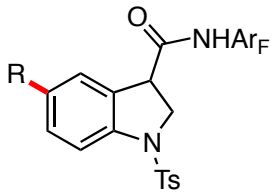
3v, 71%
4v, 43%



3w, 71%
4w, 69%

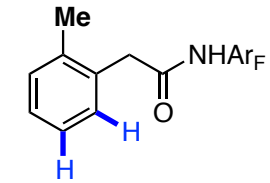


3x, 81%
4x, <10%



3y, 73%
4y, <10%

Reaction scope



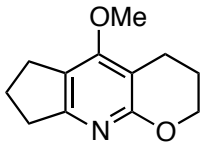
1a-1x

Ar_F = 4-(CF_3)C_6F_4

\+

Alkyl-I

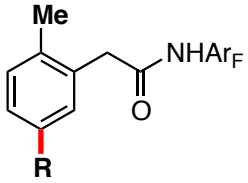
(6 eq.)

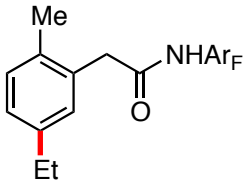


20 mol%

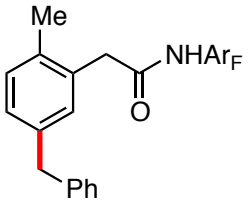
$Pd(OAc)_2$ (10 mol%)

Norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h

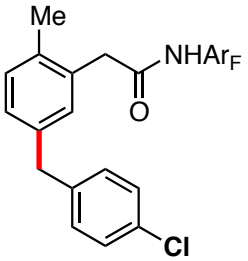




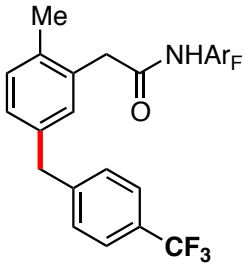
21%



66%



65%



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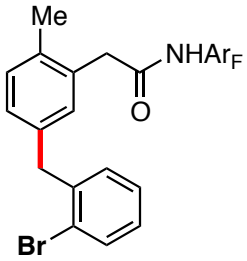

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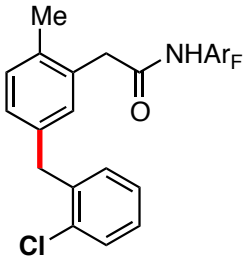

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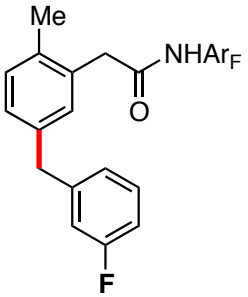

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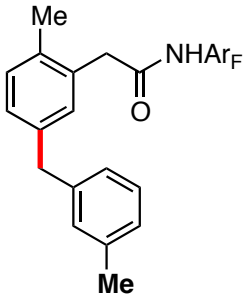

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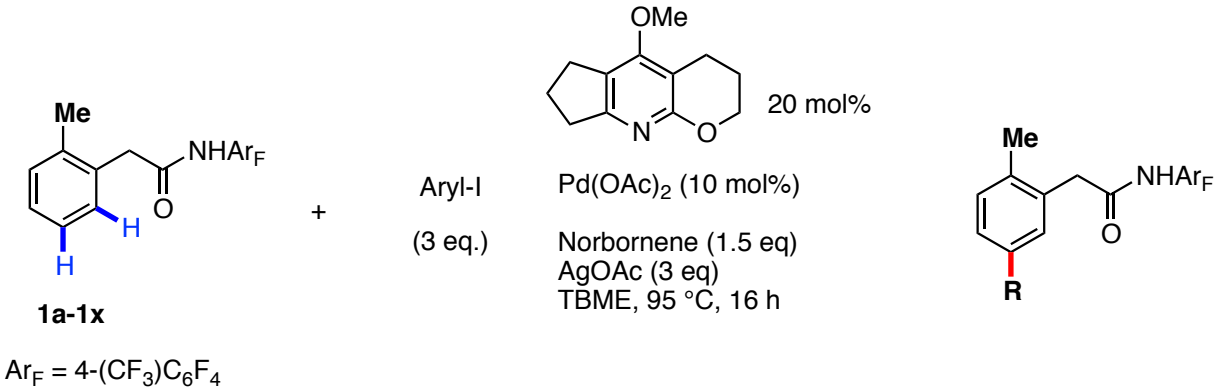
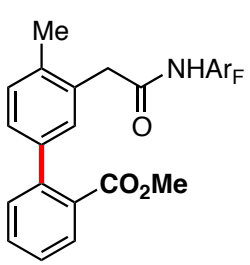
Reaction scope





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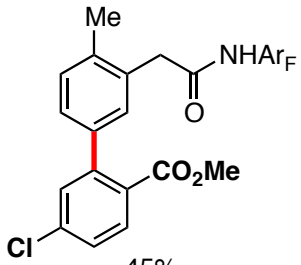

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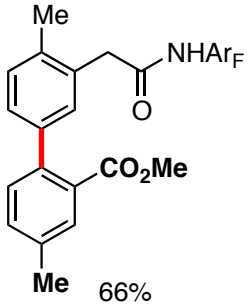

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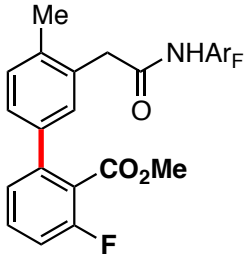

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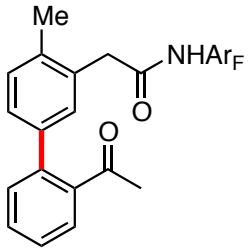

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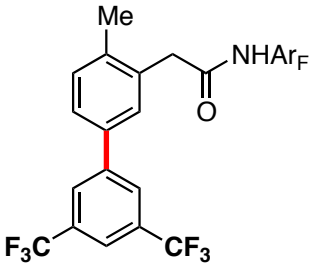

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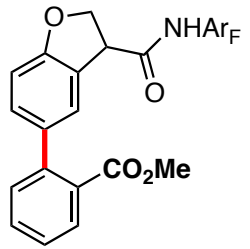

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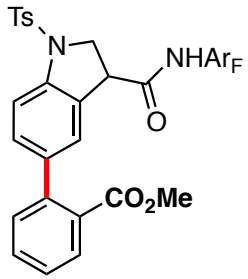
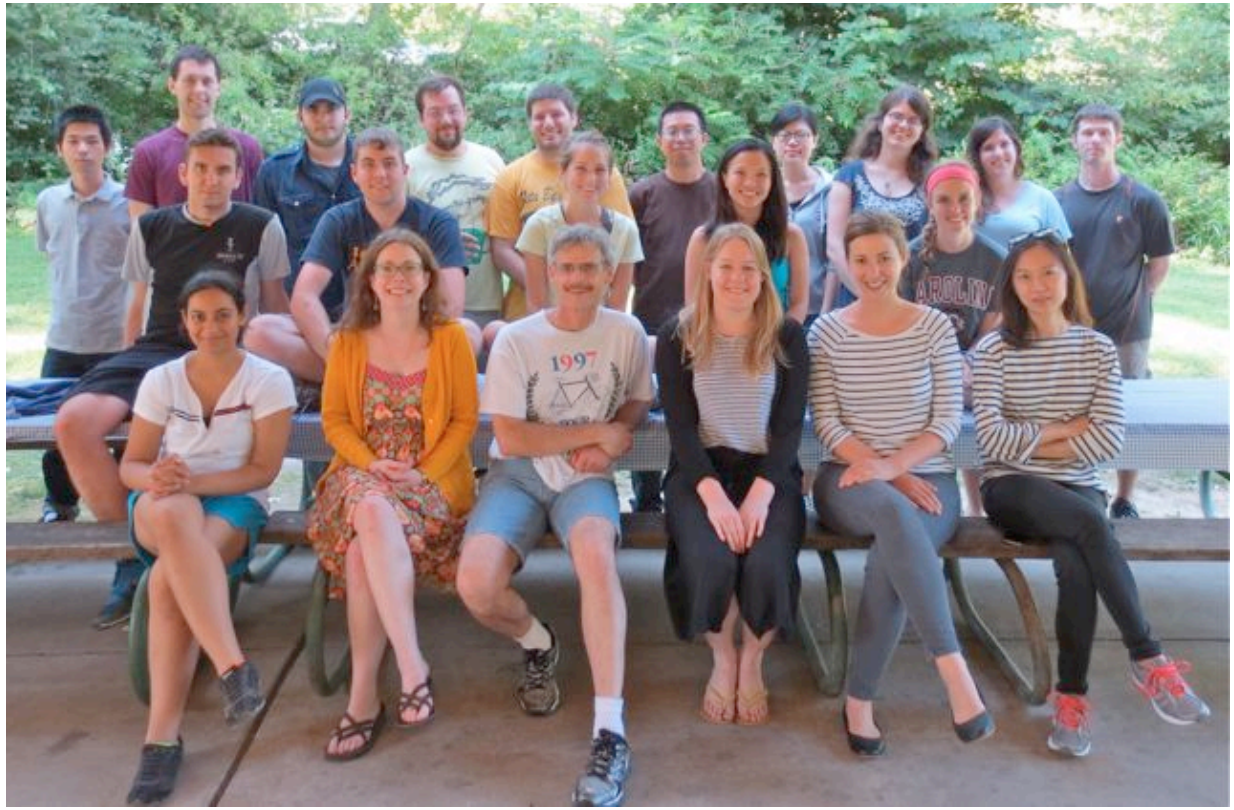


69%

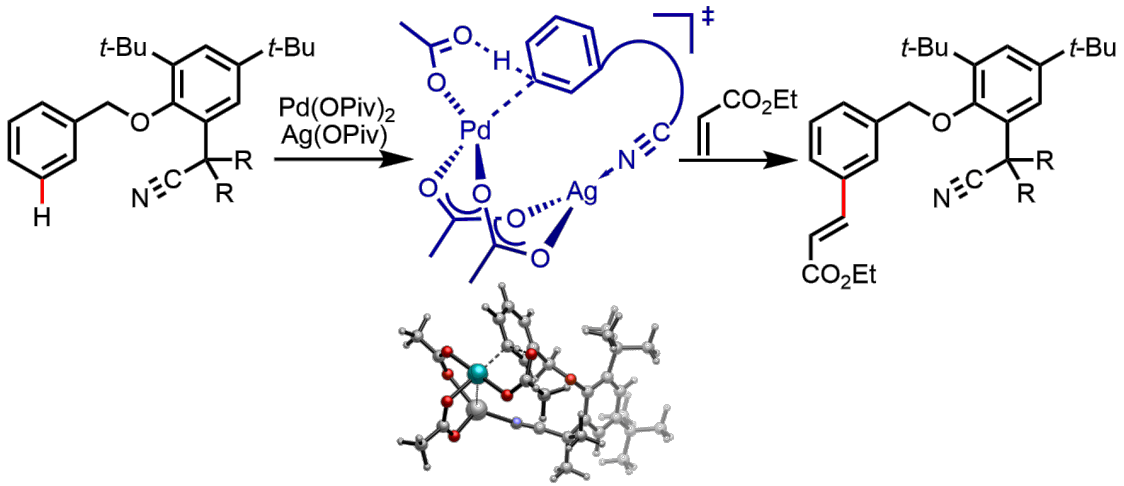
with *m*- and *p*-iodobenzoate, benzocyclobutene was the major product

Acknowledgment

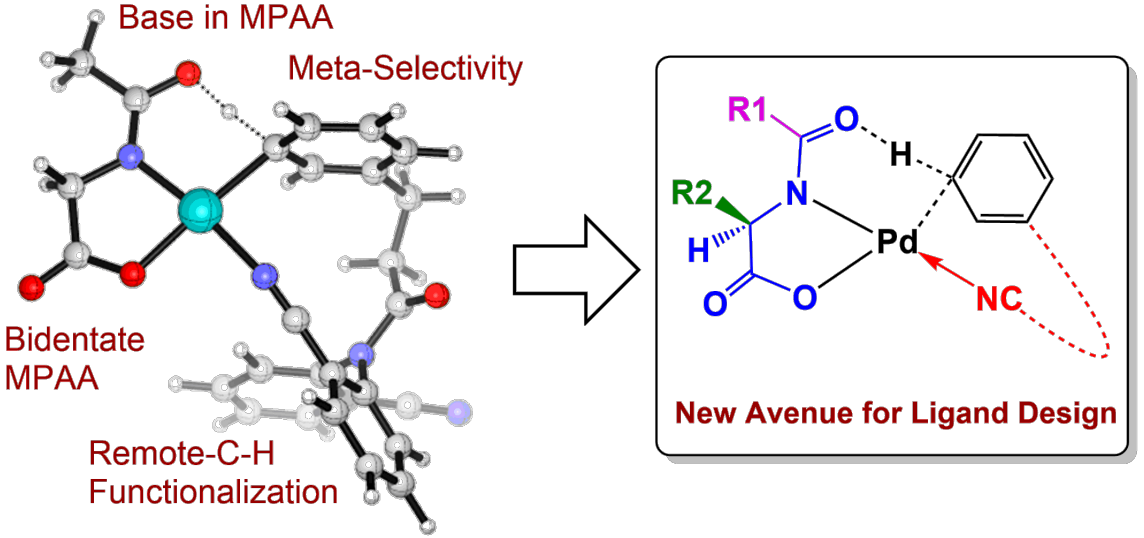
Prof. Wipf
Wipf group past & present



Lilly – LIFA (Lilly Innovation Fellowship Award)



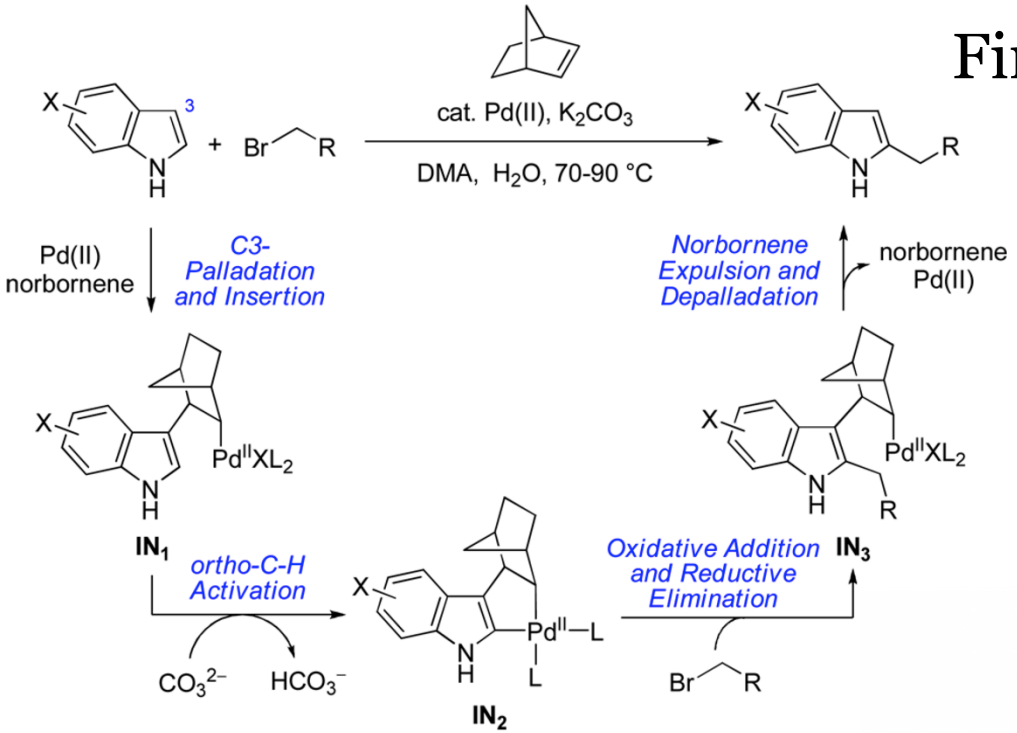
Yu et al. *J. Am. Chem. Soc.* **2014**, *136*, 344.



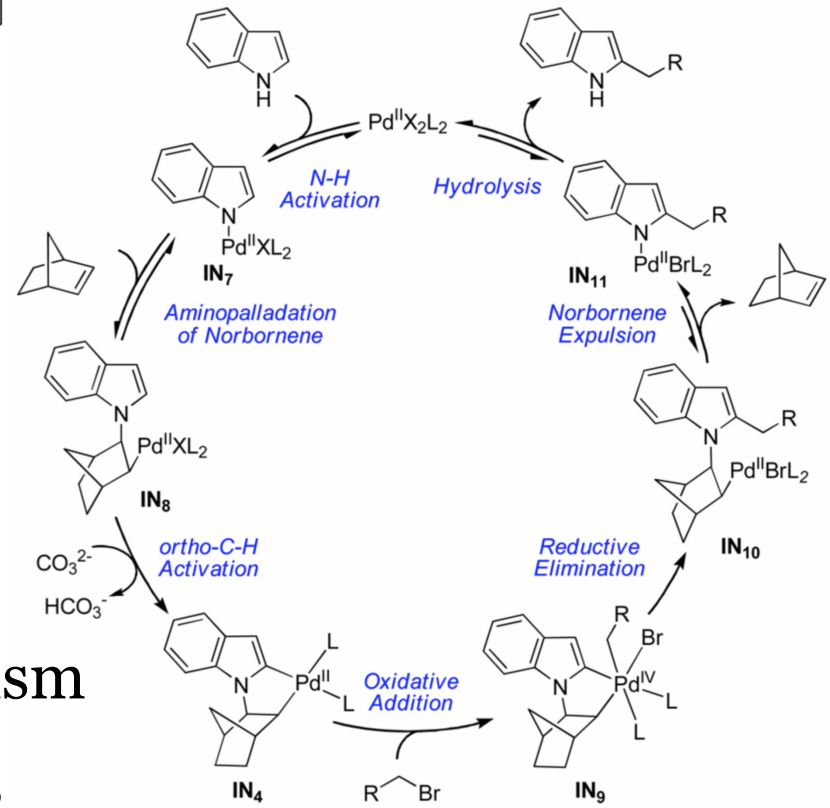
MPAA =
Mono-*N*-Protected Amino Acid

Yu et al. *Angew. Chem. Int. Ed.* **2014**, *53*, 2683

First proposed mechanism

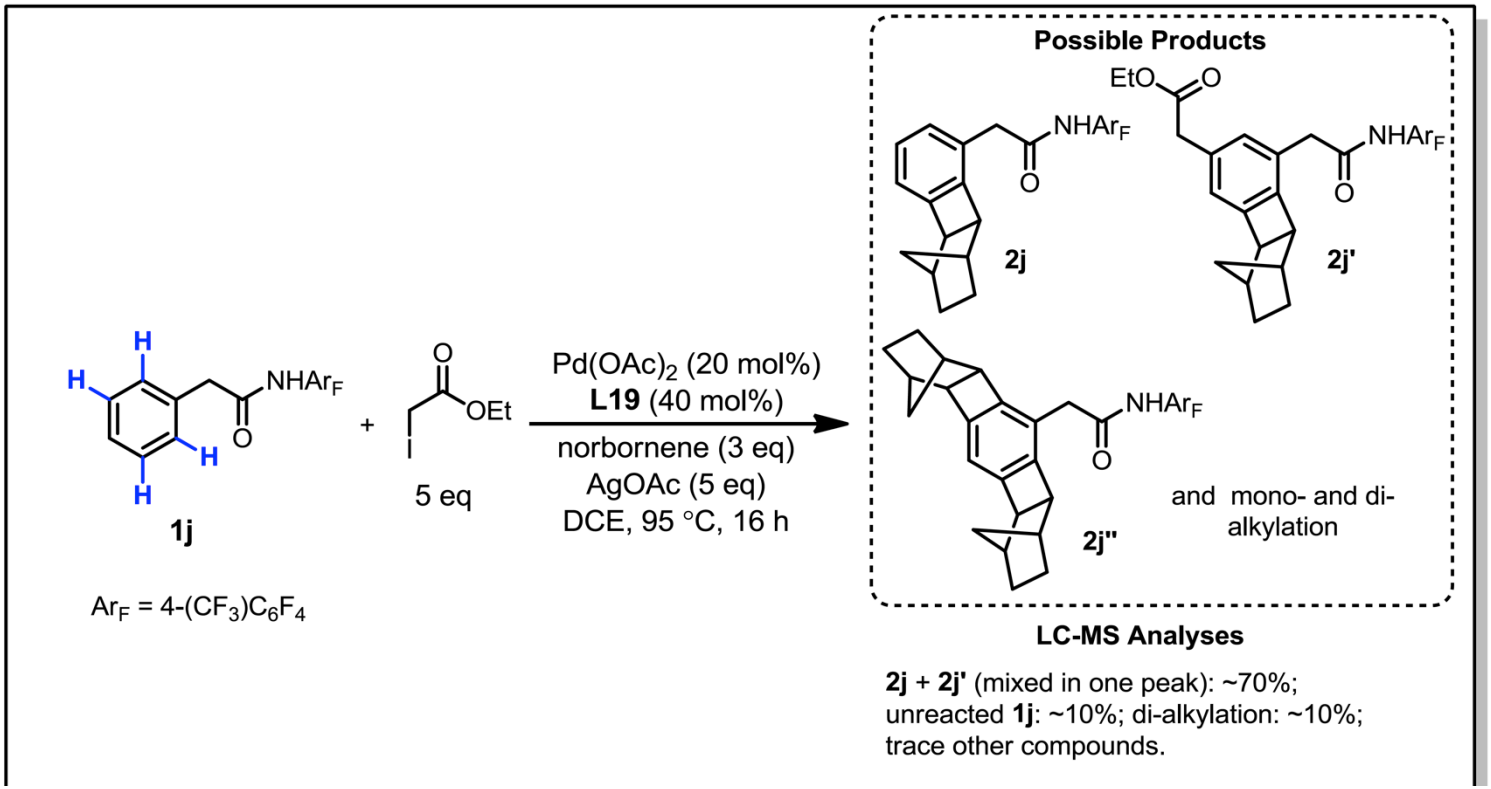


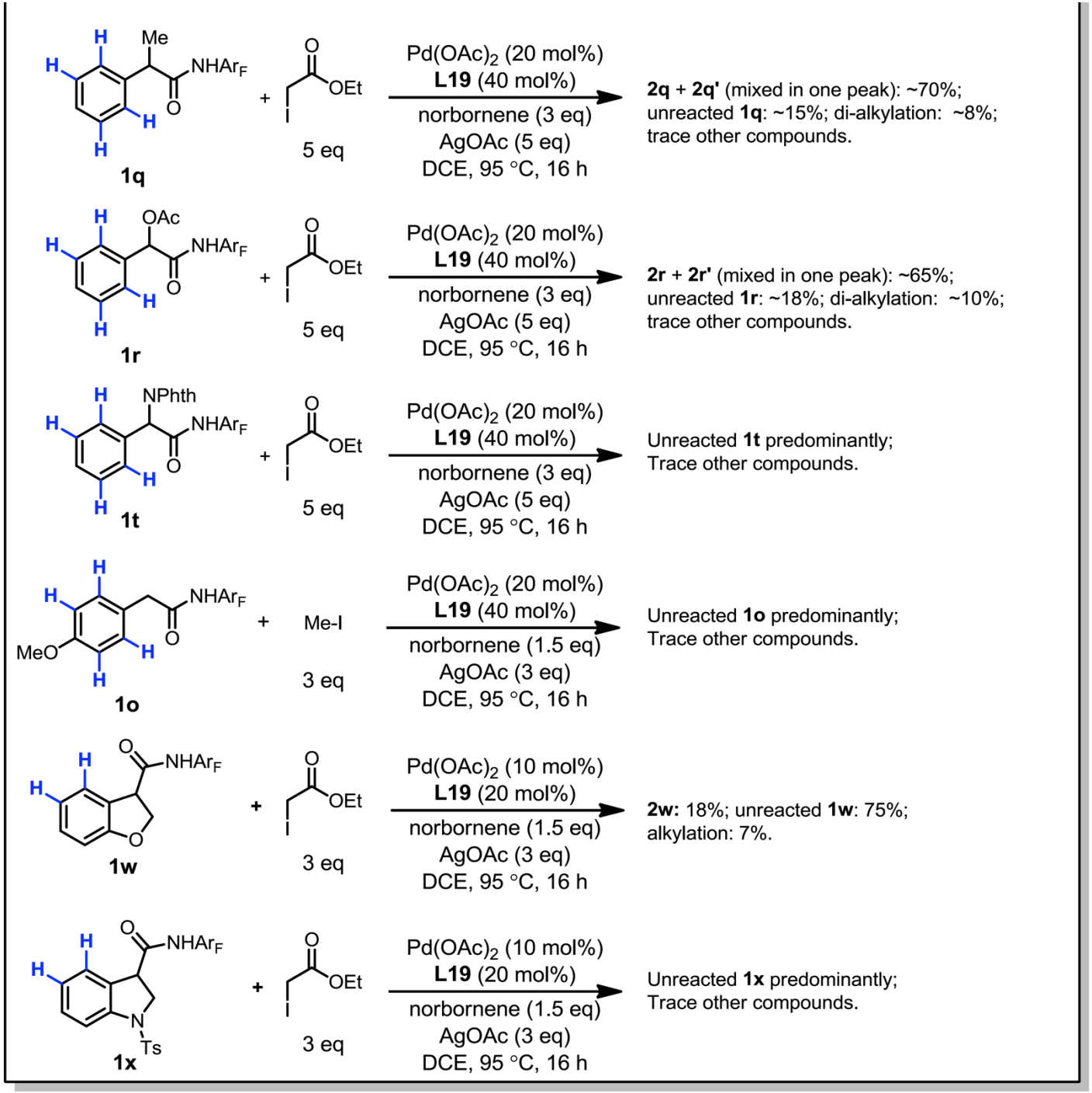
Revised mechanism



Bach et al. *J. Am. Chem. Soc.* **2012**, *134*, 14563

General Procedure: A 2-dram vial equipped with a magnetic stir bar was charged with the appropriate phenylacetic acid–derived amide substrate (0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mol%), **L19** (4.1 mg, 20 mol%), AgOAc (50 mg, 0.30 mmol) and norbornene (14.1 mg, 0.15 mmol). Methyl iodide (19 μL, 0.30 mmol) or ethyl iodoacetate (36 μL, 0.30 mmol) was then added *via* a microsyringe. Subsequently, DCE (1.5 mL) was injected, and the vial was capped and closed tightly. The reaction mixture was then stirred at 95 °C for 16 h. After being allowed to cool to room temperature, the mixture was passed through a pad of Celite with ethyl acetate as the eluent to remove any insoluble precipitate. The resulting solution was concentrated, and the residual mixture was dissolved with a minimal amount of acetone and loaded onto a silica gel column or a preparative TLC plate. The pure product was then isolated by column chromatography or preparative TLC with ethyl acetate and hexanes as the eluent. In the reactions with substrates **1j** and **1p**–**1t** where di-alkylation occurred, 20 mol% of $Pd(OAc)_2$, 40 mol% of **L19**, 5 equiv of alkyl iodide, 5 equiv of AgOAc and 3 equiv of norbornene were used, and the volume of DCE was increased to 2.5 mL. Otherwise, the conditions and workups were exactly the same as those of mono-alkylation.


Possible Products
EtO
O
NHArF
O
2j
2j'
2j''
and mono- and di-alkylation
1j
5 eq
OEt
Pd(OAc)2 (20 mol%)
L19 (40 mol%)
norbornene (3 eq)
AgOAc (5 eq)
DCE, 95 °C, 16 h
ArF = 4-(CF3)C6F4
LC-MS Analyses
2j + 2j' (mixed in one peak): ~70%;
unreacted 1j: ~10%; di-alkylation: ~10%;
trace other compounds.


1q
5 eq
Pd(OAc)2 (20 mol%)
L19 (40 mol%)
norbornene (3 eq)
AgOAc (5 eq)
DCE, 95 °C, 16 h
2q + 2q' (mixed in one peak): ~70%;
unreacted 1q: ~15%; di-alkylation: ~8%;
trace other compounds.
1r
5 eq
Pd(OAc)2 (20 mol%)
L19 (40 mol%)
norbornene (3 eq)
AgOAc (5 eq)
DCE, 95 °C, 16 h
2r + 2r' (mixed in one peak): ~65%;
unreacted 1r: ~18%; di-alkylation: ~10%;
trace other compounds.
1t
5 eq
Pd(OAc)2 (20 mol%)
L19 (40 mol%)
norbornene (3 eq)
AgOAc (5 eq)
DCE, 95 °C, 16 h
Unreacted 1t predominantly;
Trace other compounds.
1o
Me-I
3 eq
Pd(OAc)2 (20 mol%)
L19 (40 mol%)
norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h
Unreacted 1o predominantly;
Trace other compounds.
1w
3 eq
Pd(OAc)2 (10 mol%)
L19 (20 mol%)
norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h
2w: 18%; unreacted 1w: 75%;
alkylation: 7%.
1x
3 eq
Pd(OAc)2 (10 mol%)
L19 (20 mol%)
norbornene (1.5 eq)
AgOAc (3 eq)
DCE, 95 °C, 16 h
Unreacted 1x predominantly;
Trace other compounds.