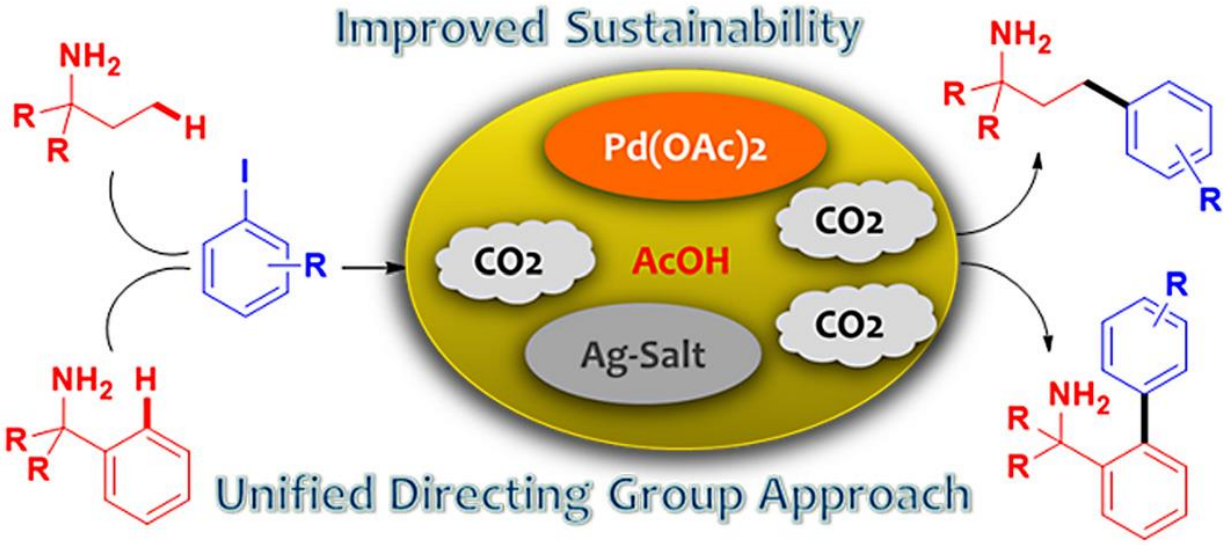
Carbon Dioxide-Mediated arylation of amines



LS 190518
D2 Shinsuke Shimizu

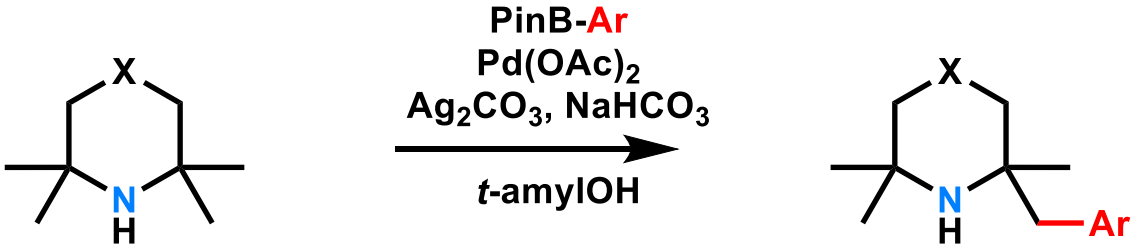
Contents

Contents

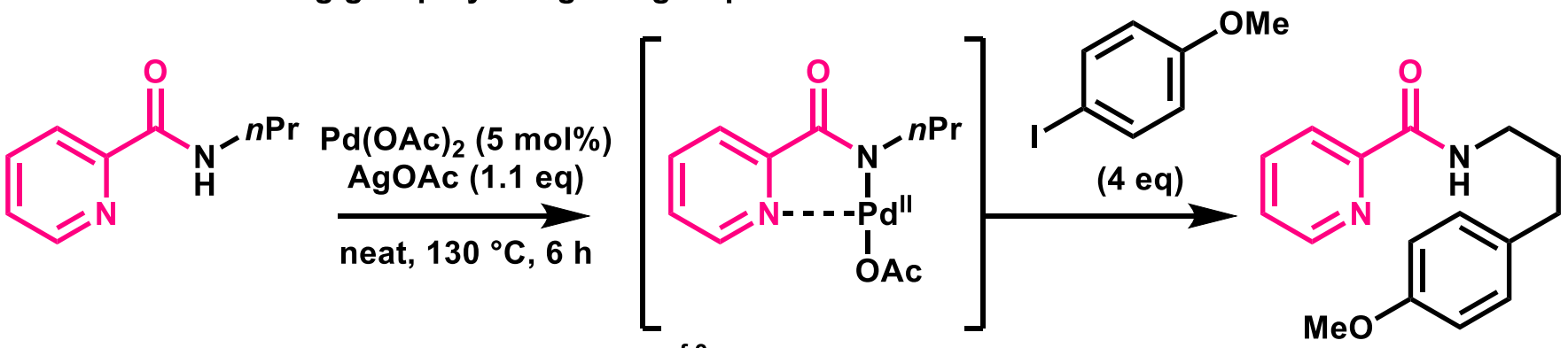
C-H Functionalization of Amines (1)

a. β-arylation of free amine by Gaunt's group [ref 1]

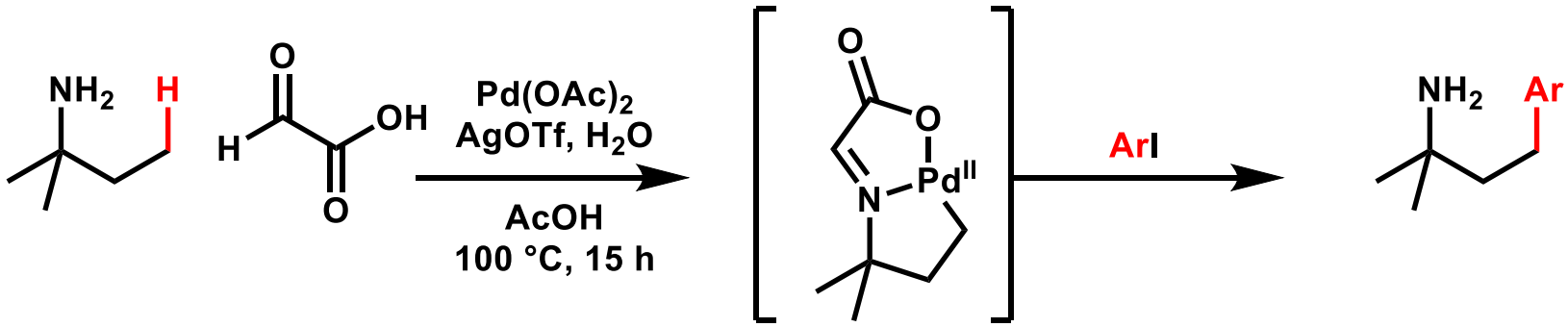
(180210_LS_Takumi_Fukuda_Remote_C-H_Functionaliation_of_amines.pdf)



b. amide as directing group by Daugulis' group [ref 2]

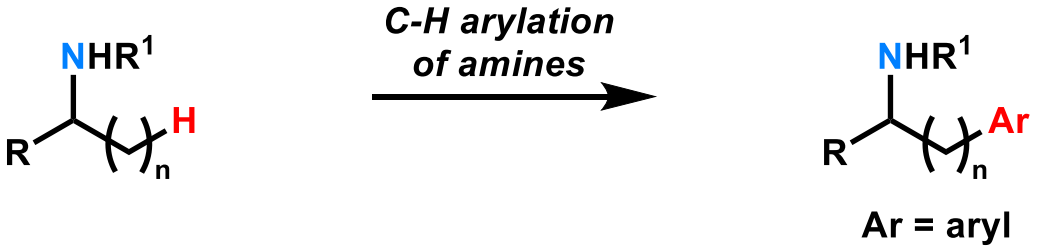


c. γ-arylation of free amine by Ge's group [ref 3] (in situ generated directing group)

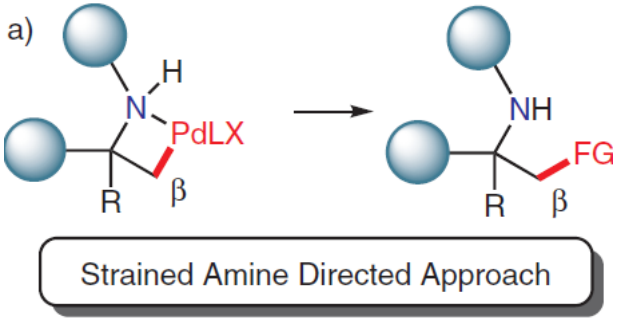


1) He, C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15840. 2) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. 3) Liu, Y.; Ge, H. *Nature Chem.* **2017**, *9*, 26.

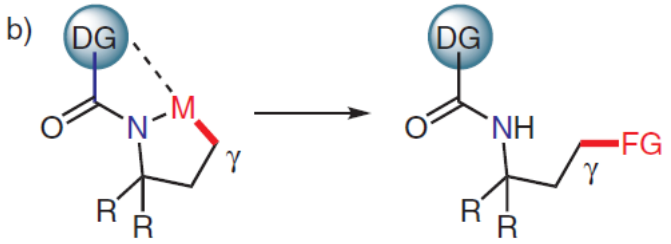
C-H Functionalization of Amines (2)



Ar = aryl

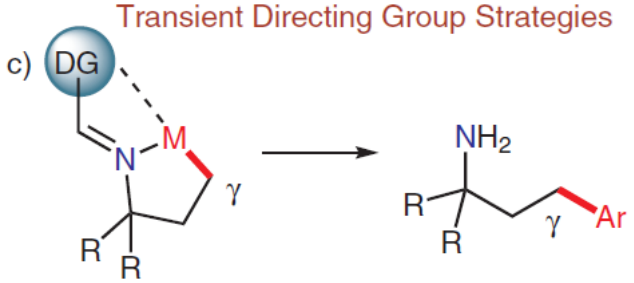


Strained Amine Directed Approach



Amide Functionality as Directing Group

Transient Directing Group Strategies



Imine Functionality as Directing Group

disadvantages

a) ... few examples.

b) ... atom and step-uneconomical.

c) ... rarely used for 2° amines.
formation of oxidation-sensitive imines.

Kapoor, M.; Chand-Thakuri, P.; Maxwell, J.; Liu, D.; Zhou, H.; Young, M. C. *Synlett* **2019**, *30*, 519.

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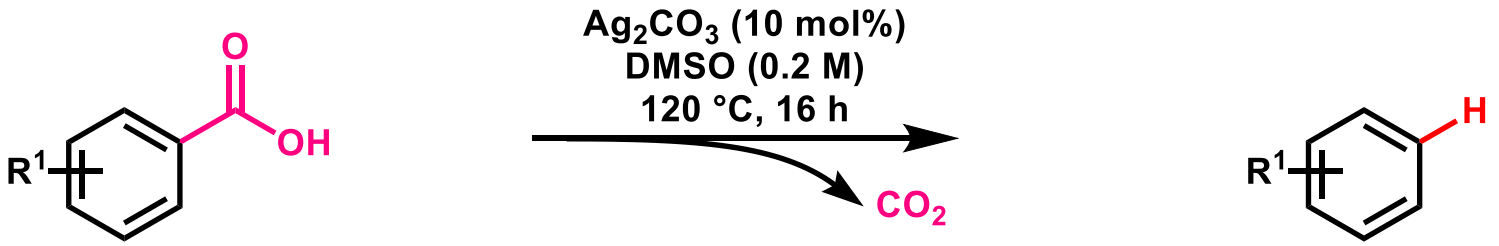
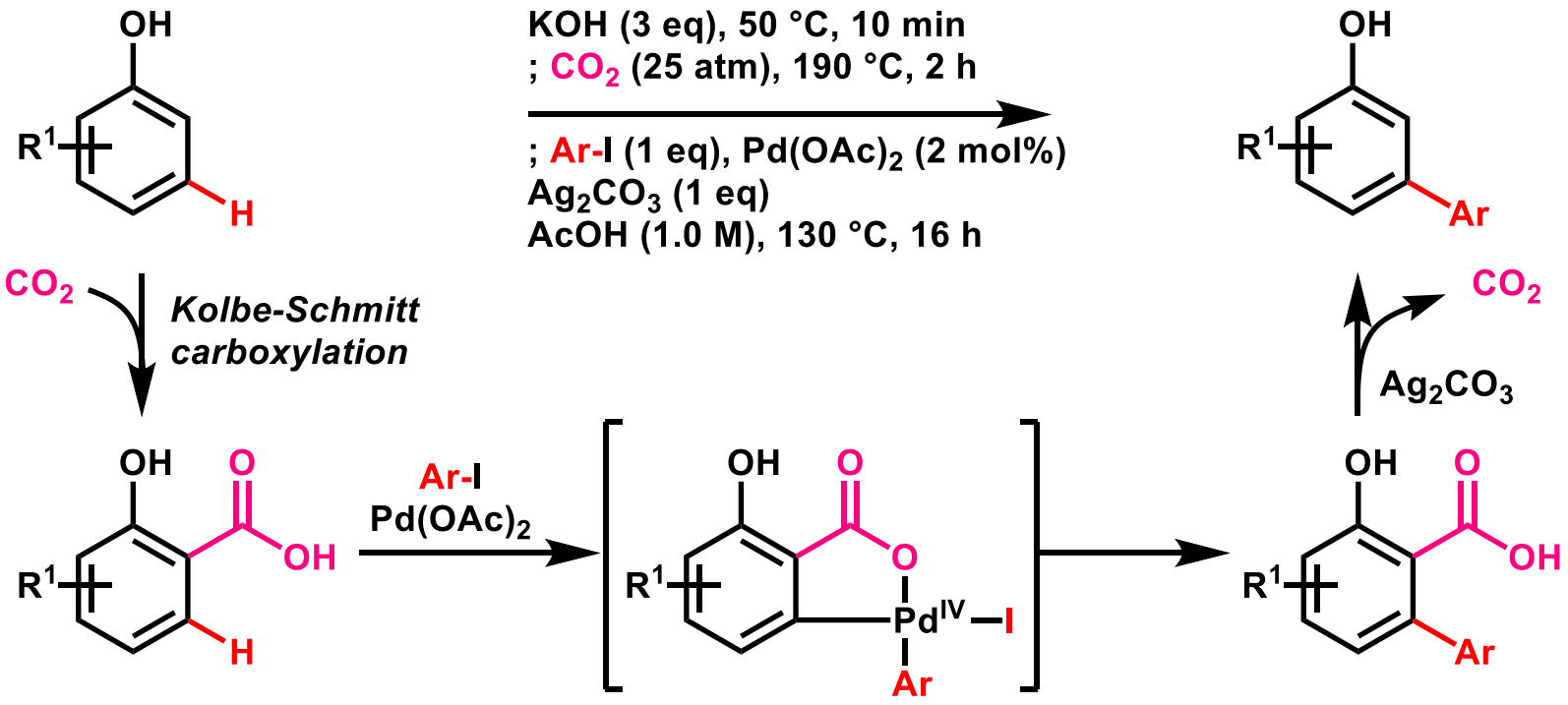
Traceless Directing Group (Larrosa group)

1. Transition metal-promoted protodecarboxylation

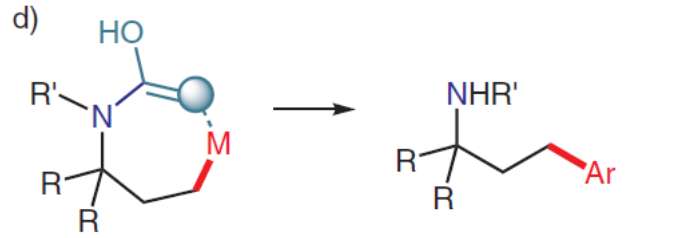


2. Carboxylation followed by C-H bond arylation/decarboxylation



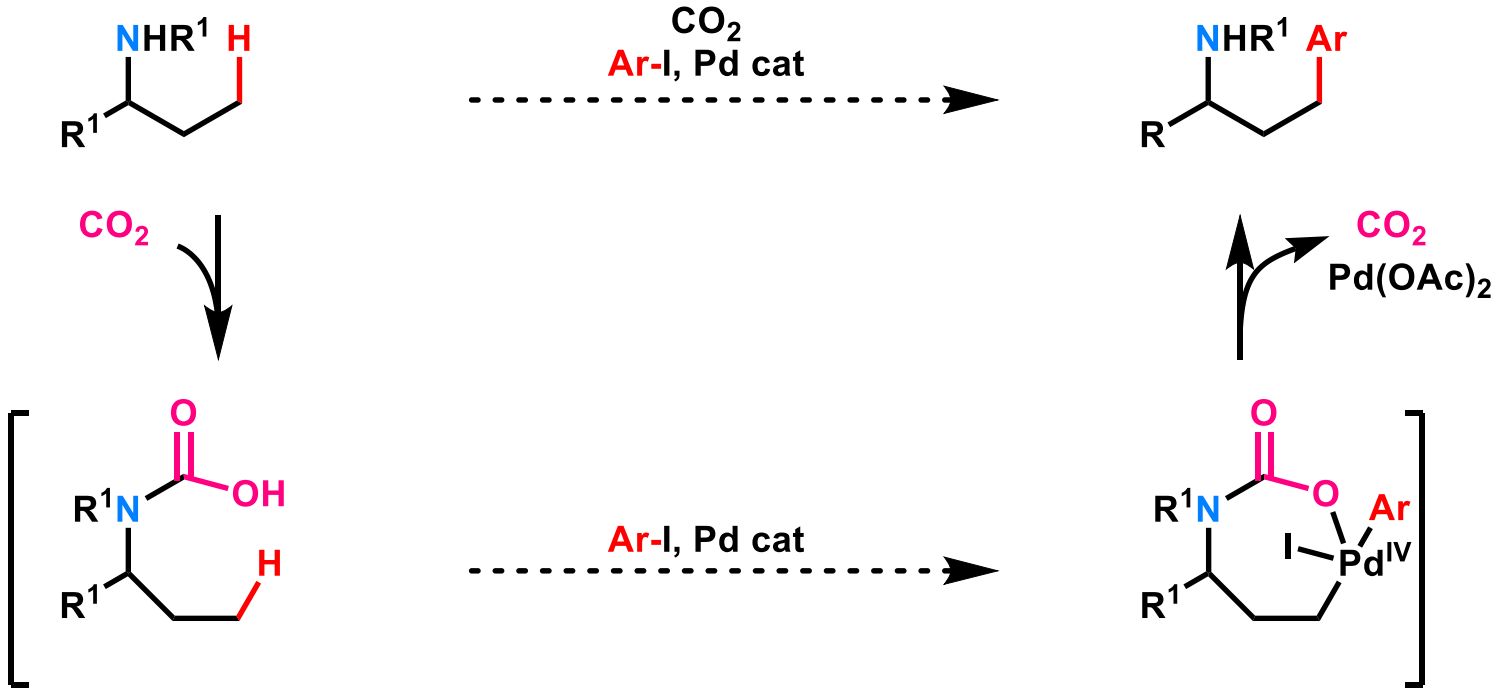
1) Font, M. Quibell, J. M.; Perry, G. J.; Larrosa, I. *Chem. Commun.* **2017**, *53*, 5584.

Young Group Research Plan



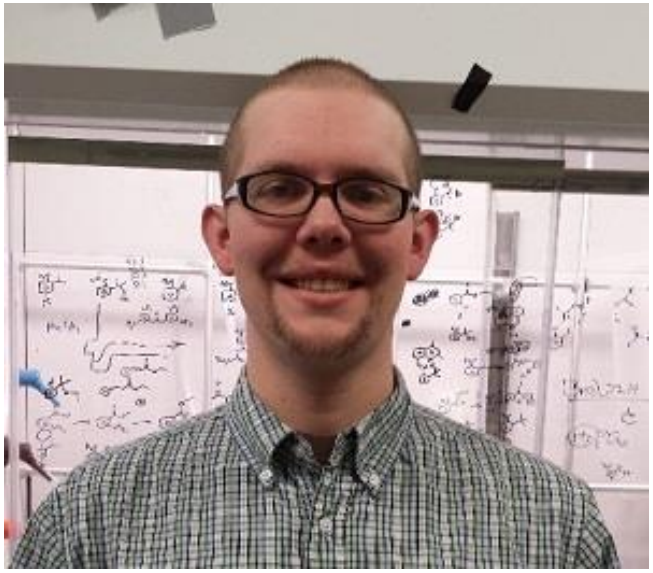
Our Approach: CO_2 Driven C-H Activation

d. γ-selective arylation of amines using carbon dioxide [ref 1]



1) Kapoor, M. Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818.

Dr. Michael C. Young



2006
B.S. Chemistry, B.S. Biology at Western Carolina University

2008
M.S. Chemistry at Werstern Carolina University
(Advisor: Prof Brian D. Dinkelmeyer)

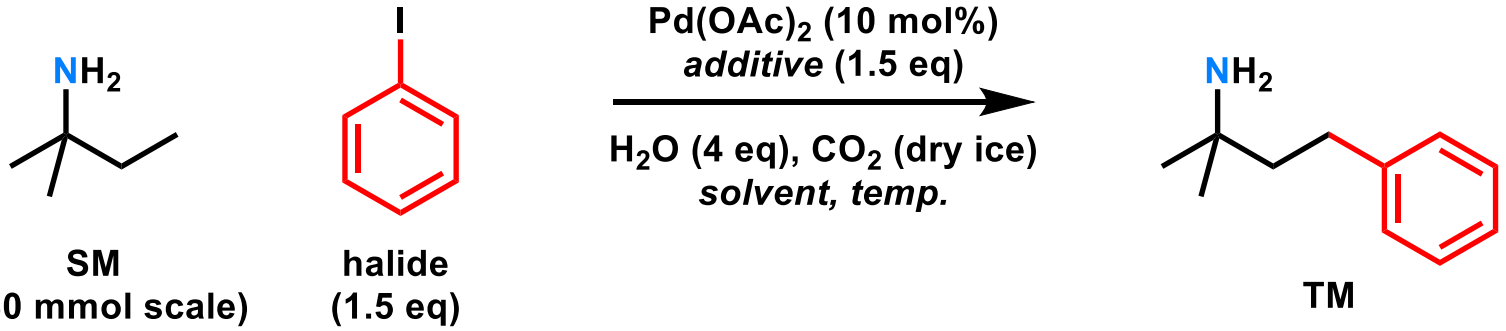
2014
Ph.D Organic Chemistry at University of California - Riverside
(Advisor: Prof. Richard J. Hooley)

2014-2016
Postdoctoral Scholar at University of Texas - Austin (Advisor: Prof. Guangbin Dong)

2016-Present
Assistant Professor at University of Toledo

Research Topic
1. Carbon Dioxide-Mediated C-H Activation
***2.* Supramolecular Scaffolds for Catalysis**
3. Strategies for Remote C-H Activation

Initial Attempt for Arylation of Free 1° Amine



SM (0.30 mmol scale) | halide (1.5 eq) | TM

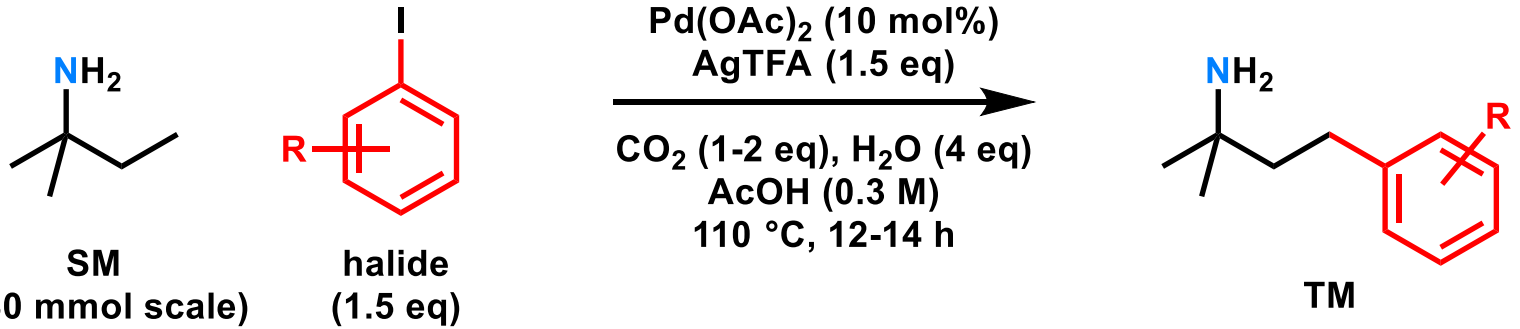
entry	*additive* (1.5 eq)	*solvent*	*temp*	CO_2	yield
1	AgTFA	AcOH (0.6 M)	110 °C	3 eq	65%
2	AgTFA	AcOH (0.6 M)	90 °C	3 eq	50%
3[a]	AgTFA	AcOH (0.6 M)	50 °C	3 eq	5%
4	-	AcOH (0.6 M)	110 °C	3 eq	10%
5	KOAc	AcOH (0.6 M)	110 °C	3 eq	10%
6	AgTFA	HFIP (0.6 M)	110 °C	3 eq	30%
7	AgTFA	TFA (0.6 M)	110 °C	3 eq	10%
8	AgTFA	AcOH (0.3 M)	110 °C	3 eq	69%
9	AgTFA	AcOH (0.3 M)	110 °C	1 eq	73%

a: time (24 h)
HFIP: hexafluoro-2-propanol

**No Pd source gave no reaction*

Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818. and SI.

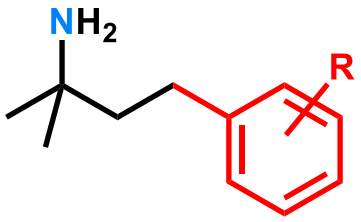
Substrate Scope (Aryl Iodide)



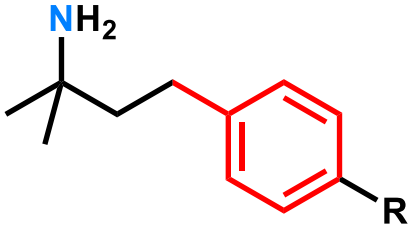
SM
(0.30 mmol scale)

halide
(1.5 eq)

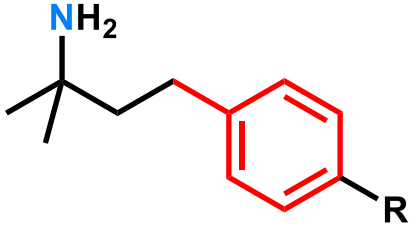
TM



R = H: 74%
R = *o*-CO_2Et: 65%
R = *m*-CO_2Et: 69%
R = *p*-CO_2Et: 71%
R = *m*-F: 65%
R = *m*-CF_3: 63%
R = *p*-NO_2: 45%



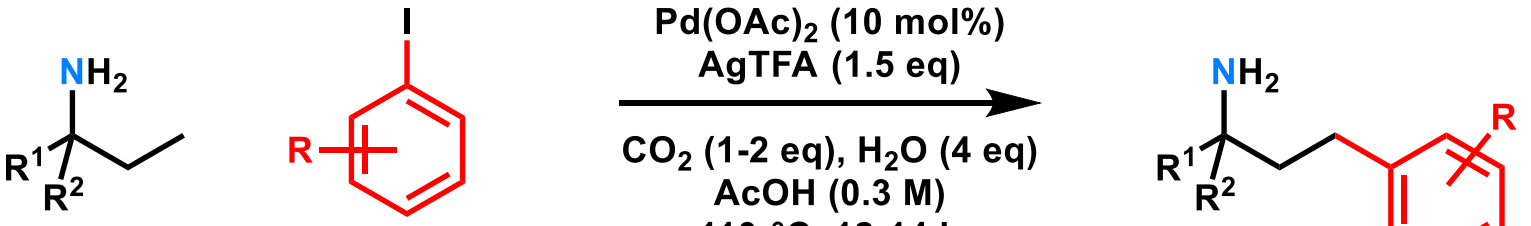
R = F: 69%
R = Br: 72%
R = I: 68%

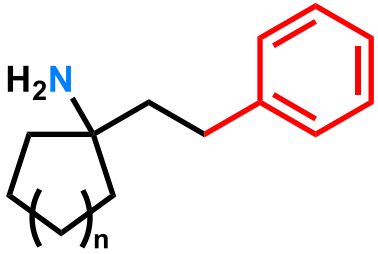


R = OMe: 78%
R = OEt: 72%
R = Me: 74%
R = Ph: 68%

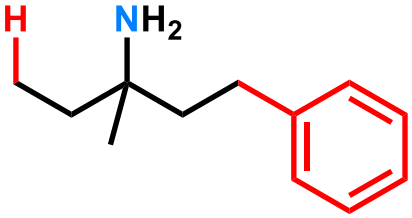
Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818.

Substrate Scope of C(sp^3)-H Arylation (1° Amine)

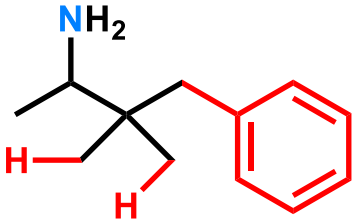




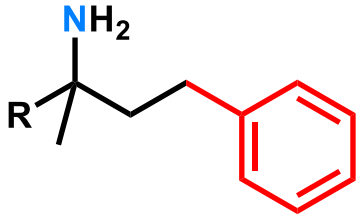
n = 1: 57%
n = 2: 62%
n = 3: 64%



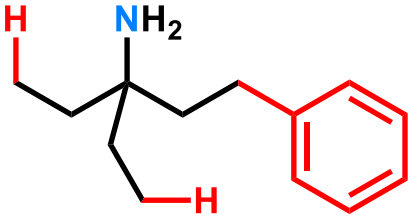
62% (1:1.6 = mono:di)



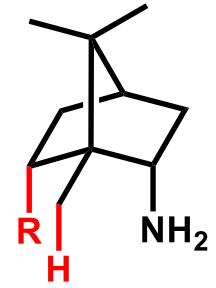
52% (90 °C)



R = *n*Bu: 67%
R = *n*Hex: 63%



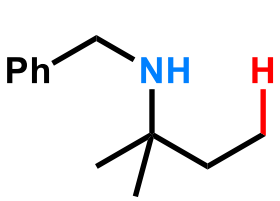
53% (1:1.5 = mono:di)



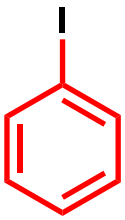
R = Ph: 53% (90 °C)
R = biphenyl: 62% (90 °C)

Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818.

Optimization and Arylation (2° Amine)



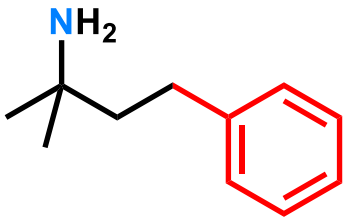
SM
(0.30 mmol scale)



halide

Pd cat
AgTFA (2.0 eq)

CO_2, H_2O (4 eq)
solvent (0.3 M), 90 °C, 24 h
(in 8 mL sealed tube)



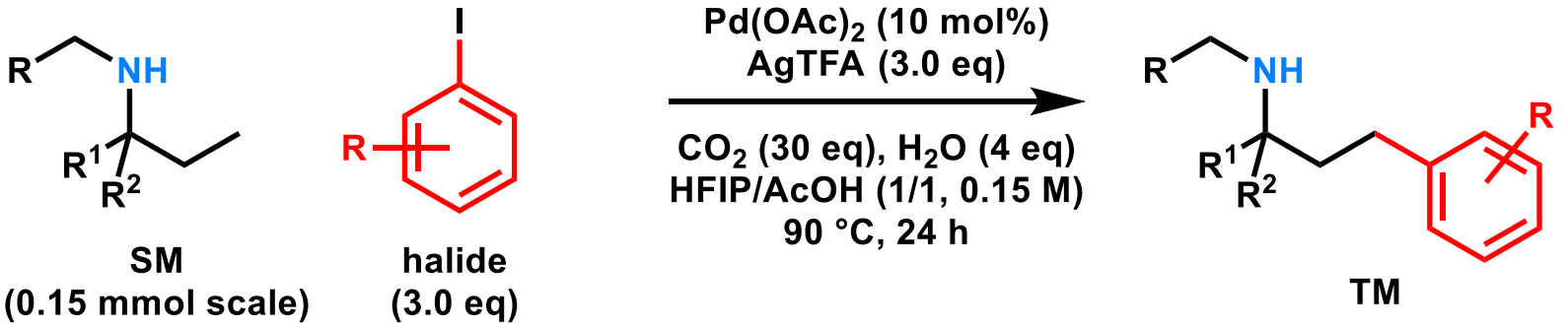
TM

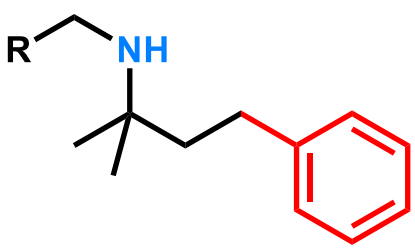
entry	*Pd cat*	*solvent*	halide	CO_2	yield
1	$Pd(OAc)_2$ (1 mol%)	AcOH	1.5 eq	20 eq	NR
2	$Pd(OAc)_2$ (5 mol%)	AcOH	1.5 eq	20 eq	NR
3	$Pd(TFA)_2$ (10 mol%)	AcOH	1.5 eq	20 eq	4%
4	$Pd(OAc)_2$ (5 mol%)	AcOH/HFIP (1/9)	1.5 eq	20 eq	22-23%
5	$Pd(OAc)_2$ (10 mol%)	AcOH/HFIP (1/9)	1.5 eq	20 eq	30%
6	$Pd(OAc)_2$ (10 mol%)	AcOH/HFIP (1/9)	3.0 eq	35 eq	30%
7	$Pd(OAc)_2$ (10 mol%)	AcOH/HFIP (1/9)	3.0 eq	50 eq	41%
8[a]	$Pd(OAc)_2$ (10 mol%)	AcOH/HFIP (5/5)	3.0 eq	50 eq	50%
9[a]	$Pd(OAc)_2$ (10 mol%)	AcOH/HFIP (5/5)	3.0 eq	30 eq	54%

NR: no reaction
HFIP: hexafluoro-2-propanol
a: 0.15 mmol scale

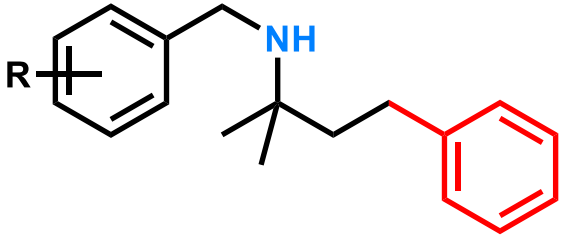
Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818. and SI.

Substrate Scope of C(sp^3)-H Arylation (2° Amine)

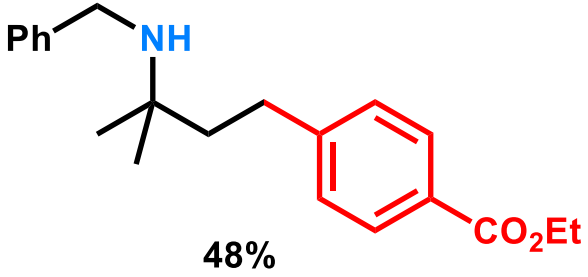




R = Et: 44%
R = *n*Pr: 45%
R = *n*Bu: 43%
R = Bn: 43%



R = H: 50%
R = *p*-OMe: 54%
R = *m*-OMe: 53%
R = *p*-Me: 51%
R = *m*-Me: 52%



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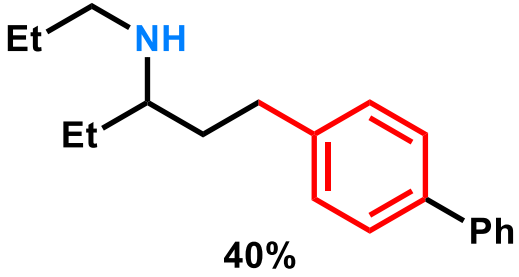
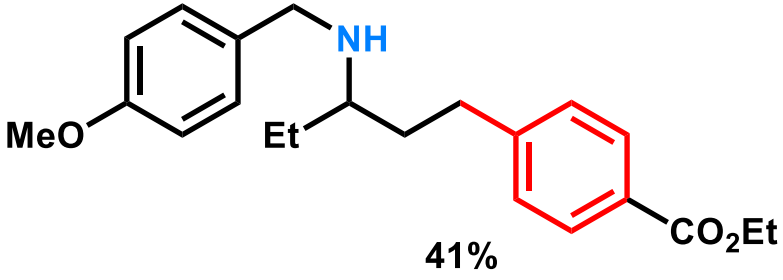


40%

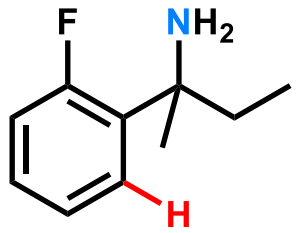


41%

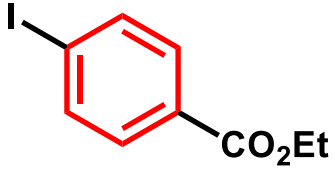
Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818.

Contents

Optimization of C(sp^2)-Arylation (1° Amine)



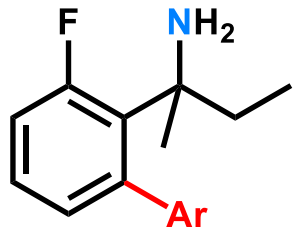
SM
(0.15 mmol scale)



halide

$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

H_2O (4 eq), CO_2
solvent (0.15 M)
temp., 12 h



TM

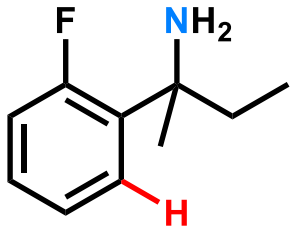
entry	halide	*additive*	*solvent*	*temp*	CO_2	yield
1	1.5 eq	AgTFA	AcOH	110 °C	3 eq	18%
2	1.5 eq	AgTFA	AcOH	100 °C	3 eq	22%
3	1.5 eq	AgTFA	AcOH	90 °C	3 eq	15%
4	1.5 eq	Ag_2CO_3	AcOH	100 °C	5 eq	5%
5	1.5 eq	AgOAc	AcOH	100 °C	5 eq	17%
6	1.5 eq	AgTFA	AcOH	100 °C	5 eq	27%
7	3.0 eq	AgTFA	AcOH	100 °C	5 eq	34%
8	3.0 eq	AgTFA	HFIP	110 °C	5 eq	71%
9	3.0 eq	AgTFA	HFIP/AcOH (7/3)	110 °C	5 eq	78%
10	3.0 eq	AgTFA	HFIP/AcOH (9/1)	110 °C	5 eq	75%

HFIP: hexafluoro-2-propanol

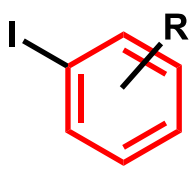
**No Pd source gave no reaction*

Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Substrate Scope of C(sp^2)-H Arylation (Aryl Halide)



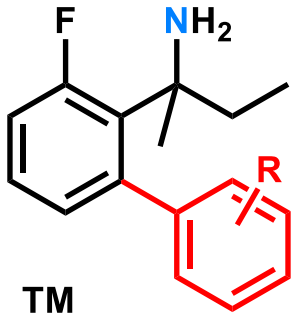
SM
(0.15 mmol scale)



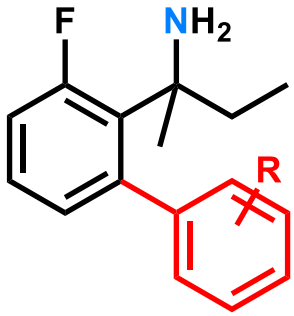
halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

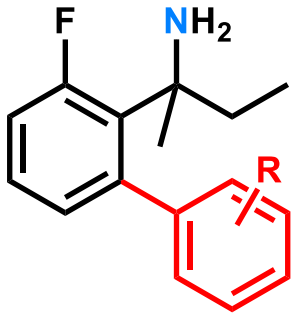
H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



TM

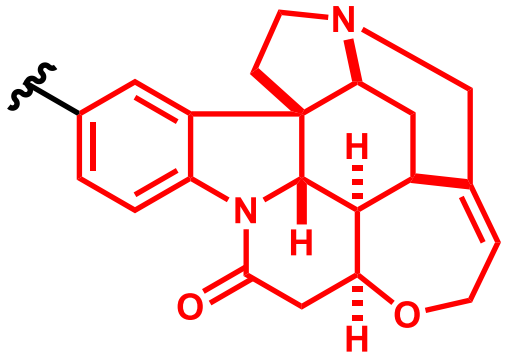


R = H: 71%
R = *p*-F: 63%
R = *m*-F: 64%
R = *p*-CF_3: 61%
R = *m*-CF_3: 69%
R = *p*-Br: 72%
R = *p*-I: 70%



R = *p*-CO_2Et: 77%
R = *m*-CO_2Et: 73%
R = *p*-$COCH_3$: 64%
R = 3,5-CO_2Me: 64%

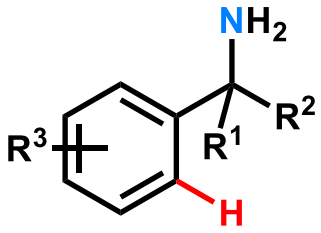
R = *p*-Me: 81%
R = *m*-Me: 75%
R = *p*-OMe: 59%
R = *m*-OMe: 61%



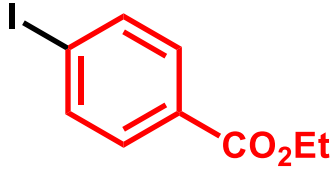
34%

Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Substrate Scope of C(sp^2)-H Arylation (1° Amine)



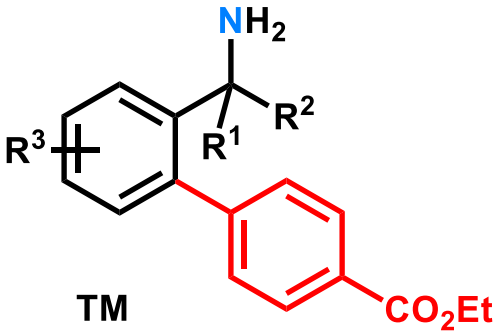
SM
(0.15 mmol scale)



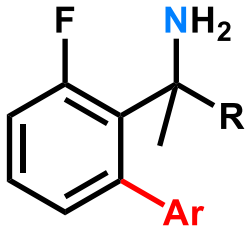
halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

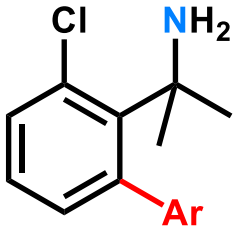
H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



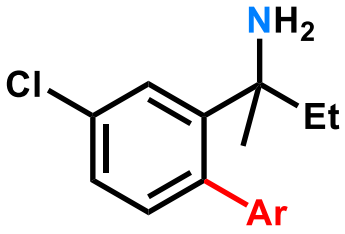
TM



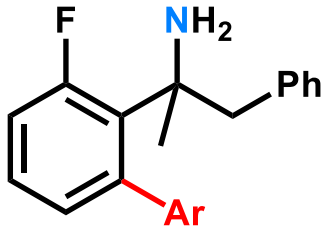
R = Me: 72%
R = *n*Pr: 70%
R = *n*Bu: 63%
R = *n*Hex: 59%



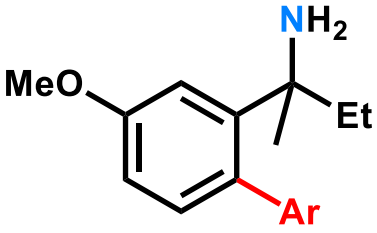
61%



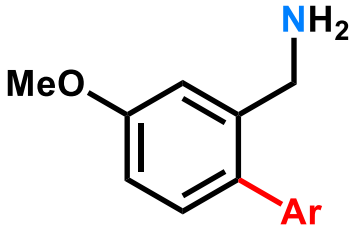
75%



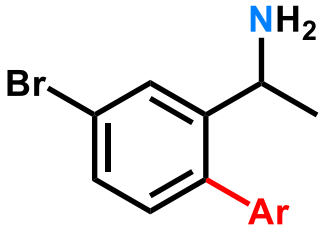
68%



77%



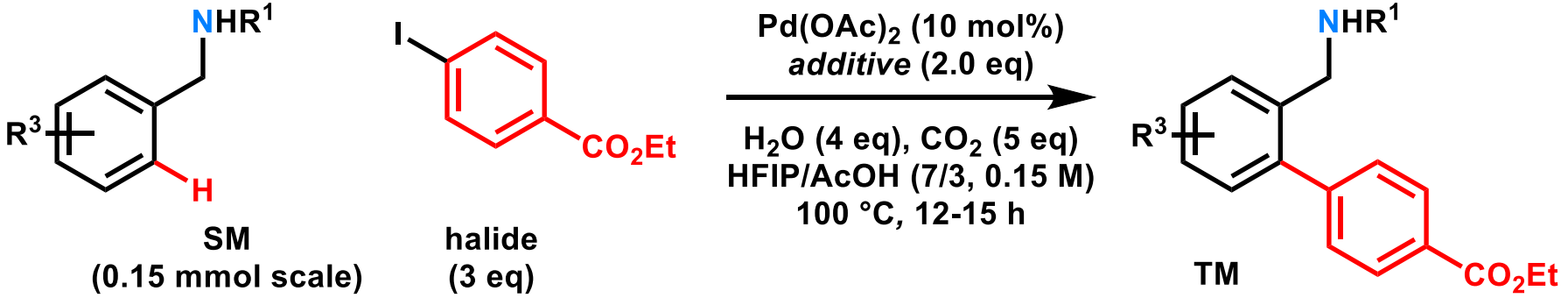
68%

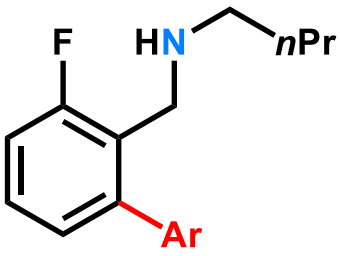


80%

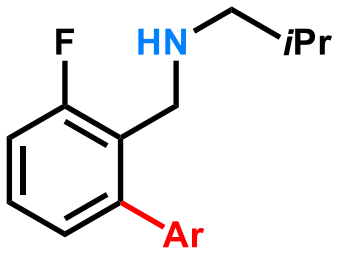
Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Substrate Scope of C(sp^2)-H Arylation (2° Amine)

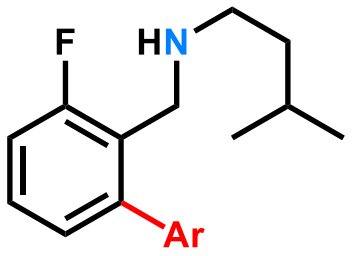




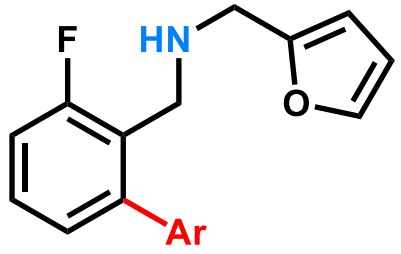
61%



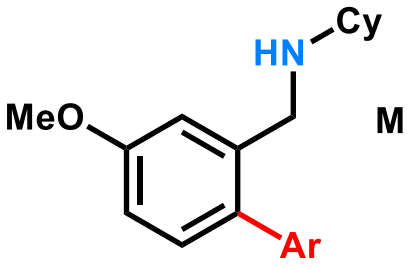
61%



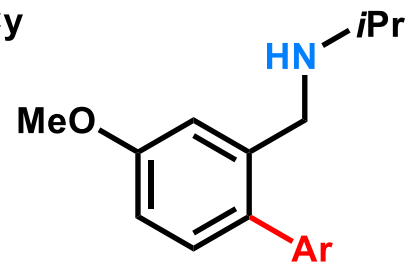
75%



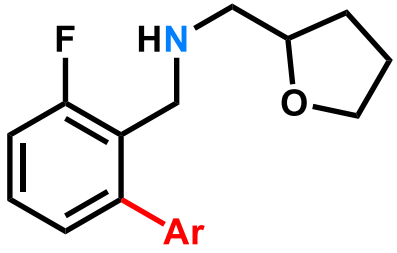
77%



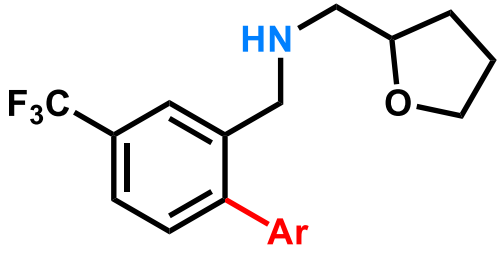
61%



68%

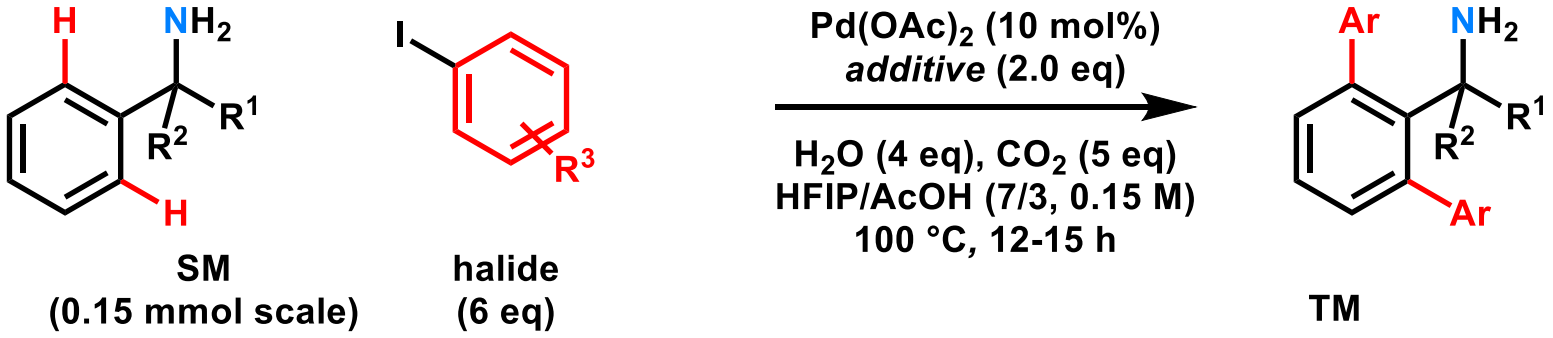


68%

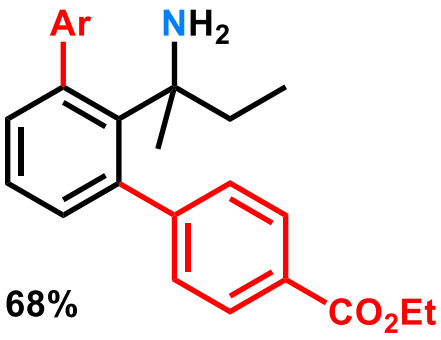


80%

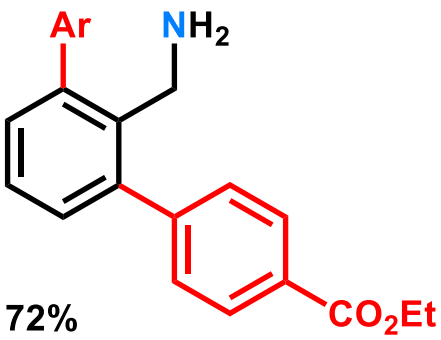
di-C(sp^2)-Arylation (1° Amine)



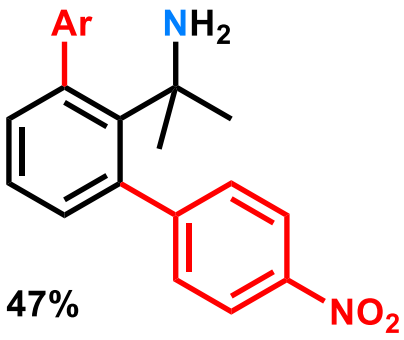
SM (0.15 mmol scale) | halide (6 eq) | TM



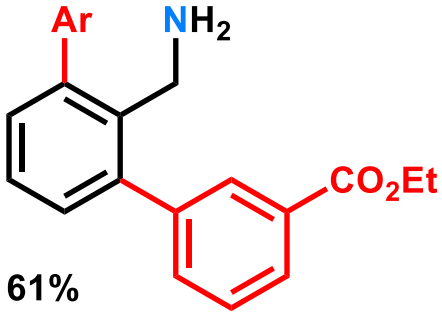
68%



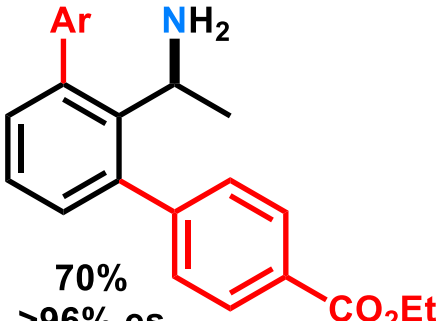
72%



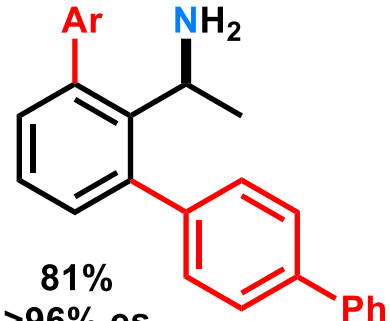
47%



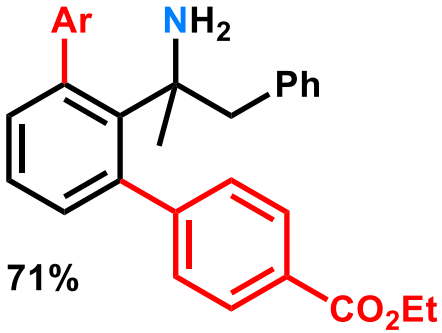
61%



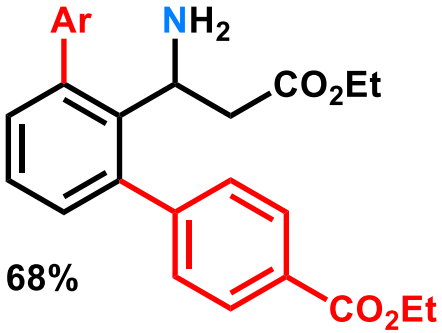
70%
>96% es
(>96% ee)



81%
>96% es
(>96% ee)



71%

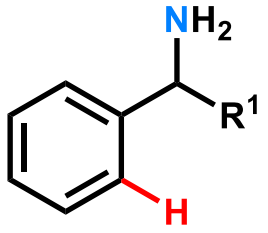


68%

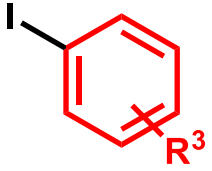
es = enantiospecificity (ee of TM / ee of SM)

Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

mono-C(sp^2)-Arylation (1° Amine)



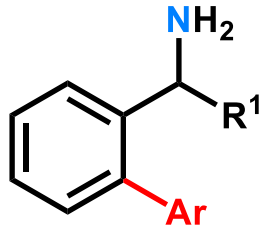
SM
(0.15 mmol scale)



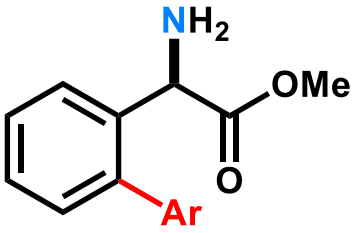
halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
AgTFA (2.0 eq)

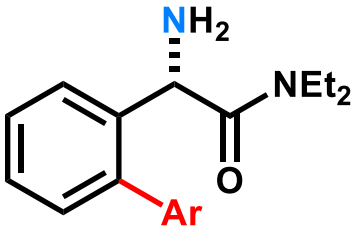
H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



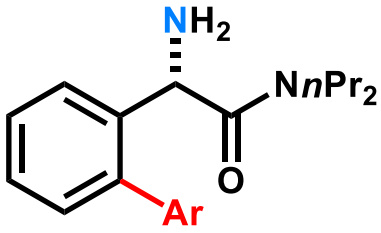
TM



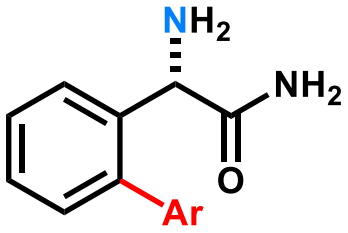
69%, 15% es
(15% ee)



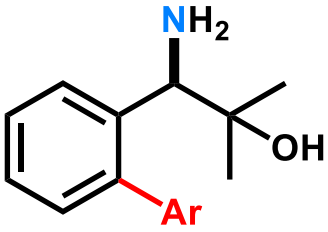
65%, 50% es
(50% ee)



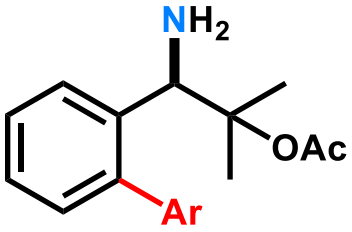
57%, 61% es
(60% ee)



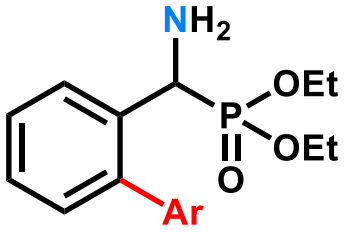
47%, <4% es
(<4% ee)



61%, 90% es
(88% ee)



47%, 88% es
(86% ee)



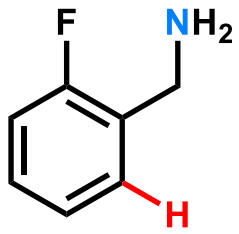
52%

es = enantiospecificity (ee of TM / ee of SM)

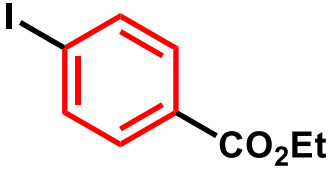
Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Application for Scale-up Synthesis

- scale-up synthesis



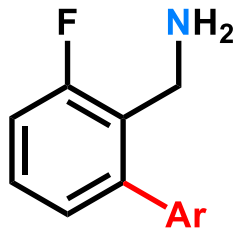
SM
(*15 mmol scale*)



halide
(3 eq)

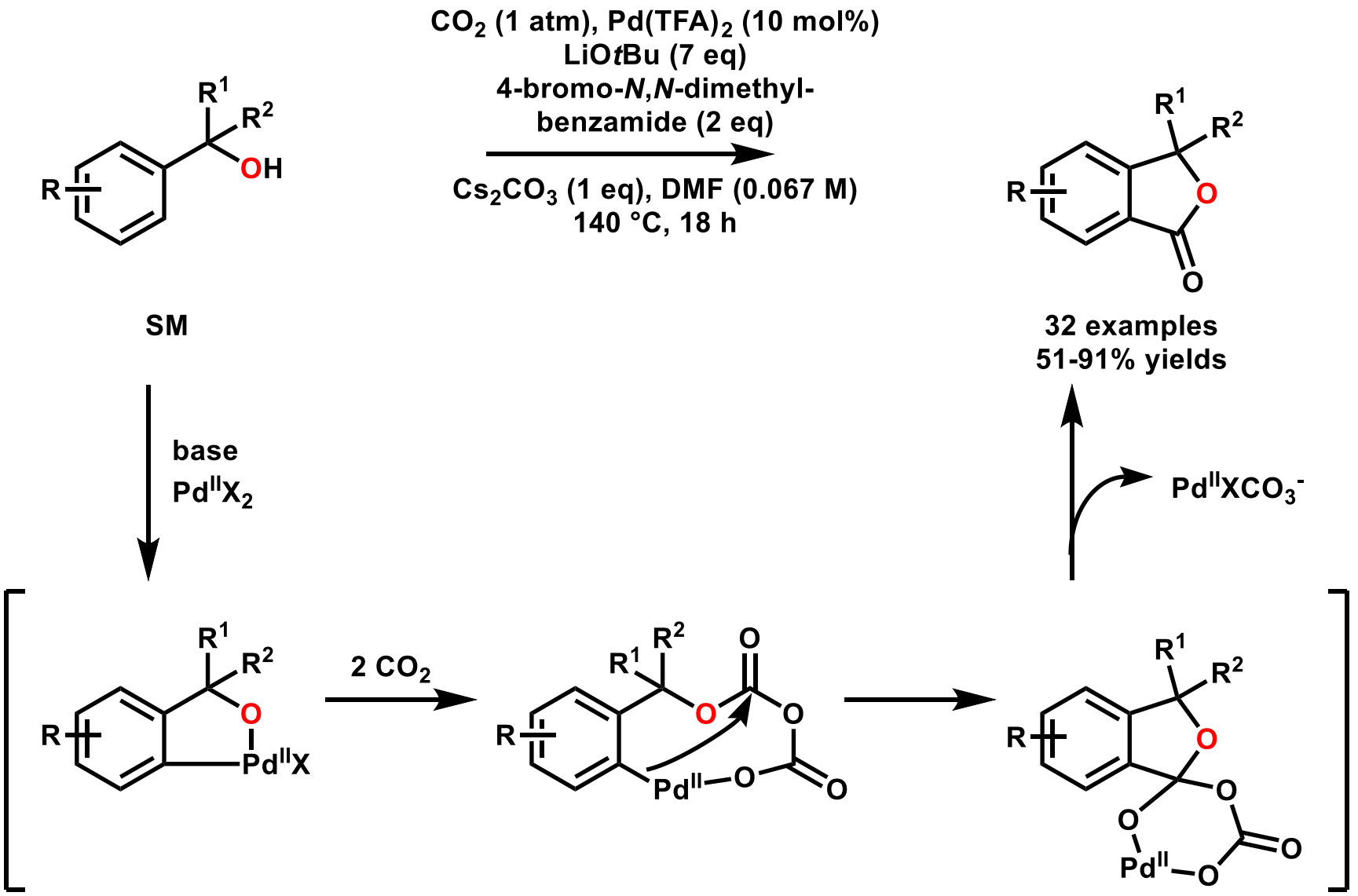
$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

H_2O (4 eq), CO_2
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



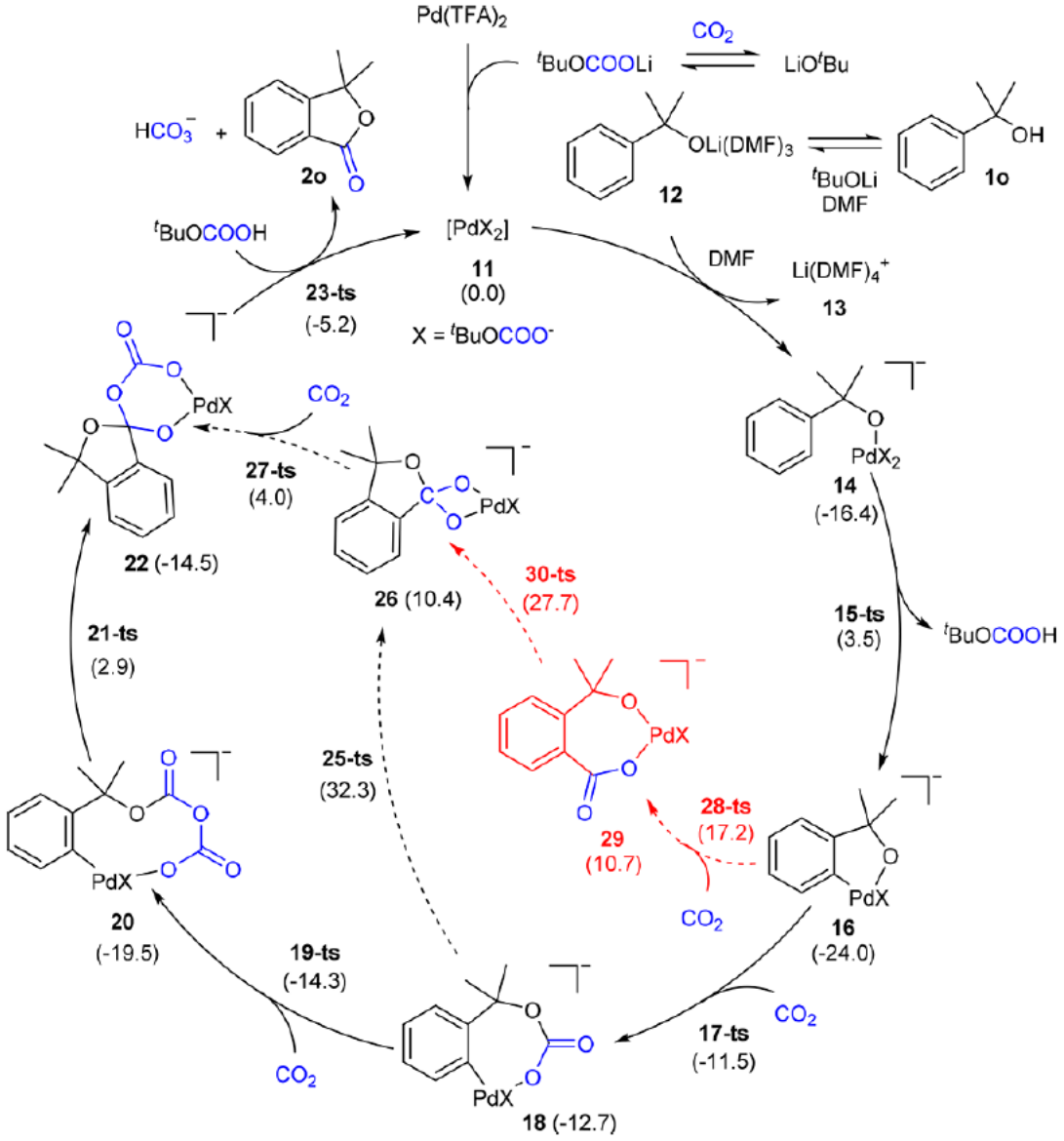
TM
71% (sealed tube, CO_2: 5 eq)
30% (manifold, CO_2: 1 atm)

Carbonate Formation by Yu's Group (1)



Song, L.; Zhu, L.; Zhang, A.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. *Org. Lett.* **2018**, *20*, 3776.

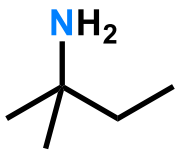
Carbonate Formation by Yu's Group (2)



DFT: M06-L method in DMF solvent. The values are given in kcal/ mol.

Song, L.; Zhu, L.; Zhang, A.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. *Org. Lett.* **2018**, *20*, 3776.

Mechanistic Study



SM
(0.30 mmol scale)

$Pd(OAc)_2$ (10 mol%)
H_2O (4 eq), CO_2

$CDCl_3$/AcOH (7/3, 0.3 M)
rt, 15 min
; Celite filtration; evp.

The crude was immediately subjected to ESI-MS analysis.

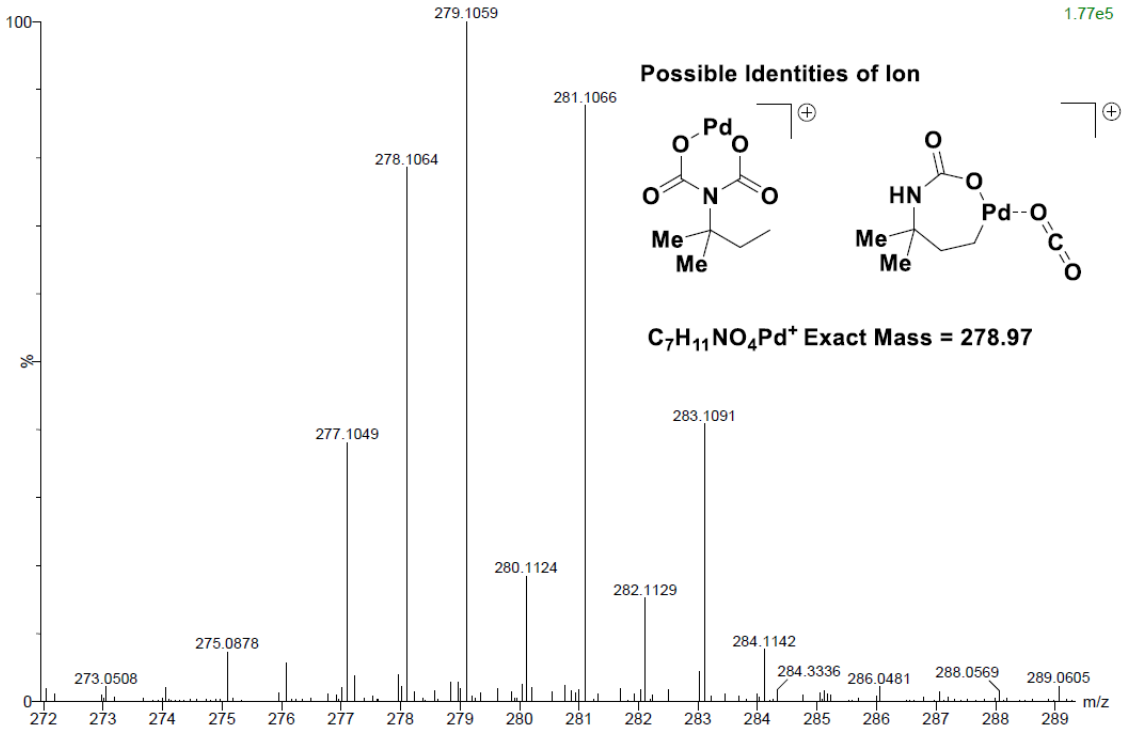
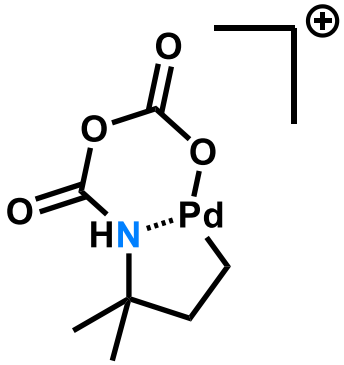
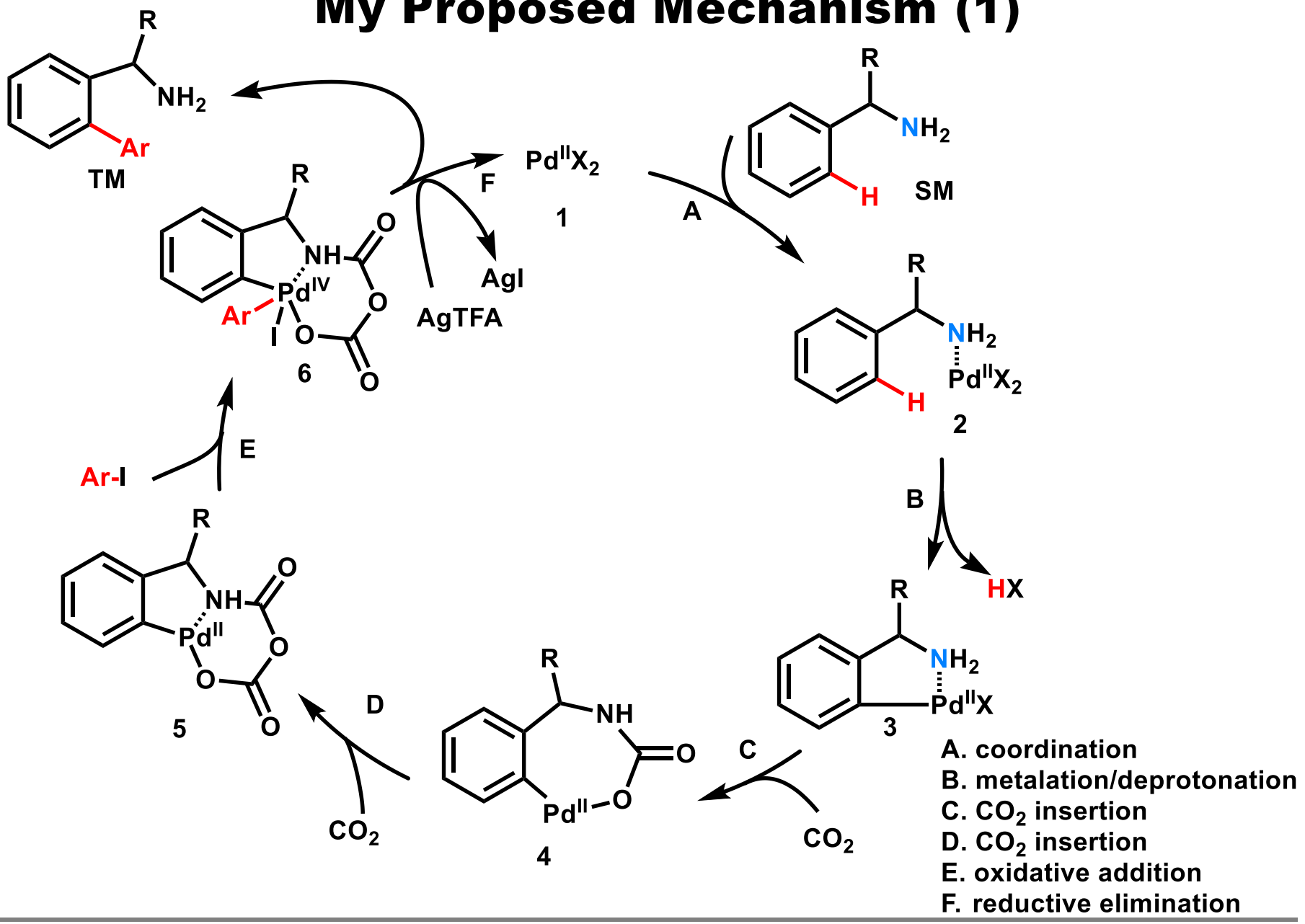


Figure S-209. Close-up of a potential Pd-Carbamate Ion by ESI-MS.



formation of 5-6 ring system occurred? (my proposal)

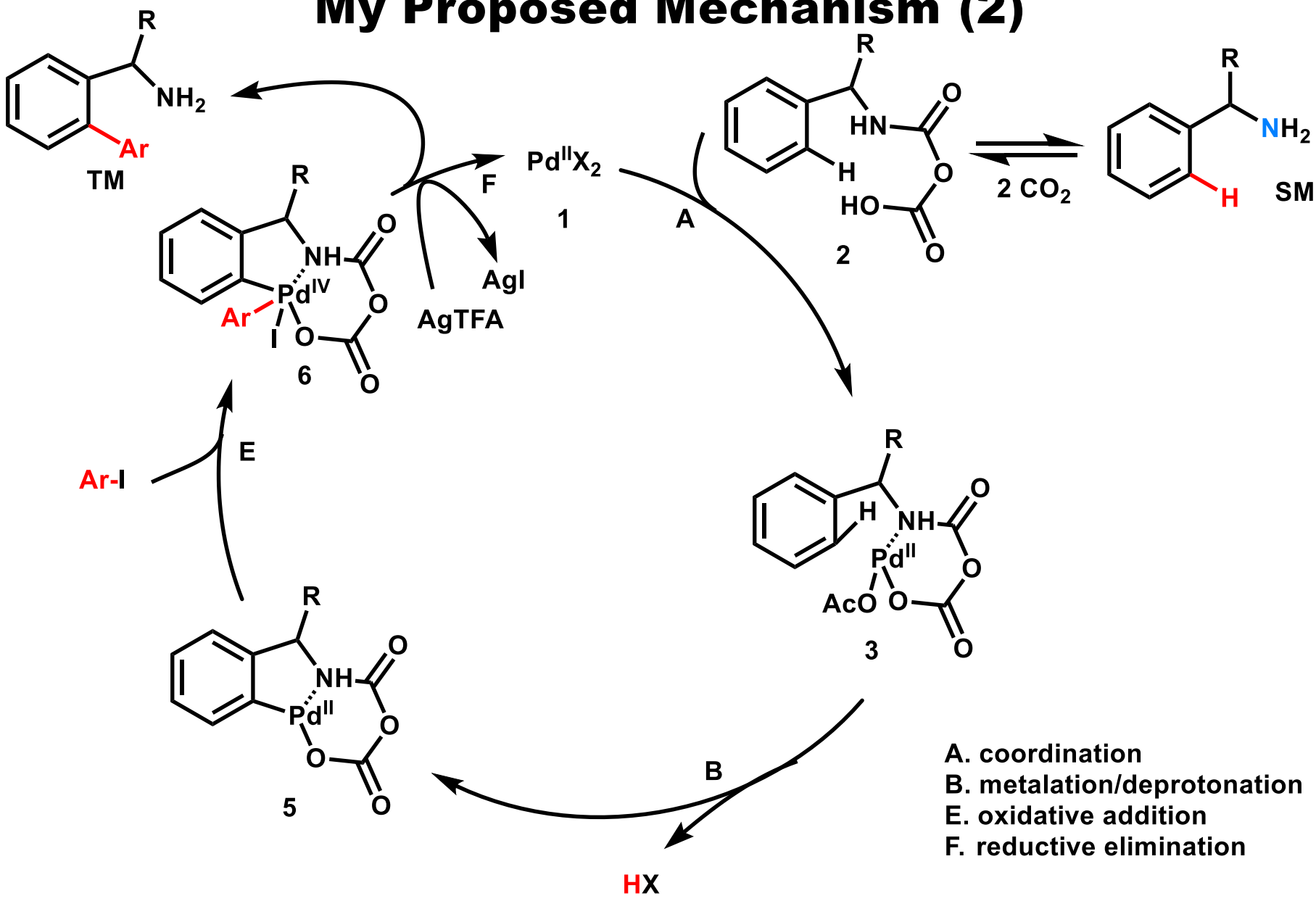
My Proposed Mechanism (1)



A. coordination
B. metalation/deprotonation
C. CO_2 insertion
D. CO_2 insertion
E. oxidative addition
F. reductive elimination

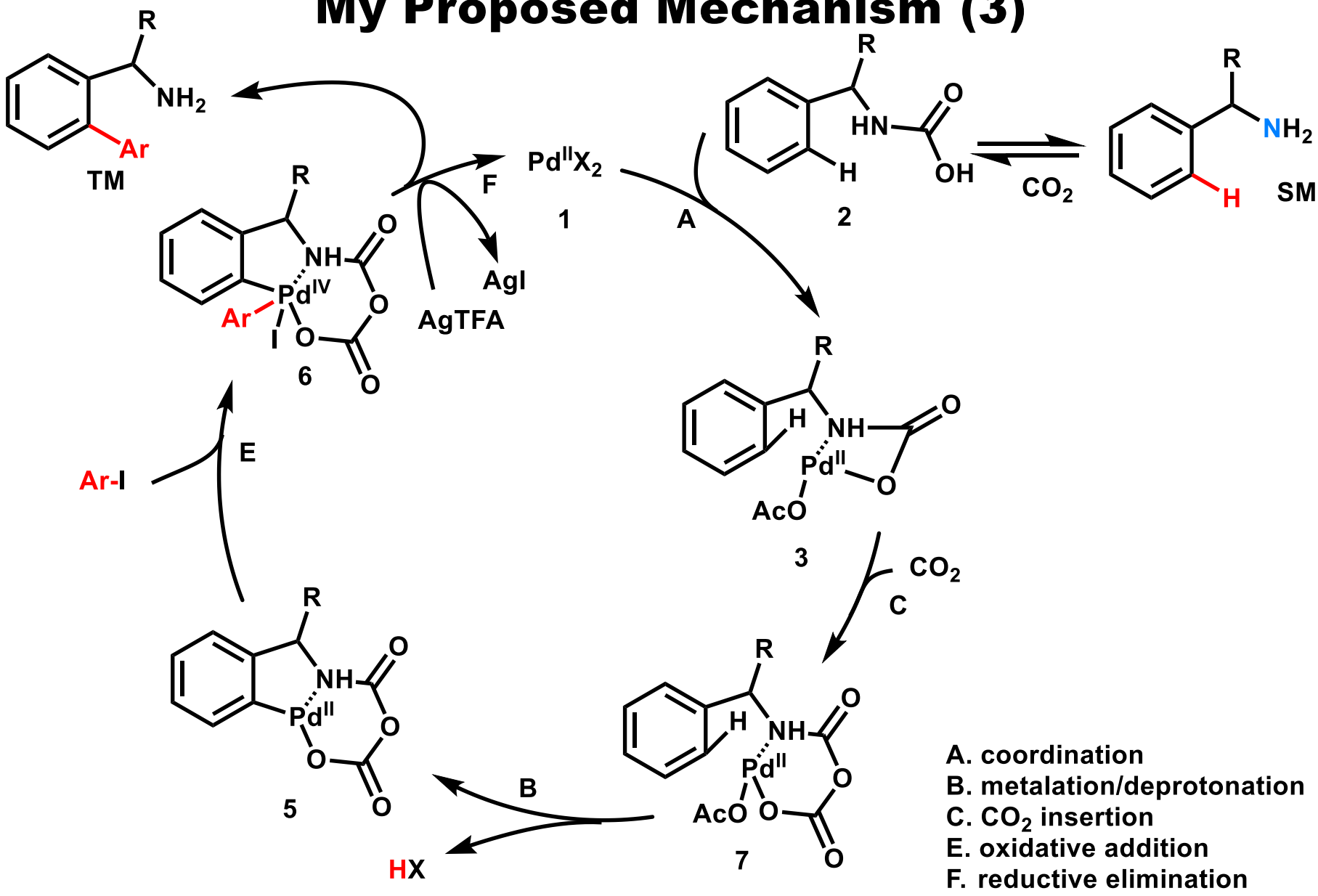
Song, L.; Zhu, L.; Zhang, A.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. *Org. Lett.* **2018**, *20*, 3776.

My Proposed Mechanism (2)



Song, L.; Zhu, L.; Zhang, A.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. *Org. Lett.* **2018**, *20*, 3776.

My Proposed Mechanism (3)

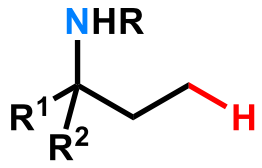


Song, L.; Zhu, L.; Zhang, A.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. *Org. Lett.* **2018**, *20*, 3776.

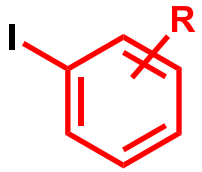
Summary

γ-sp^3 and sp^2 Bond activation by using CO_2 as transient directing group.

1. Arylation of *aliphatic* amines (1° and 2°)



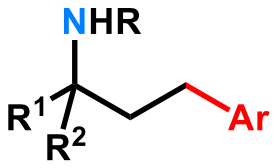
SM
(0.15-3.0 mmol)



halide
(3.0 eq)

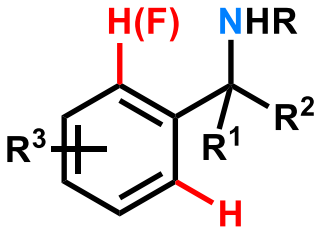
$Pd(OAc)_2$ (10 mol%)
AgTFA (1.5 eq)

CO_2 (1-2 eq), H_2O (4 eq)
HFIP/AcOH (1/1, 0.15 M)
110 °C, 12 h

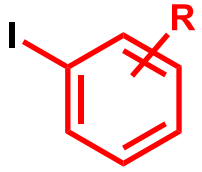


TM
44 examples
79-31% yields

2. Arylation of aromatic amines (1° and 2°)



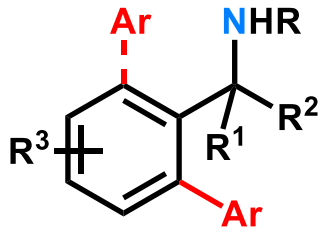
SM
(0.15-15 mmol)



halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
AgTFA (2.0 eq)

H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



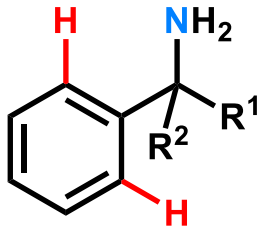
72 examples
88-32% yields

Future. alcohol and thiol will be functionalized by using this methodology??

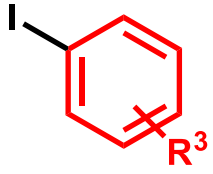
1) Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. 2) Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818. and SI.

Appendix

di-C(sp^2)-Arylation (1° Amine)



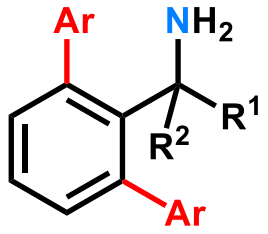
SM
(0.15 mmol scale)



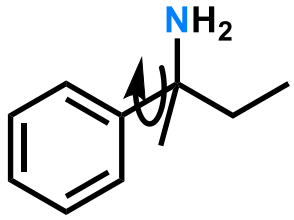
halide
(6 eq)

$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

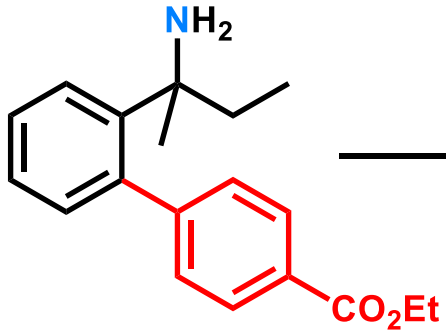
H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h

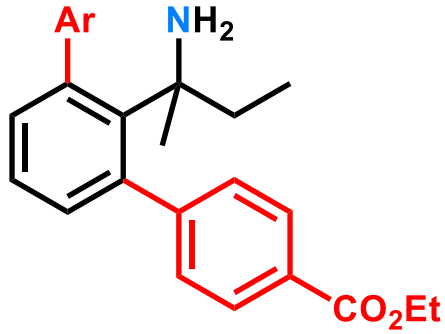


TM



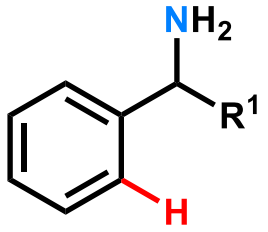
rotate freely



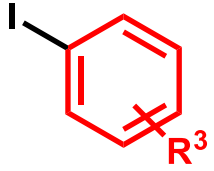


Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

mono-C(sp^2)-Arylation (1° Amine)



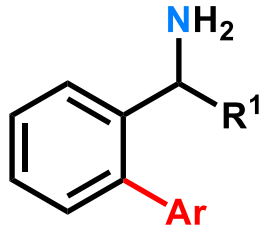
SM
(0.15 mmol scale)



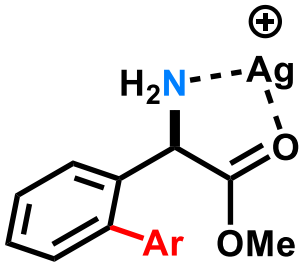
halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
AgTFA (2.0 eq)

H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



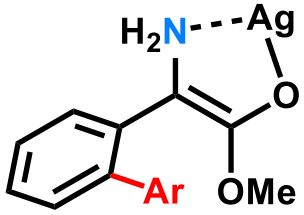
TM



69%, 15% es
(15% ee)

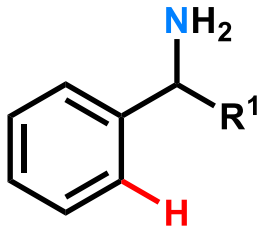
low reactivity for second arylation?

racemization

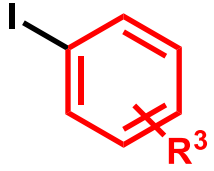


Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

mono-C(sp^2)-Arylation (1° Amine)



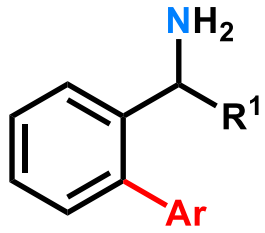
SM
(0.15 mmol scale)



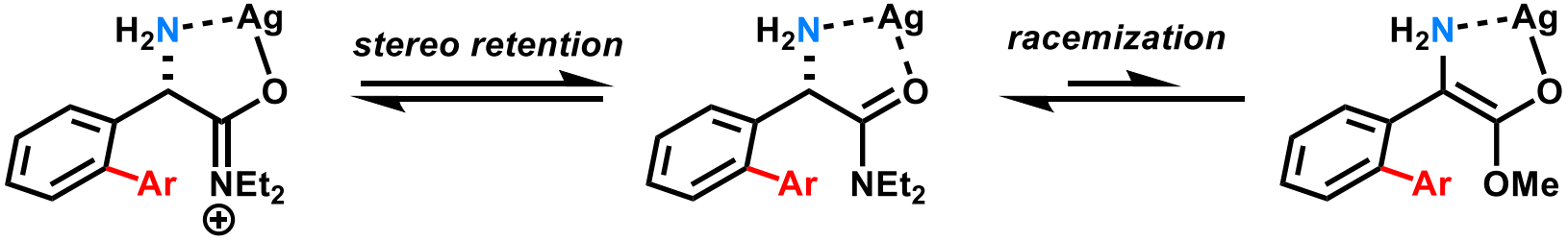
halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
AgTFA (2.0 eq)

H_2O (4 eq), CO_2 (5 eq)
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



TM

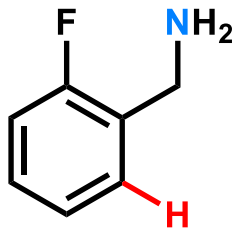


65%, 50% es
(50% ee)

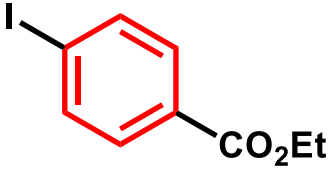
Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Application for Scale-up Synthesis

• scale-up synthesis



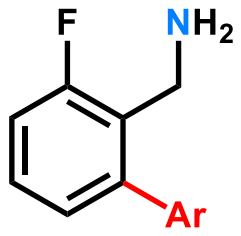
SM
(*15 mmol scale*)



halide
(3 eq)

$Pd(OAc)_2$ (10 mol%)
additive (2.0 eq)

H_2O (4 eq), CO_2
HFIP/AcOH (7/3, 0.15 M)
100 °C, 12-15 h



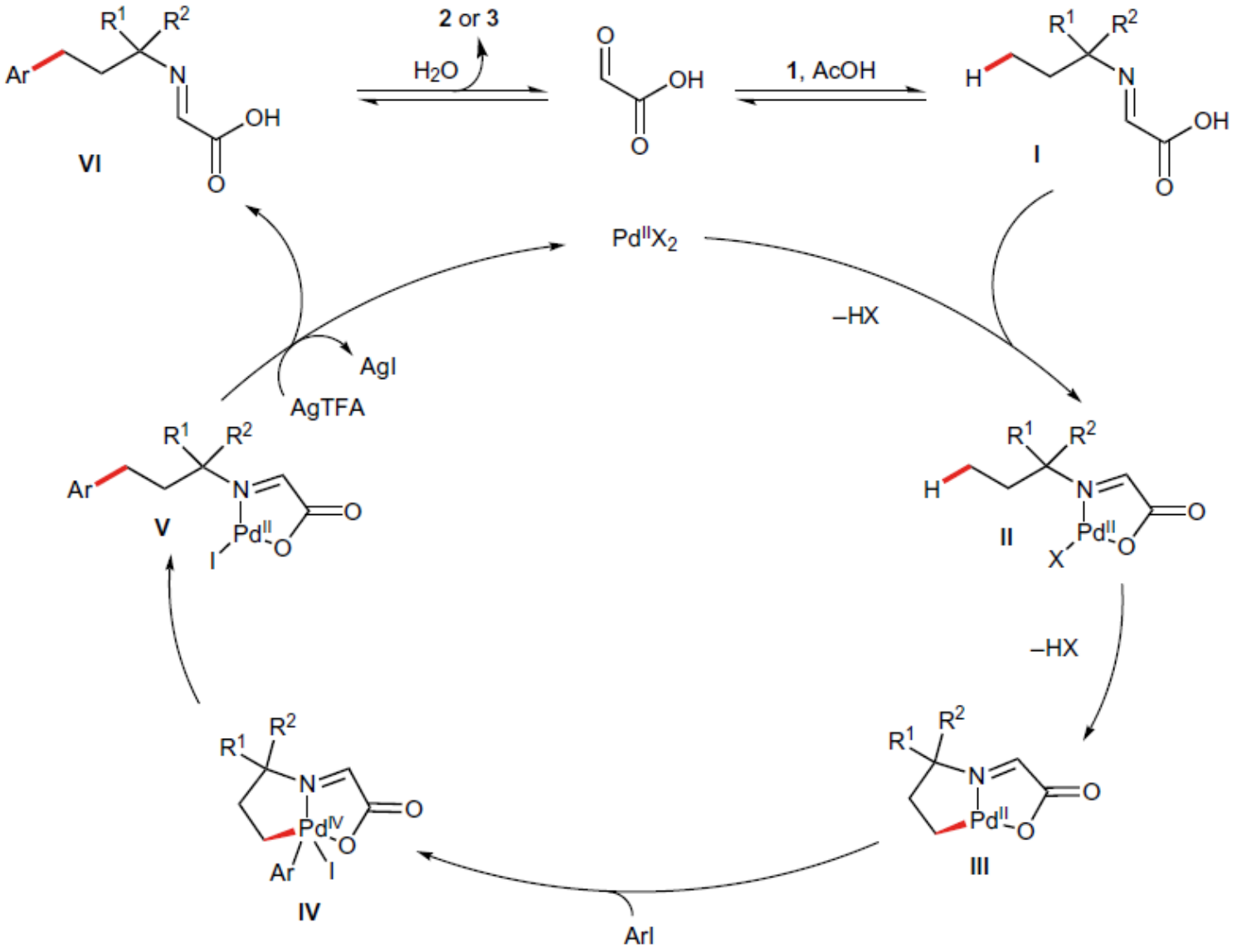
TM
71% (sealed tube, CO_2: 5 eq)
30% (manifold, CO_2: 1 atm)

Simple calculation

sealed tube: 42 atm
manifold: 1 atm

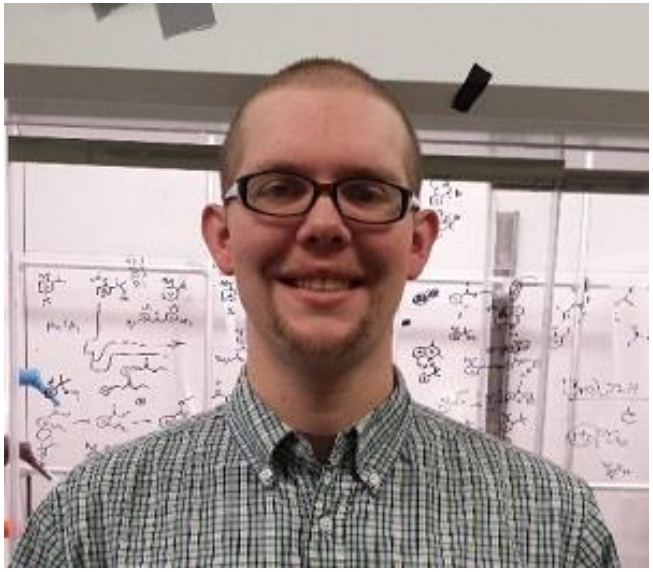
Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

Ge's proposed mechanism



Liu, Y.; Ge, H. *Nature Chem.* **2017**, *9*, 26.

Prof. Michael C. Young



2006
B.S. Chemistry, B.S. Biology at Western Carolina University

2008
M.S. Chemistry at Werstern Carolina University
"1,4-Topochemical Polymerization of 1,3-Butadiene Derivatives in a Host-Guest Matrix"
(Advisor: Prof Brian D. Dinkelmeyer)

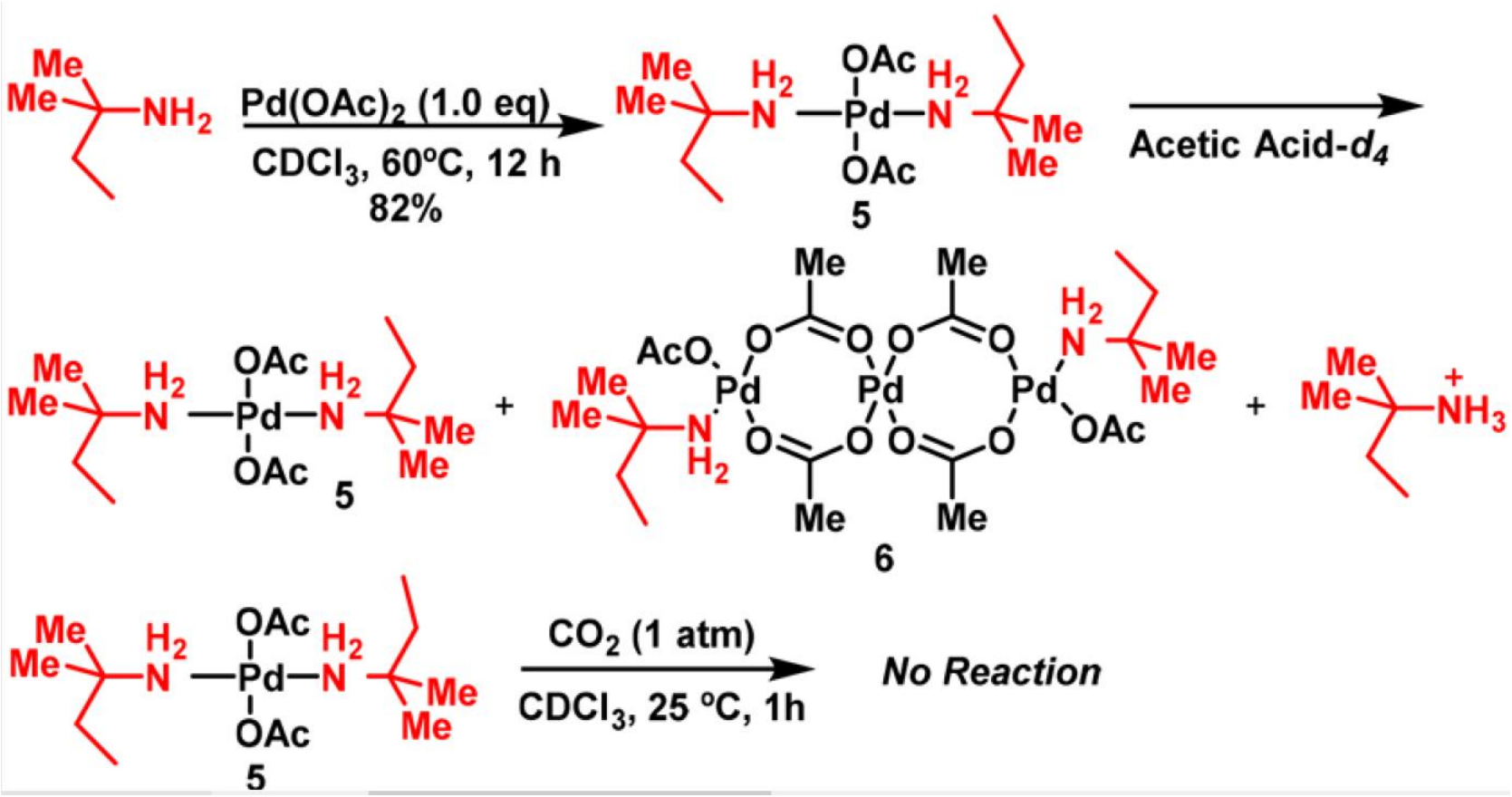
2014
Ph.D Organic Chemistry at University of California - Riverside
"Self-Assembly of Functionalized Supramolecular Structures"
(Advisor: Prof. Richard J. Hooley)

2014-2016
Postdoctoral Scholar at University of Texas - Austin
Project: "Dynamic Covalent Directing Group Strategies for Ketone and Amine Functionalization"
(Advisor: Prof. Guangbin Dong)

2016-Present
Assistant Professor at University of Toledo
Department of Chemistry & Biochemistry, School of Green Chemistry & Engineering

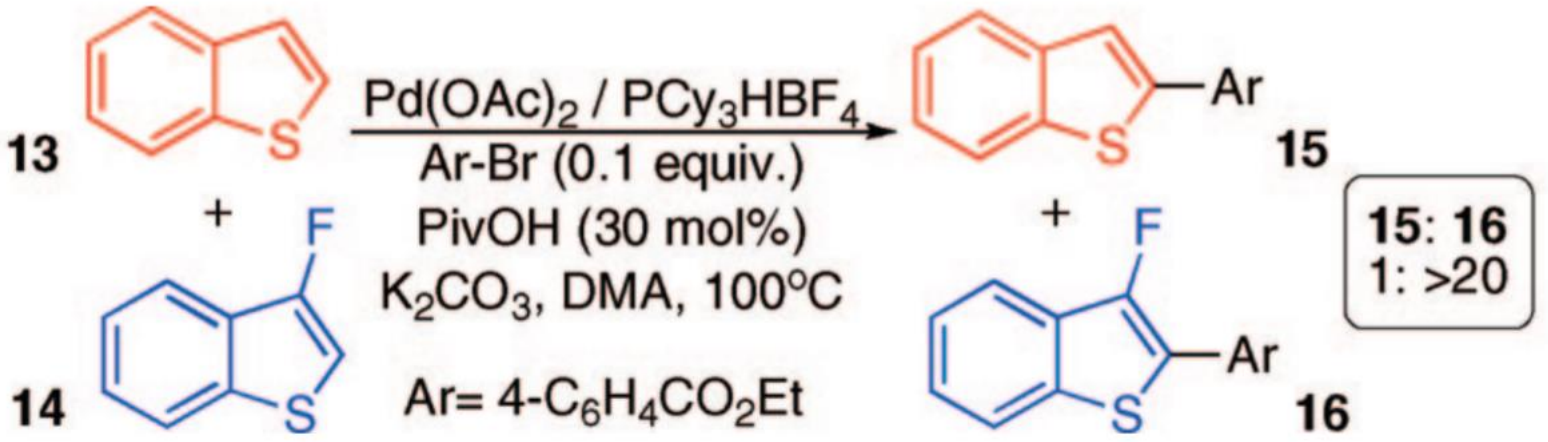
Research Topic
1. Hydrogen bond-directing strategies for allowing late-stage functionalization of complex molecules.
2. Sustainable-directing group strategies for transition metal catalysis.
3. Kinetic stabilization of reactive metals.
4. Supramolecular chemical sensors.

Disruption of inactive Pd-diamine complex



Kapoor, M.; Liu, D.; Young, M. C. *J. Am. Chem. Soc.* **2018**, *140*, 6818.

Resioselectivity of Furan for CMD Mechanism (2)



Redioselectivity of Furan for CMD Mechanism (2)

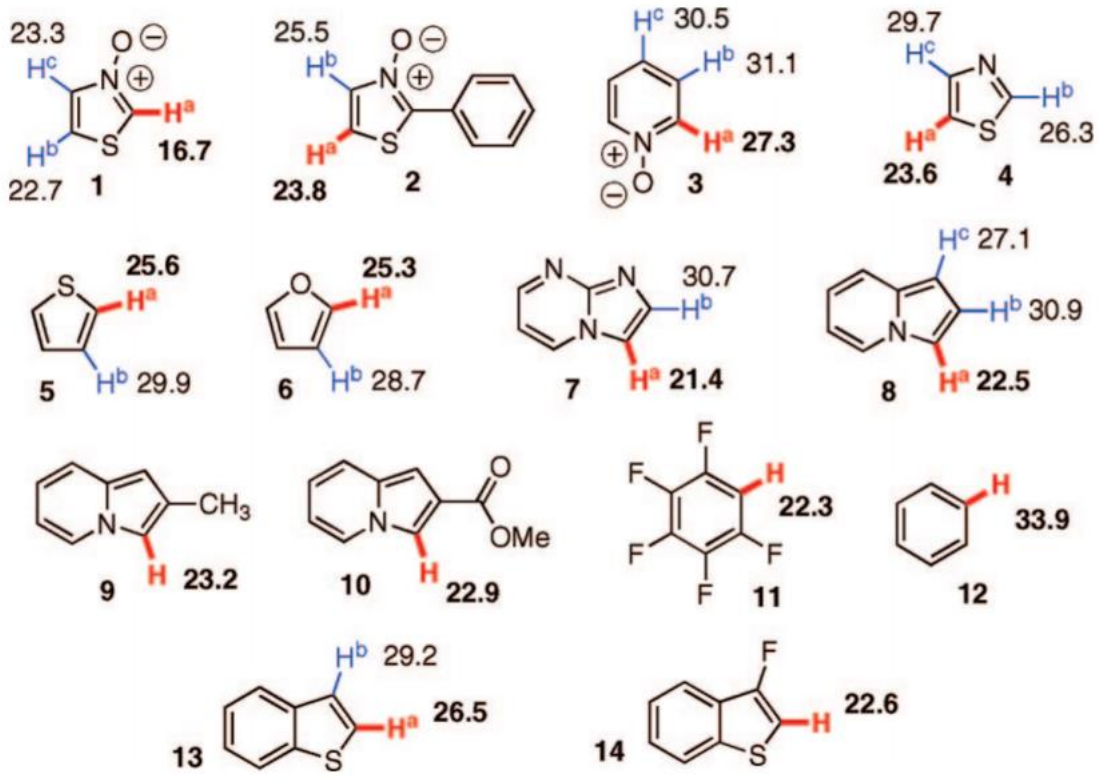
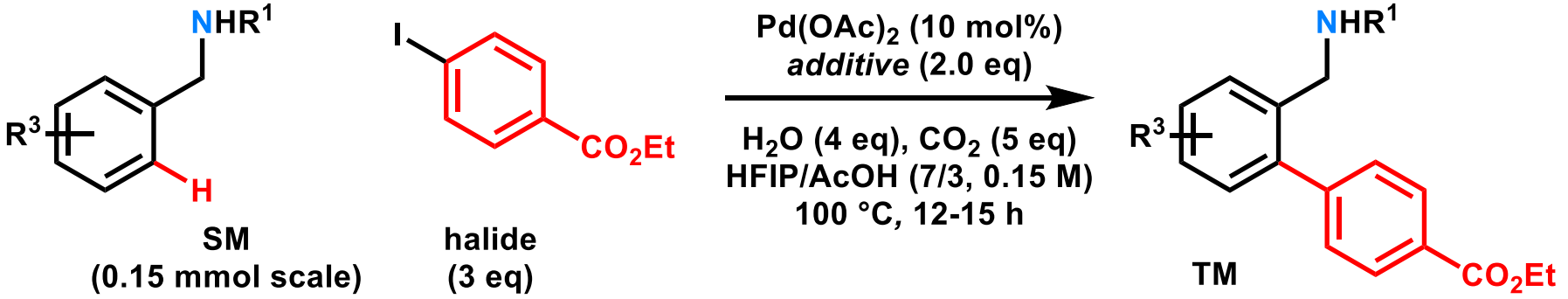


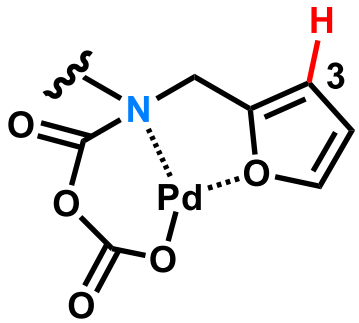
Figure 1. Free energy of activation ($\Delta G^{\ddagger}_{298K}$, kcal mol^{-1}) for direct arylation via the CMD pathway involving an acetate ligand. Red bonds indicate the experimentally observed sites of arylation.

inductive effect of oxygen atom resulted in good regioselectivity?

Gorelsky, S.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

Reactivity of Furan Ring

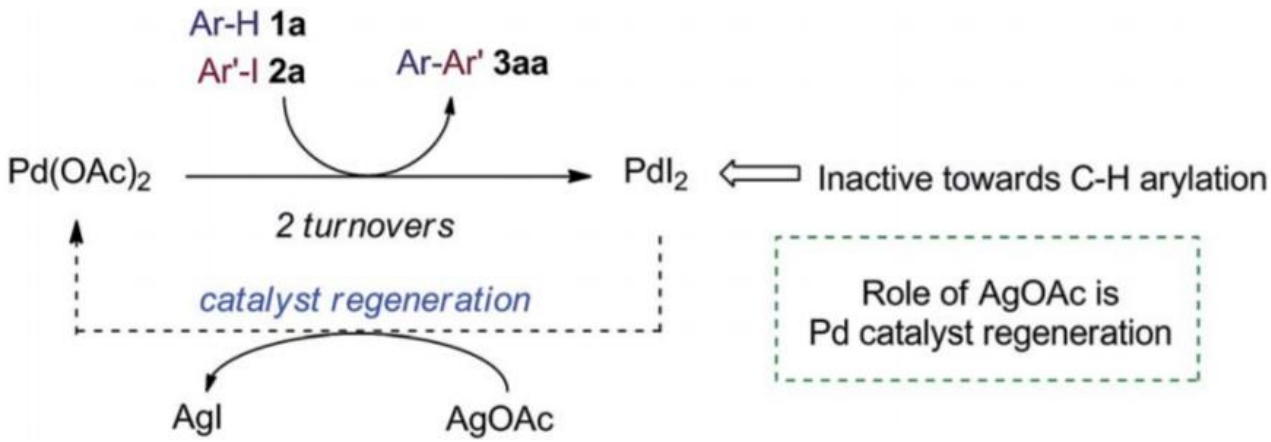




This species inhibit CMD at furan C3 position? (proposal)

Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* in press. and SI.

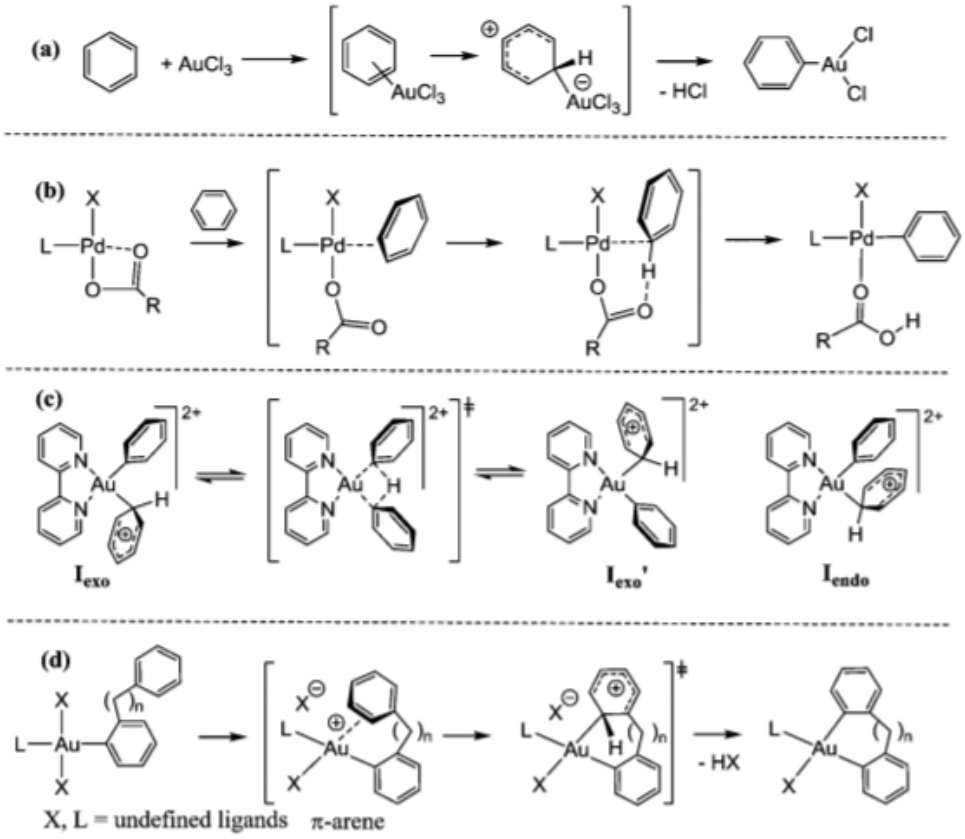
Effect of Ag Salt



Scheme 2 Poisoning and regeneration of Pd catalyst in C–H arylation.

Larrosa, I. et atl *Chem. Sci.* **2014**, *5*, 3509.

Appendix



Scheme 1 (a) Arene auration by $AuCl_3$ *via* the S_EAr mechanism;[7] (b) arene metalation by concerted metalation–deprotonation (CMD);[11–13] (c) hypothetical degenerate H-exchange in an Au^{III}(phenyl)(benzene) model complex;[14] (d) proposed arene C–H activation pathway in Au^{III}-catalysed arene–arylsilane coupling.[15]

Larrosa, I. et atl *Chem. Sci.* **2014**, *5*, 3509.