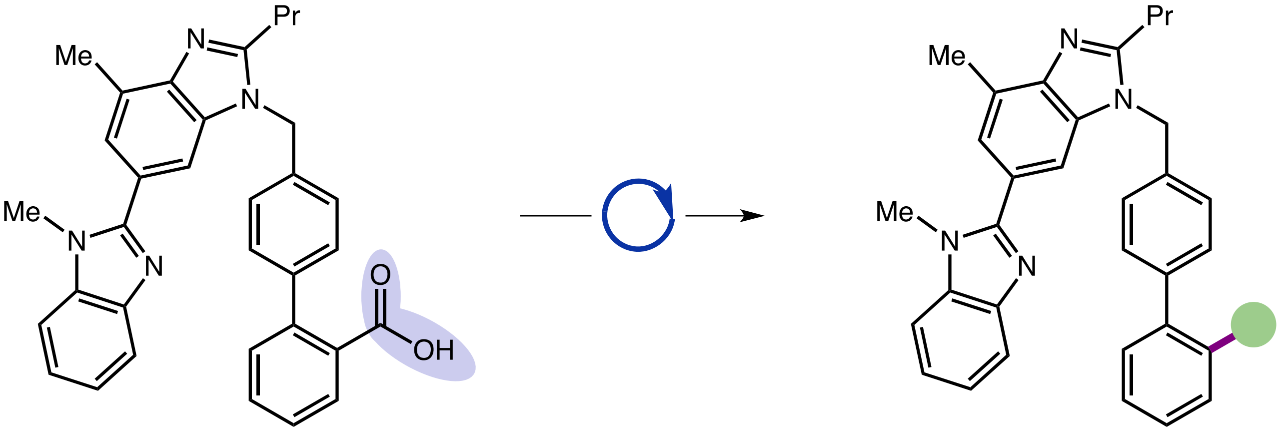
Decarboxylative/Decarbonylative Couplings of (Hetero)Aryl Carboxylic Acids and Derivatives



Telmisartan

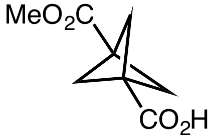
Yufan Liang

MacMillan Group Meeting

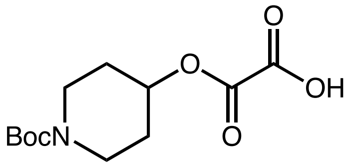
January 17, 2019

Arylating Reagents

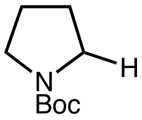
■ New alkylating reagents: innovations for novel alkylating reactions



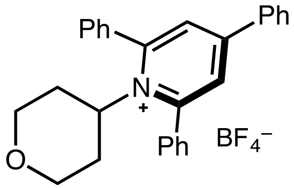
alkyl carboxylic acid



alkyl oxalate

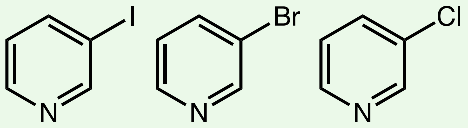


C–H nucleophile

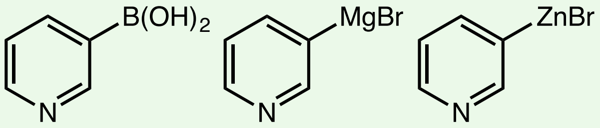


alkyl amine

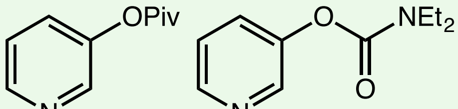
■ Arylating reagents in cross-couplings: overview



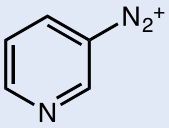
aryl halide



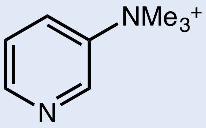
aryl organometallic reagents



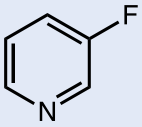
phenol derivative



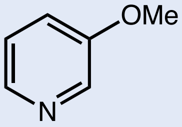
aryl diazonium



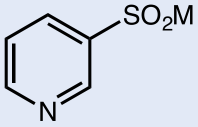
aniline



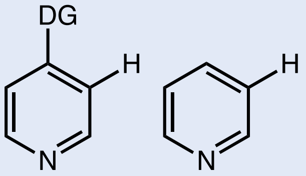
aryl fluoride



aryl ether



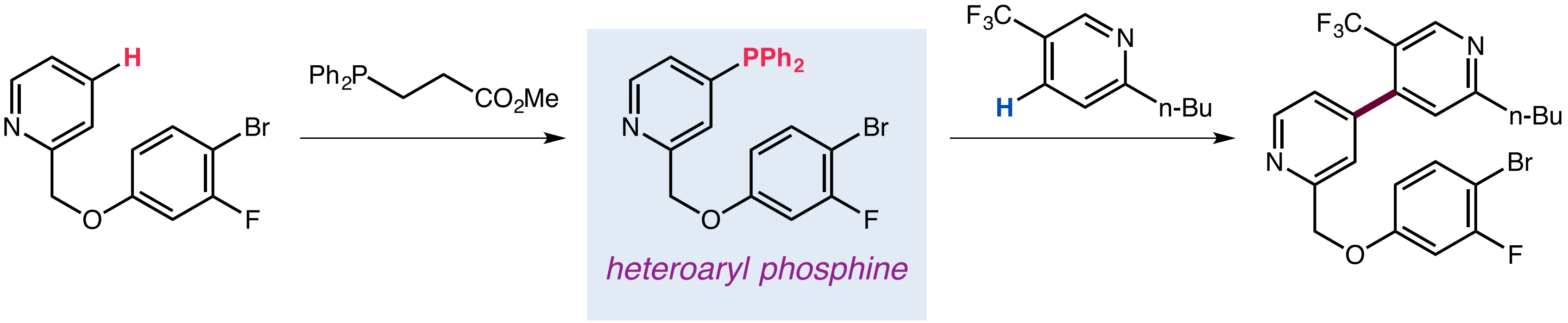
aryl sulfinate



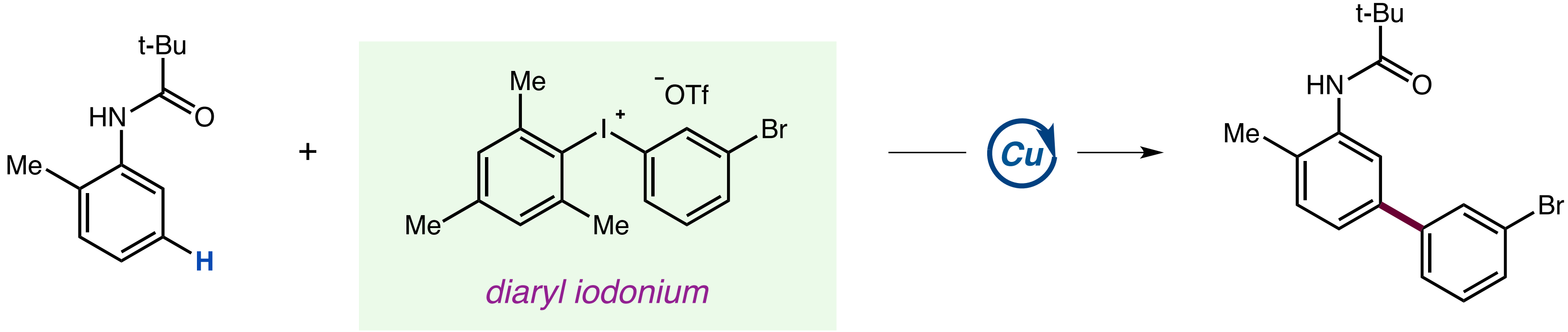
arene

Arylating Reagents in New Arylation Reactions

■ Aryl phosphine: heterobiaryl synthesis



■ Diaryl iodonium salts: *meta*-selective C–H arylation

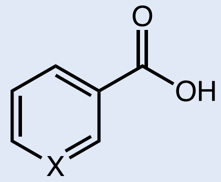


Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. *Science* **2018**, *362*, 799–804

Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597

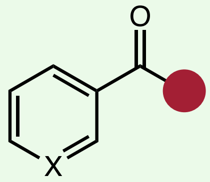
(Hetero)Aryl Carboxylic Acid

Aryl carboxylic acids and derivatives



aryl carboxylic acid

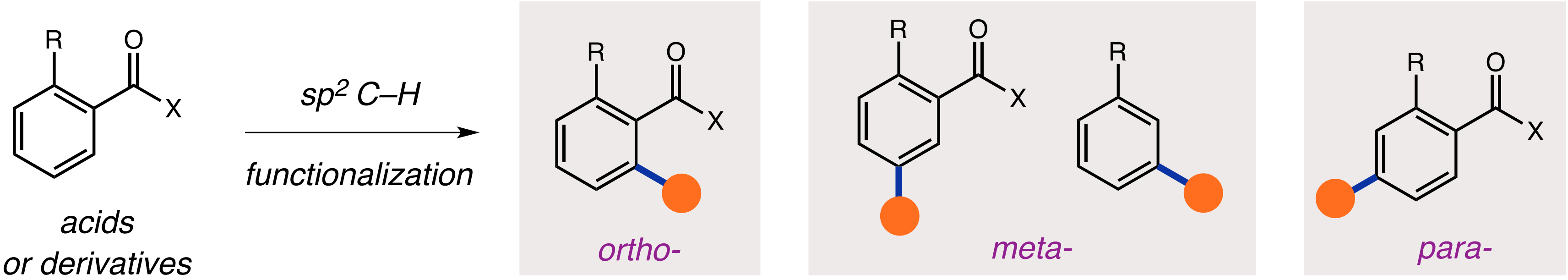
- Commercially available
- Structurally diverse
- Bench-stable, easy to handle



aryl amide/ester

- Easily available
- One-step, trivial synthesis
- Highly tunatble

Carboxylic acids are versatile directing groups for *sp*^{2} C–H functionalization

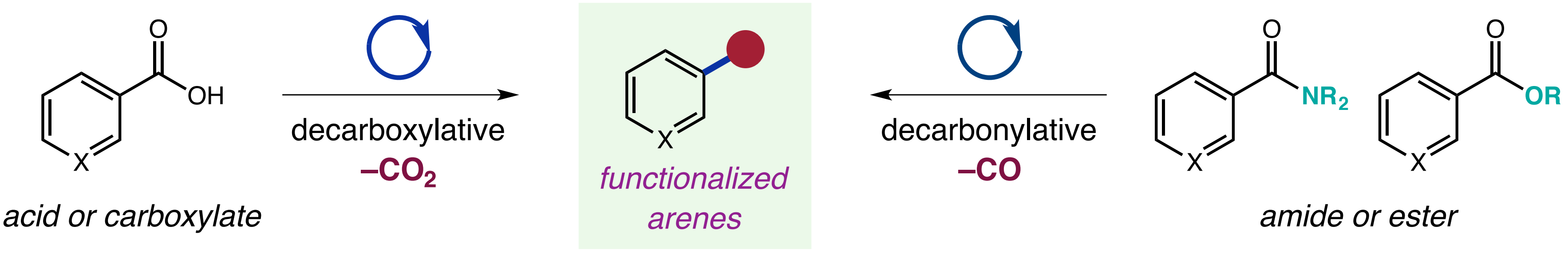


Drapeau, M. P.; Goossen, L. J. *Chem. Eur. J.* **2016**, *22*, 18654

Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. *Chem. Commun.* **2017,** 5*3,* 5584

Decarboxylative and Decarbonylative Couplings of Aryl Acids and Derivatives

What will be covered



acid or carboxylate

decarboxylative
$-CO_2$

functionalized arenes

decarbonylative
$-CO$

amide or ester

Related review articles

◆ Decarboxylative coupling:

Igor Larrosa *Eur. J. Org. Chem.* **2017**, 3517 (biaryl synthesis)

Jessica M. Hoover *Comments Inorg. Chem.* **2017,** *37*, 169 (mechanistic studies)

Weiping Su *Chem. Rev.* **2017,** *117*, 8864 (decarboxylative C–H functionalization)

Igor Larrosa *Synthesis* **2012**, 653 (C–C bond)

Lukas J. Goossen *Chem. Soc. Rev.* **2011**, *40*, 5030 (C–C bond)

Lukas J. Goossen *Isr. J. Chem.* **2010**, *50*, 617

◆ Decarbonylative coupling:

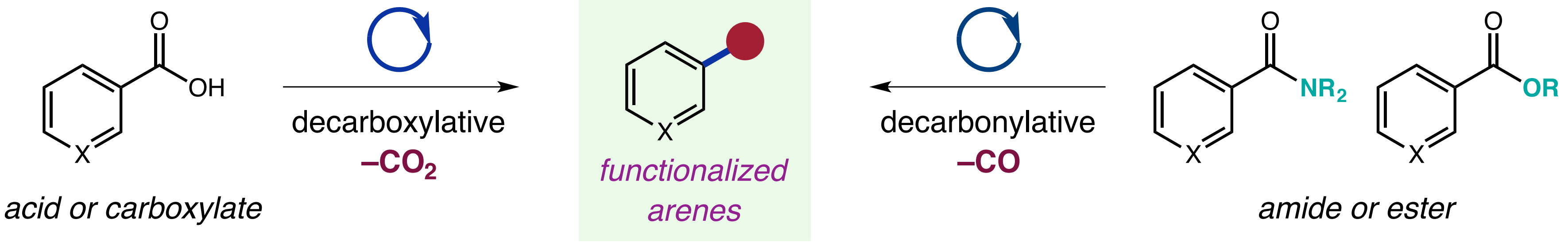
Magnus Rueping *Chem. Eur. J.* **2018**, *24*, 7794

Michal Szosak *Org. Biomol. Chem.* **2018**, *16*, 7998–8010 (amide as substrate)

Junichiro Yamaguchi *Chem. Soc. Rev.* **2017**, *46*, 5864

Decarboxylative and Decarbonylative Couplings of Aryl Acids and Derivatives

■ What will be covered



decarboxylative $-CO_2$

functionalized arenes

decarbonylative $-CO$

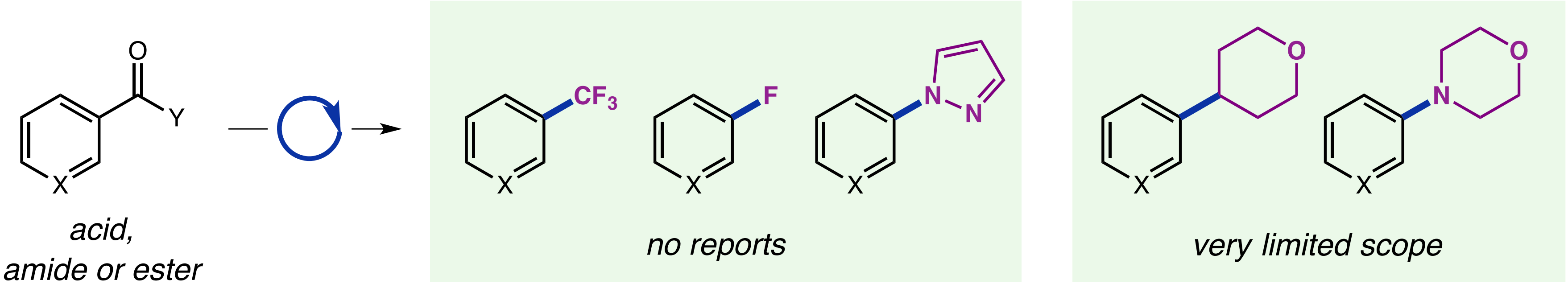
acid or carboxylate

amide or ester

■ Summary of common features

- ◆ High temperature (>150 °C)
- ◆ *Ortho* effect in decarboxylation step
- ◆ Concerted mechanism

■ What transformations haven't been accomplished



acid, amide or ester

no reports

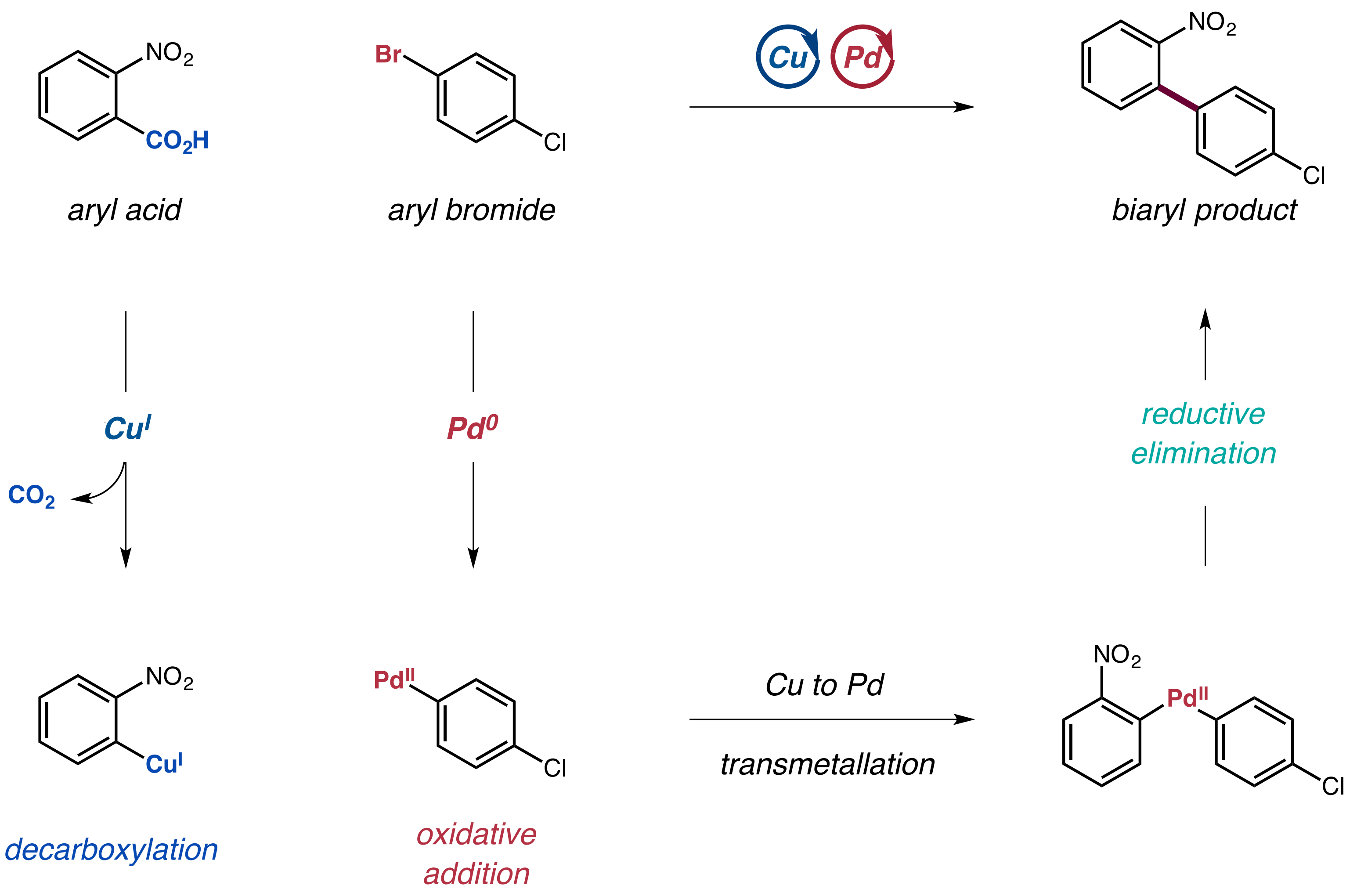
very limited scope

Outline

- Decarboxylative coupling using aryl acid
    - C–C bond formation
    - C–O and C–N bond formation
    - *Ortho* effect and lower-temperature system
- Decarbonylative coupling using activated ester and amide
    - C–C bond formation
    - C–heteroatom bond formation and mechanistic study
- Radical strategy

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

■ Biaryl synthesis via Cu/Pd bimetallic catlysis



aryl acid

aryl bromide

biaryl product

Cu^I

Pd^0

CO_2

decarboxylation

oxidative addition

Cu to Pd

transmetallation

reductive elimination

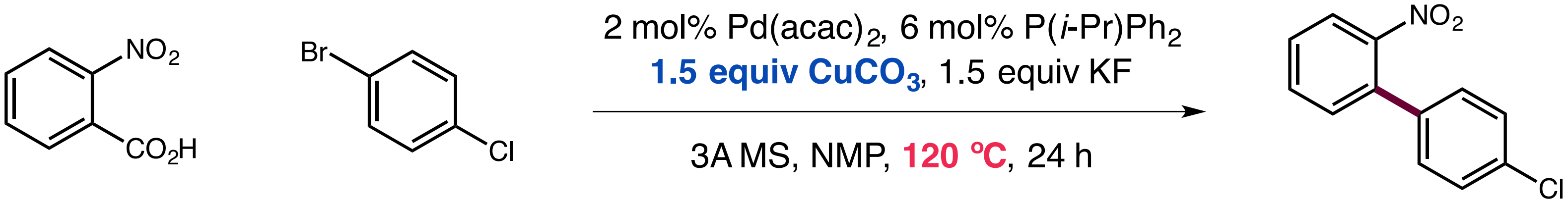
Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664

Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

■ Optimal contidions

stoichiometric in Cu



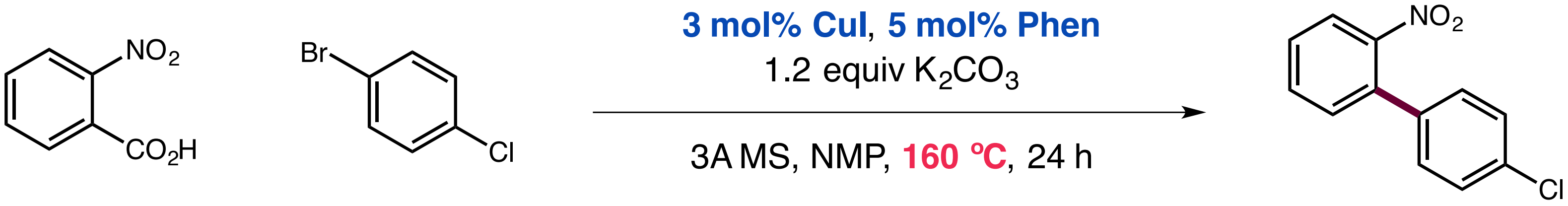
2 mol% Pd(acac)$_2$, 6 mol% P(*i*-Pr)Ph$_2$
1.5 equiv CuCO$_3$, 1.5 equiv KF

3A MS, NMP, **120 ℃**, 24 h

1.5 equiv

96% yield

catalytic in Cu



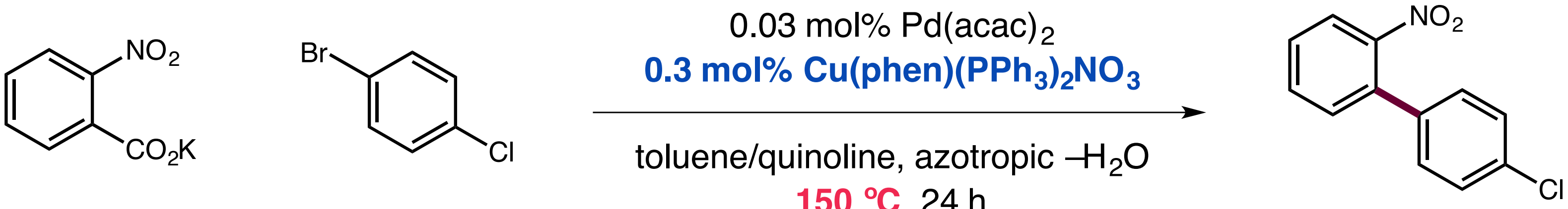
1 mol% Pd(acac)$_2$
3 mol% CuI, **5 mol% Phen**
1.2 equiv K$_2$CO$_3$

3A MS, NMP, **160 ℃**, 24 h

1.5 equiv

99% yield

large scale



0.03 mol% Pd(acac)$_2$
0.3 mol% Cu(phen)(PPh$_3$)$_2$NO$_3$

toluene/quinoline, azotropic –H$_2$O
150 ℃, 24 h

1.0 equiv
80 mmol

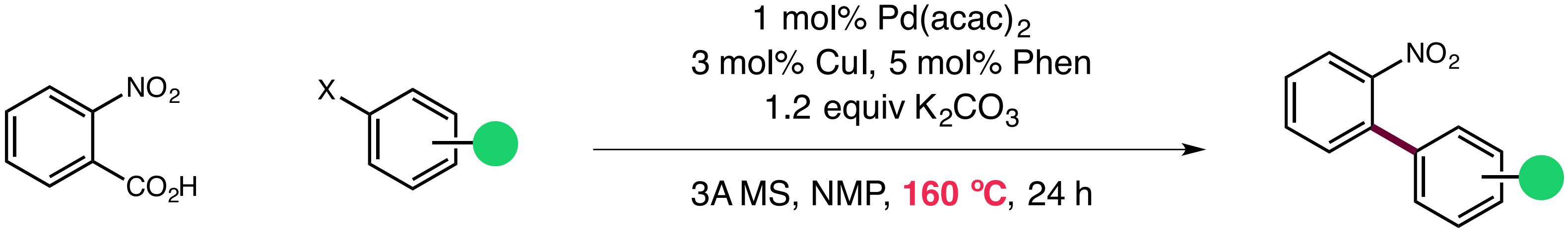
92% yield
>17 g

Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664

Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

■ Scope of aryl halide

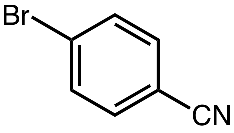


1 mol% Pd(acac)$_2$
3 mol% CuI, 5 mol% Phen
1.2 equiv K_2CO_3

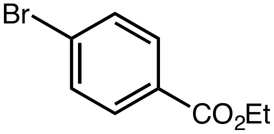
3A MS, NMP, **160 ℃**, 24 h

1.5 equiv

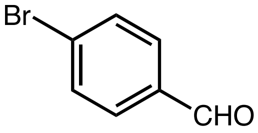
biaryl product
(1.5 equiv Cu yield)



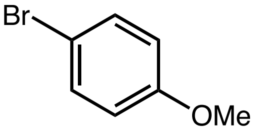
93% yield



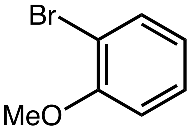
96% yield



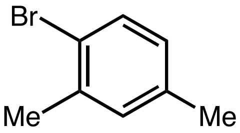
78% yield



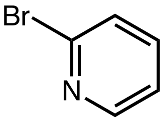
68% yield



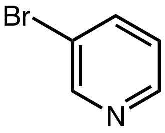
30% yield
(80% yield)



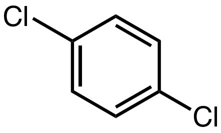
23% yield
(93% yield)



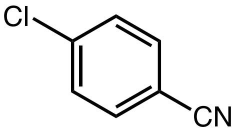
53% yield



98% yield



66% yield

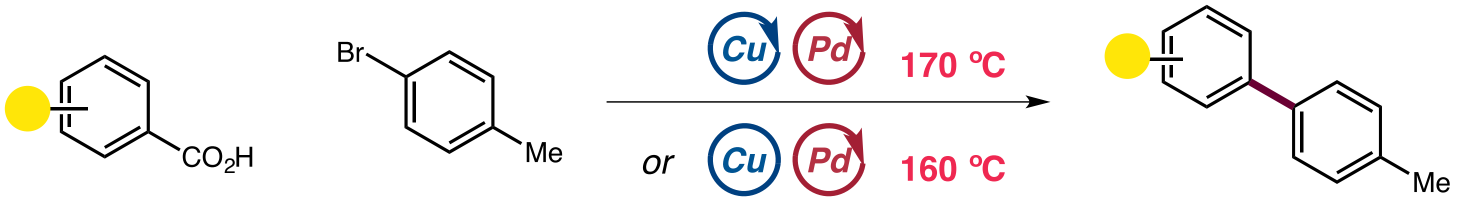


96% yield

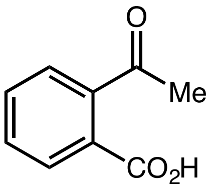
Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664
Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

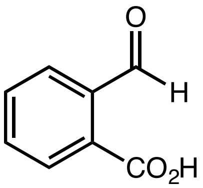
■ Scope of aryl acid



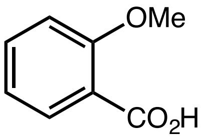
(yield with 1.2 equiv Cu)



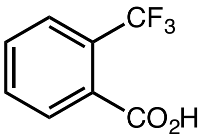
69% yield



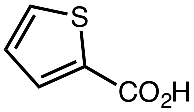
61% yield



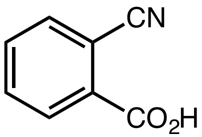
46% yield



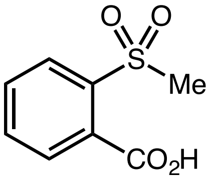
31% yield



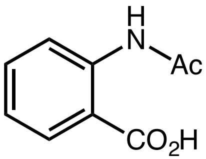
62% yield



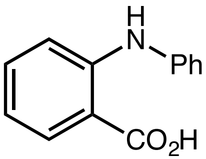
34% yield
(55% yield)



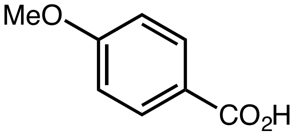
42% yield
(97% yield)



0% yield
(42% yield)



0% yield
(91% yield)

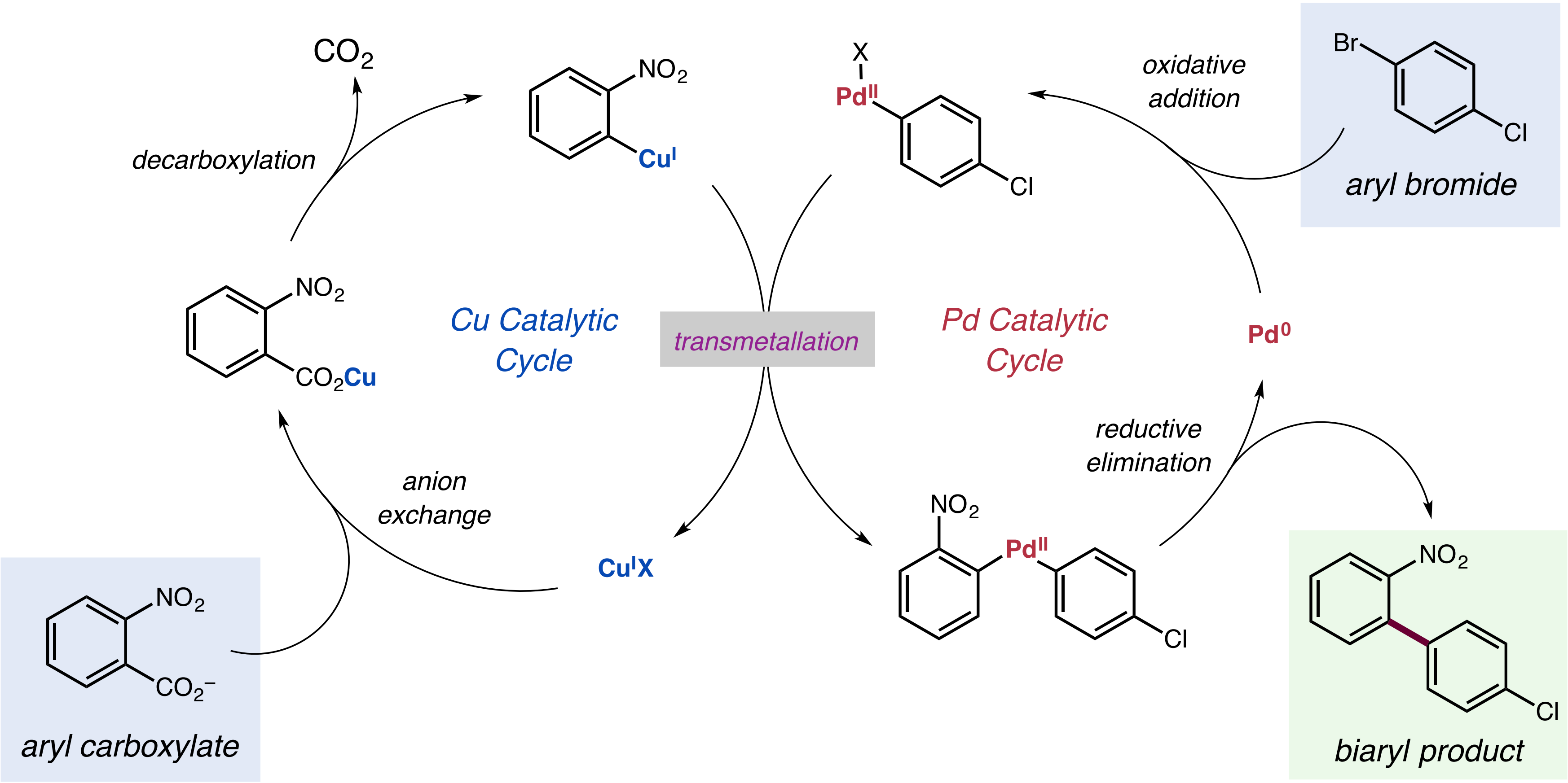


0% yield
(41% yield)

Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664
Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

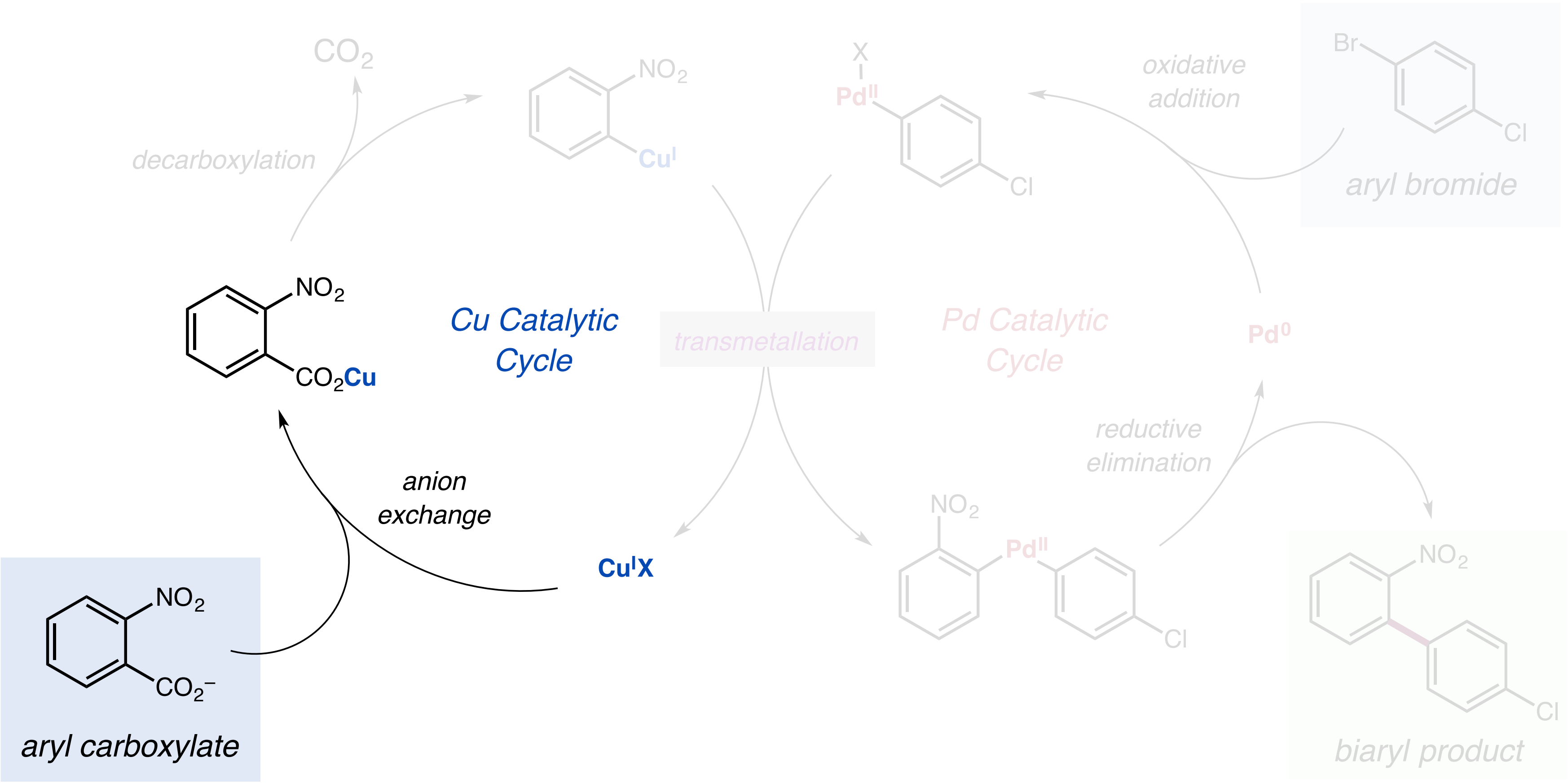
■ Proposed mechanism: synergistic Cu/Pd catalysis



Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

Proposed mechanism: synergistic Cu/Pd catalysis

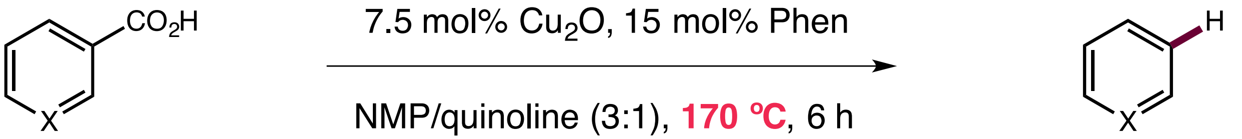


- Anion exchange step determines if turn-over of Cu is possible

Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

■ Influence of bromide anion in decarboxylation step

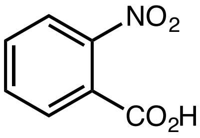


7.5 mol% Cu_2O, 15 mol% Phen

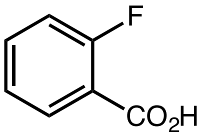
NMP/quinoline (3:1), 170 °C, 6 h

aryl acid

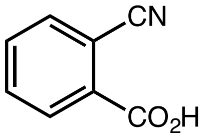
arene
(yield with 15 mol% KBr)



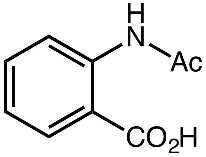
100% yield
(100% yield)



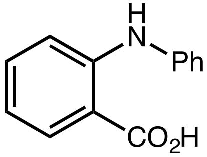
75% yield
(75% yield)



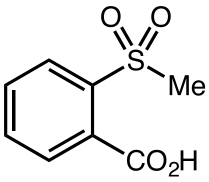
40% yield
(25% yield)



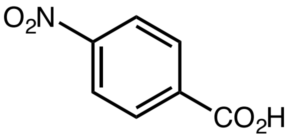
48% yield
(0% yield)



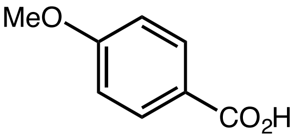
96% yield
(23% yield)



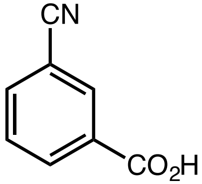
54% yield
(43% yield)



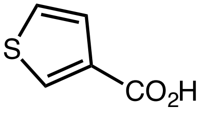
52% yield
(25% yield)



23% yield
(0% yield)



72% yield
(24% yield)

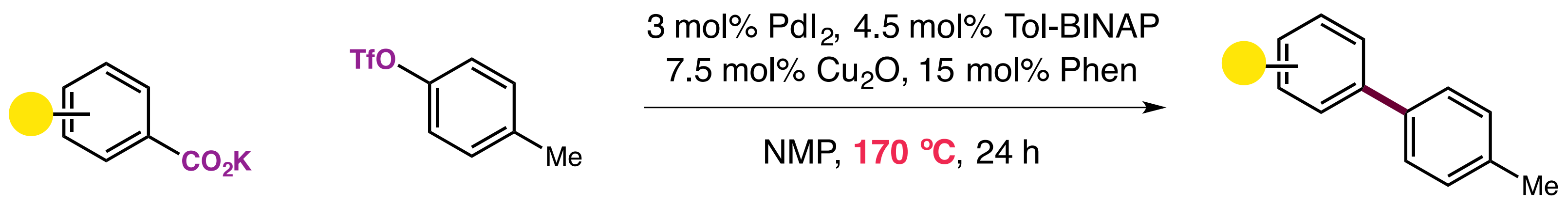


44% yield
(7% yield)

Goossen, L. J.; Rodriguez, N.; Melzer, B. M.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833

Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

■ Improved system for biaryl synthesis: ArOTf as electrophile



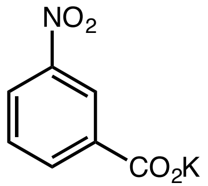
3 mol% PdI_2, 4.5 mol% Tol-BINAP
7.5 mol% Cu_2O, 15 mol% Phen

NMP, **170 ºC**, 24 h

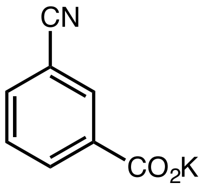
potassium carboxylate

aryl triflate

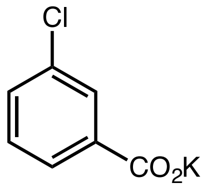
biaryl product



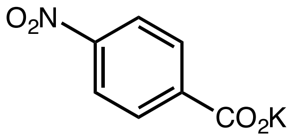
72% yield



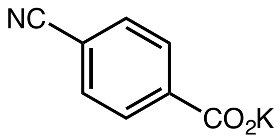
52% yield



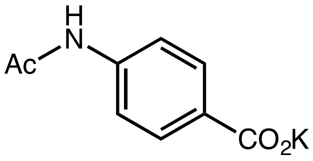
40% yield



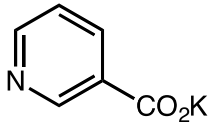
68% yield



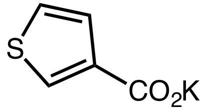
58% yield



53% yield



41% yield



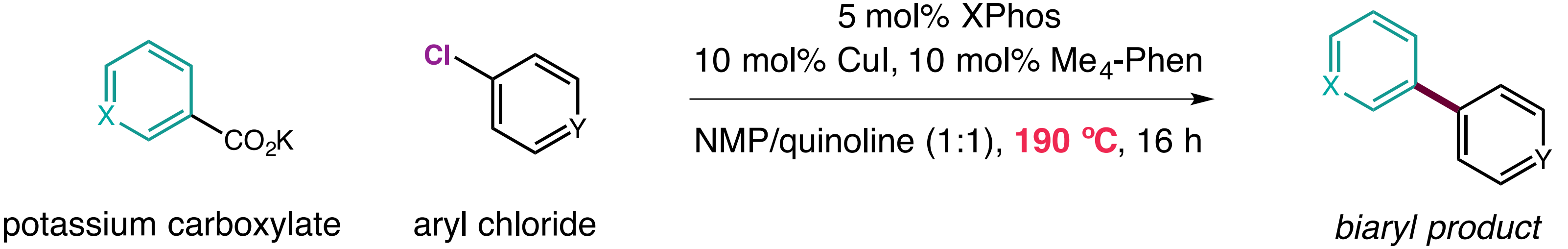
54% yield

Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249

For using ArOTs and ArOMs: Goossen, L. J. et al., *Angew. Chem. Int. Ed.* **2010**, *49*, 1111–1114; *Angew. Chem. Int. Ed.* **2013**, *52*, 2954–2958

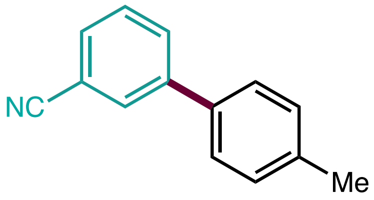
Decarboxylative Arylation for Biaryl Synthesis: Cu/Pd System

Cross-couplings of aryl chlorides

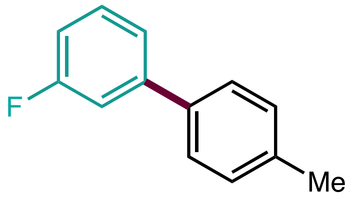


2 mol% $[Pd(MeCN)_4](OTf)_2$
5 mol% XPhos
10 mol% CuI, 10 mol% Me_4-Phen

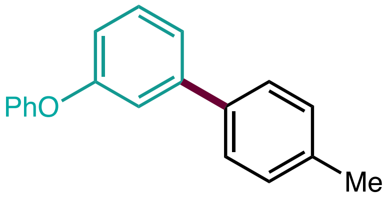
NMP/quinoline (1:1), **190 °C**, 16 h



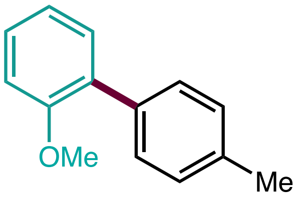
70% yield



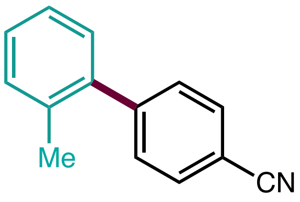
48% yield



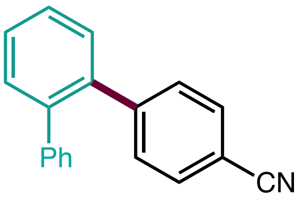
50% yield



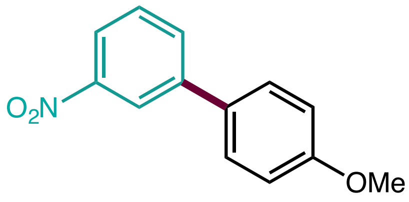
79% yield



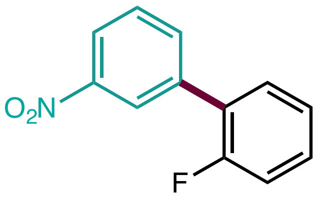
18% yield



32% yield



40% yield



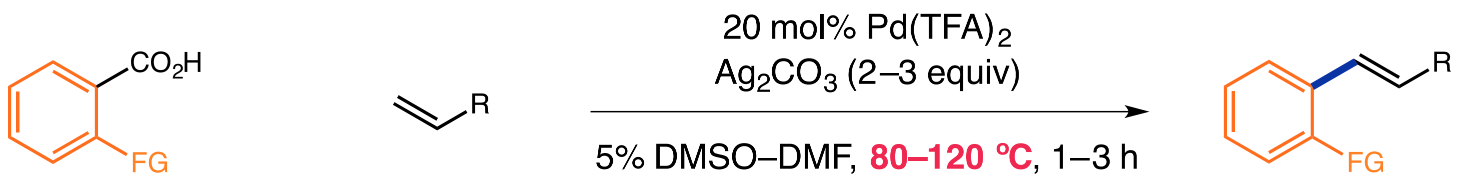
52% yield

Tang, J.; Biafora, A.; Goossen, L. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 13130–13133

For first generation conditions: Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 7103–7106

Decarboxylative Heck Reaction

■ Pd-catalyzed decarboxylative Heck: *ortho*-substituted acid



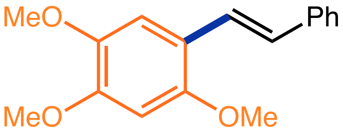
20 mol% $Pd(TFA)_2$
Ag_2CO_3 (2–3 equiv)

5% DMSO–DMF, **80–120 °C**, 1–3 h

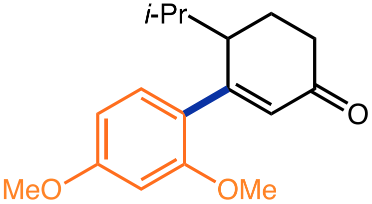
ortho-substituted acid

alkene

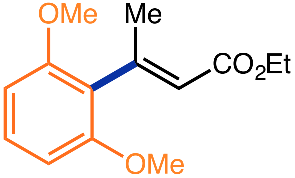
Heck product



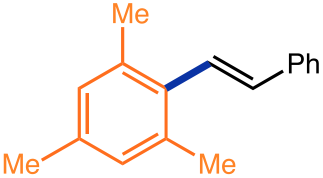
91% yield



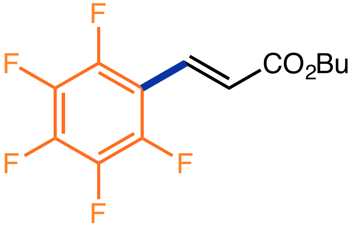
86% yield



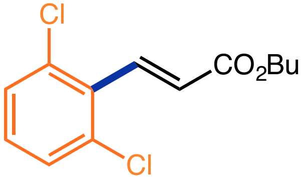
66% yield



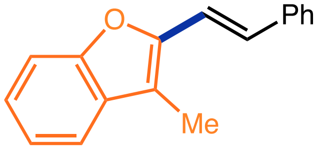
99% yield



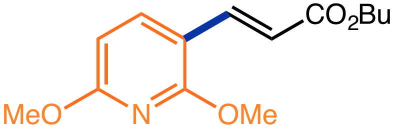
66% yield



47% yield



90% yield



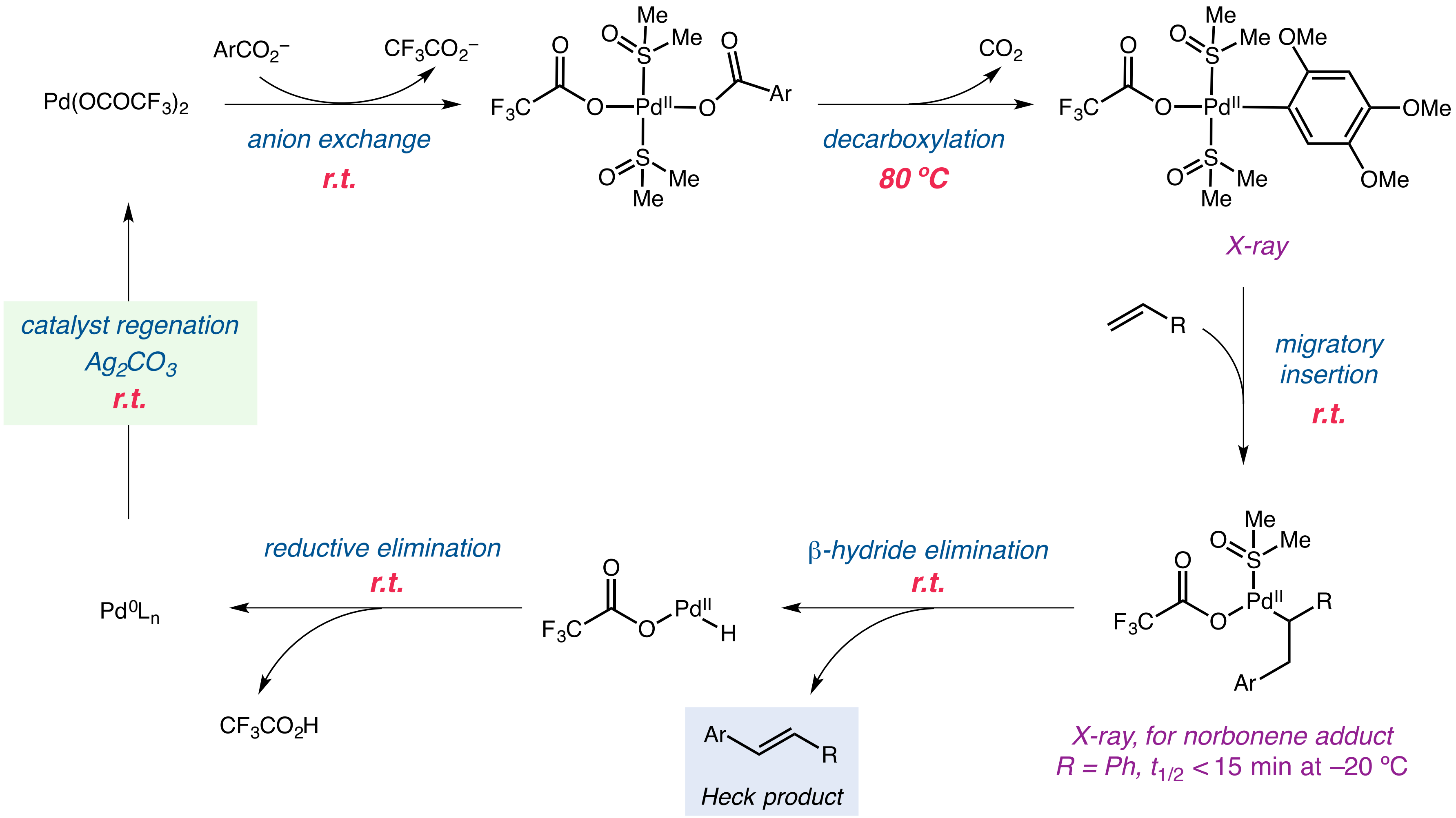
66% yield

Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251

Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433–446

Decarboxylative Heck Reaction

■ Pd-catalyzed decarboxylative Heck: proposed mechanism



anion exchange
_r.t._

decarboxylation
_80 °C_

X-ray

migratory insertion
_r.t._

X-ray, for norbonene adduct
R = Ph, $t_{1/2} < 15$ min at –20 °C

β-hydride elimination
_r.t._

Heck product

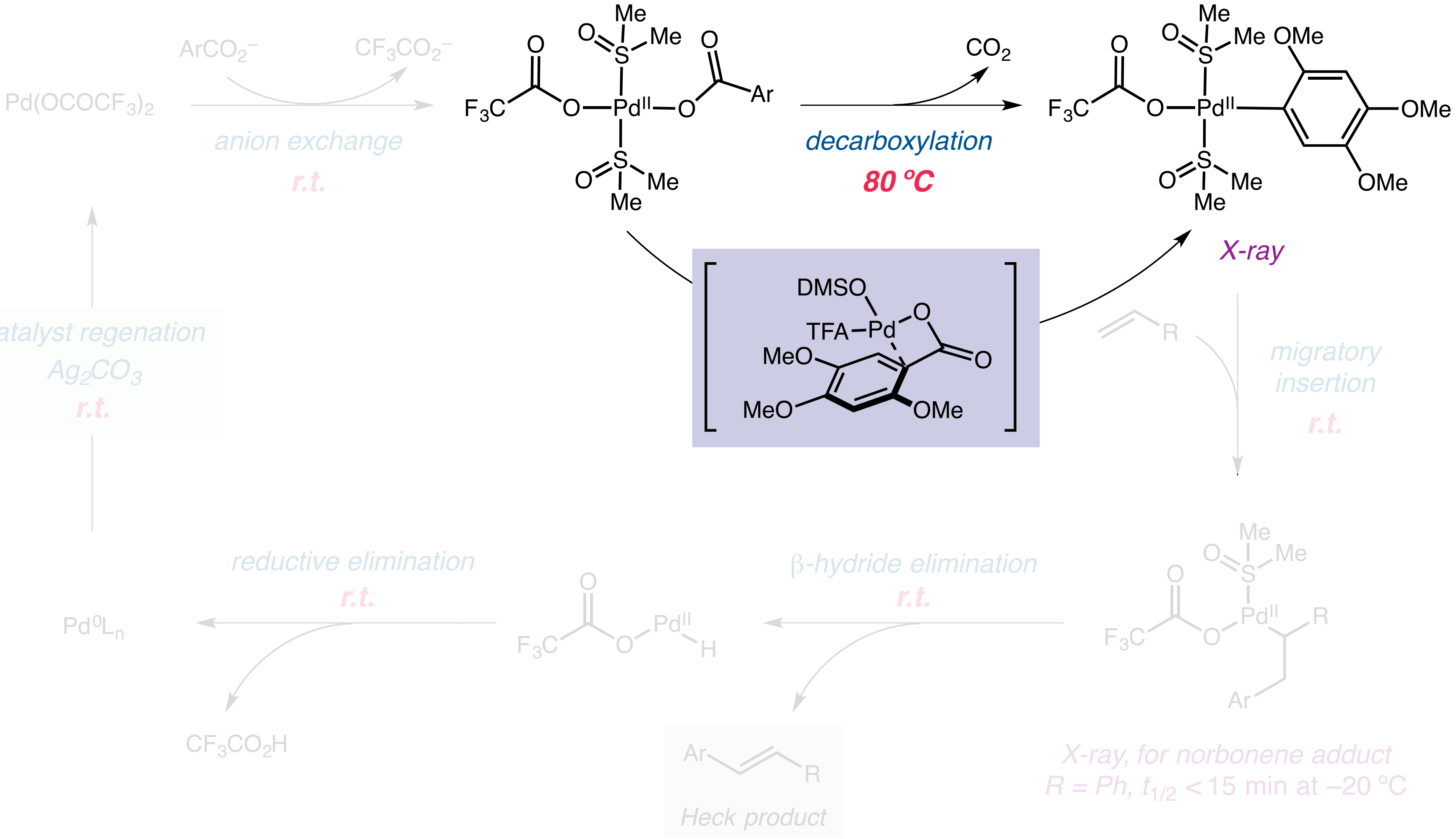
reductive elimination
_r.t._

catalyst regenation
Ag_2CO_3
_r.t._

Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333

Decarboxylative Heck Reaction

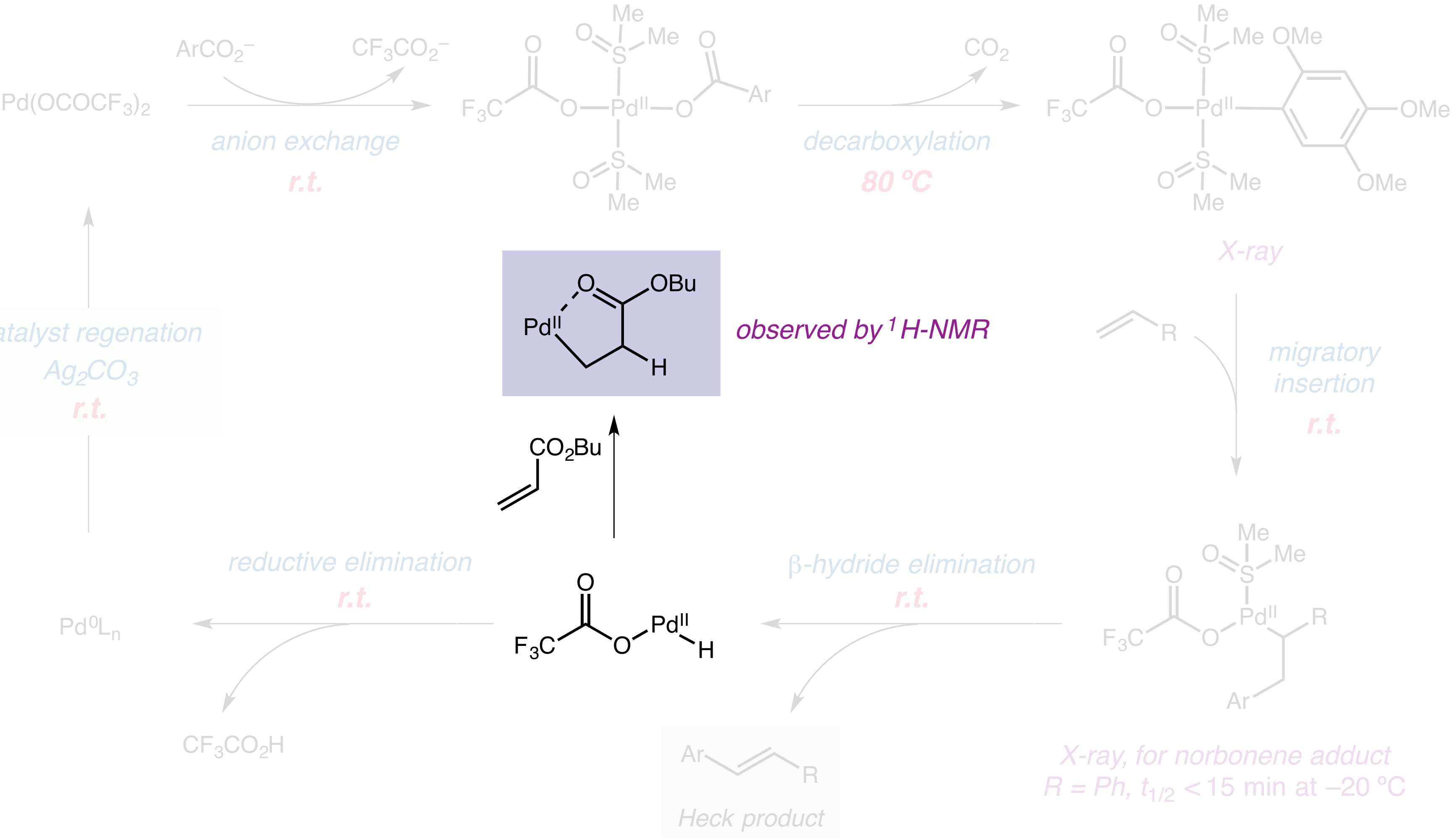
Pd-catalyzed decarboxylative Heck: proposed mechanism



Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333

Decarboxylative Heck Reaction

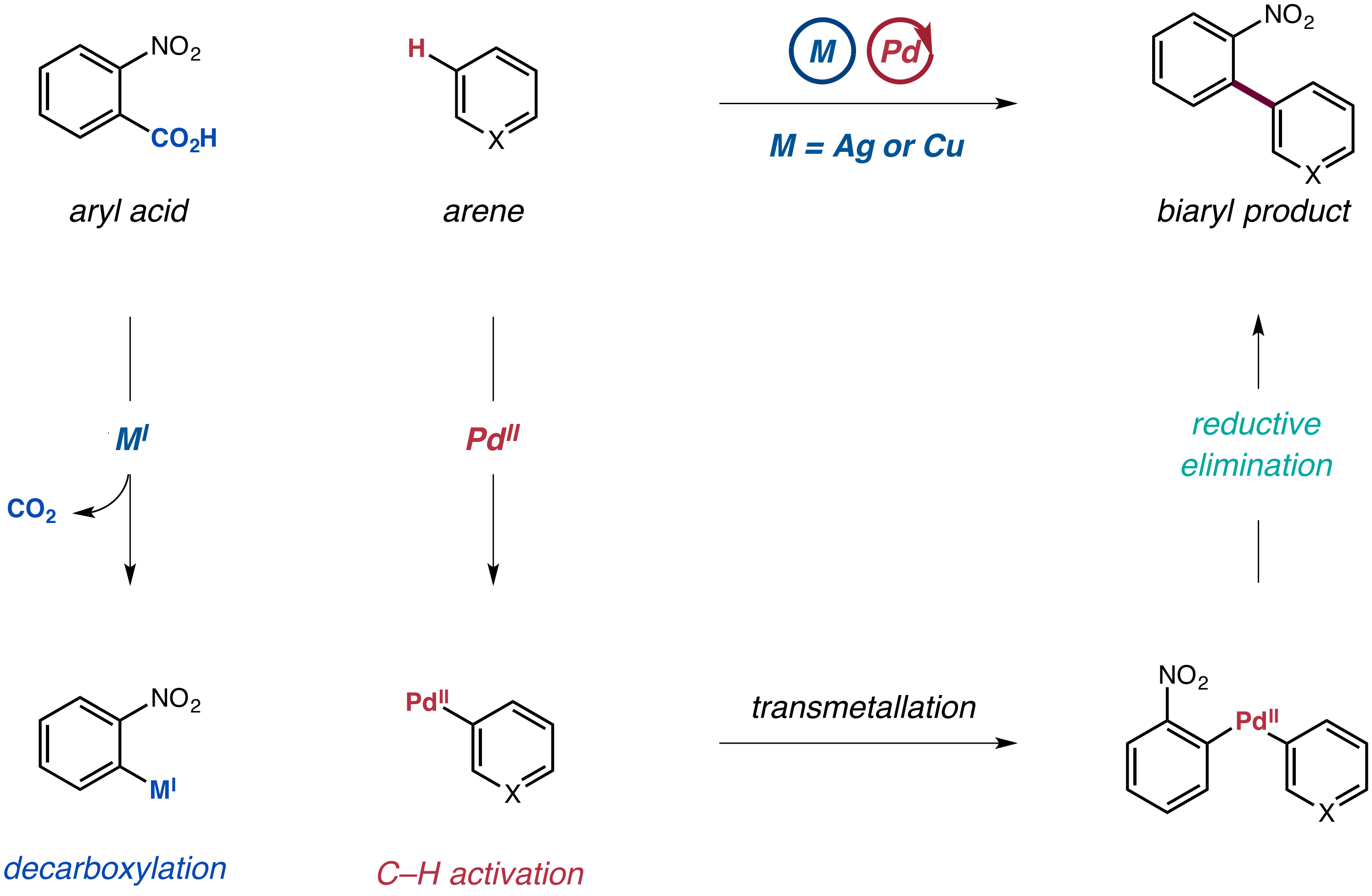
Pd-catalyzed decarboxylative Heck: proposed mechanism



Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333

Decarboxylative C–H Functionalization

■ Biaryl synthesis via decarboxylative C–H arylation



aryl acid

arene

M = Ag or Cu

biaryl product

M^I

Pd^{II}

reductive elimination

decarboxylation

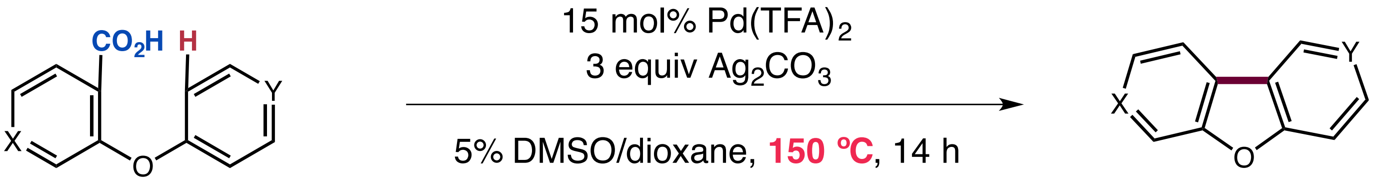
C–H activation

transmetallation

Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864–8907

Decarboxylative C–H Coupling for Biaryl Synthesis

Intramolecular coupling

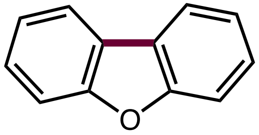


15 mol% Pd(TFA)$_2$
3 equiv Ag$_2$CO$_3$

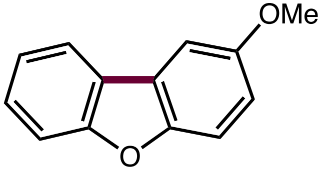
5% DMSO/dioxane, **150 ℃**, 14 h

diaryl ether

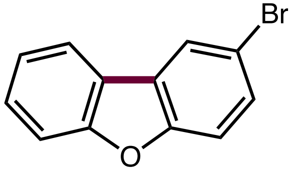
dibenzofuran



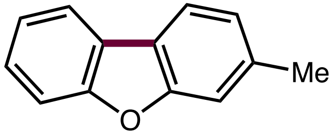
85% yield



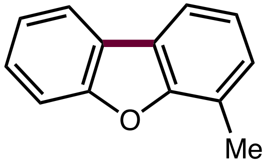
73% yield



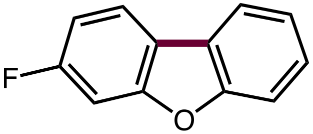
39% yield



69% yield
r.r. = 26:1



63% yield



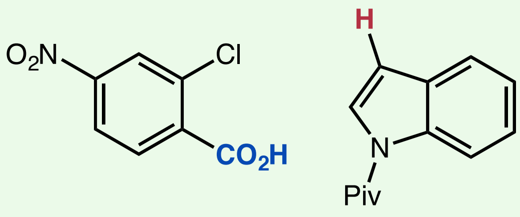
70% yield

Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195

Decarboxylative C–H Coupling for Biaryl Synthesis

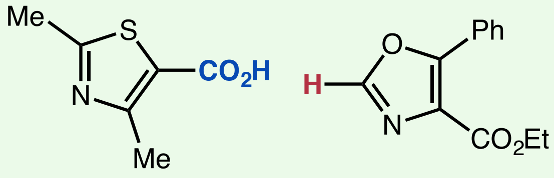
■ Selected examples for intermolecular transformation

Ag ***Pd*** **110 ºC**



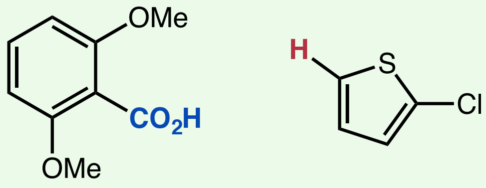
Igor Larrosa *Org. Lett.* **2009**, 5506

Cu ***Pd*** **140 ºC**



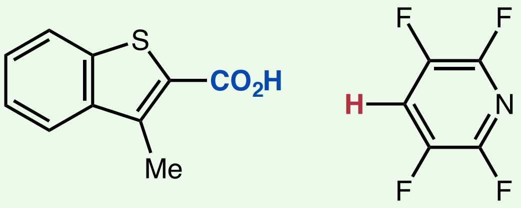
Michael Greaney *ACIE* **2010**, 2768

Ag ***Pd*** **120 ºC**



Weiping Su *ACIE* **2012**, 227

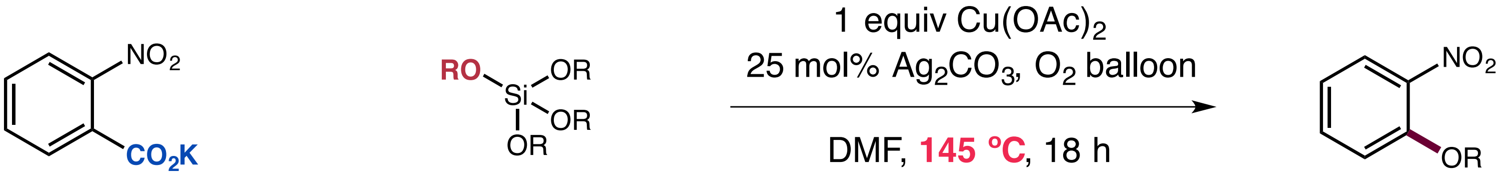
Ag ***Pd*** **140 ºC**



Weiping Su *JOC* **2011**, 882

Decarboxylative C–O Coupling

■ Etherification with silicate esters



1 equiv Cu(OAc)$_2$
25 mol% Ag$_2$CO$_3$, O$_2$ balloon

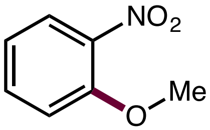
DMF, **145 °C**, 18 h

potassium carboxylate

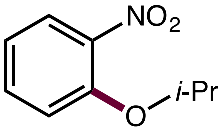
silicate ester

aryl ether

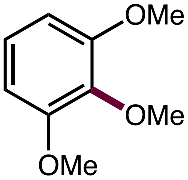
- Cu is responsible for C–O formation
- Ag to Cu transmetalltion



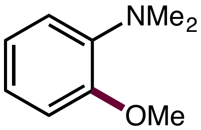
85% yield



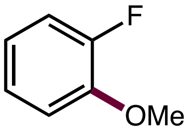
81% yield



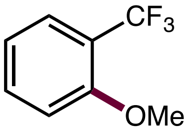
79% yield



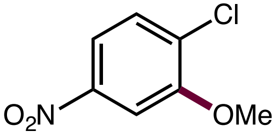
55% yield



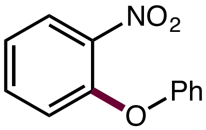
73% yield



58% yield



58% yield

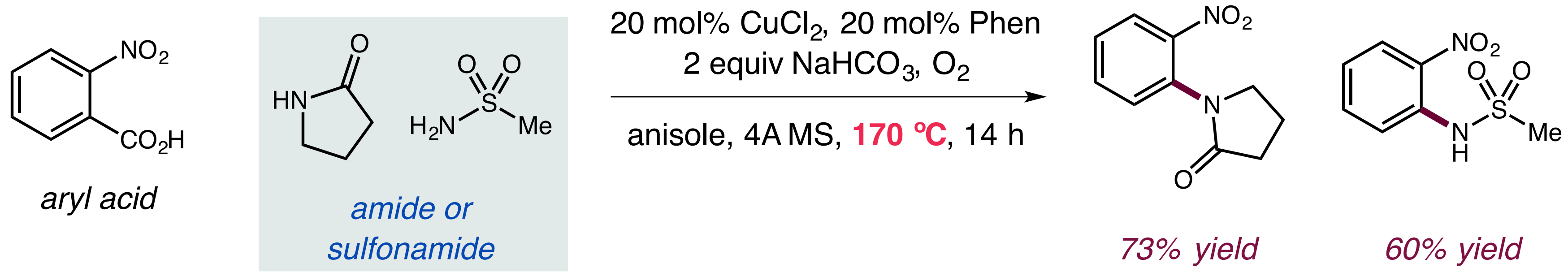


48% yield
with B(OPh)$_3$

Bhadra, S.; Dzik, W. I.; Goossen, L. J. *J. Am. Chem. Soc.* **2012**, *134*, 9938–9941

Decarboxylative C–N Coupling

With amide and sulfonamide



aryl acid

amide or sulfonamide

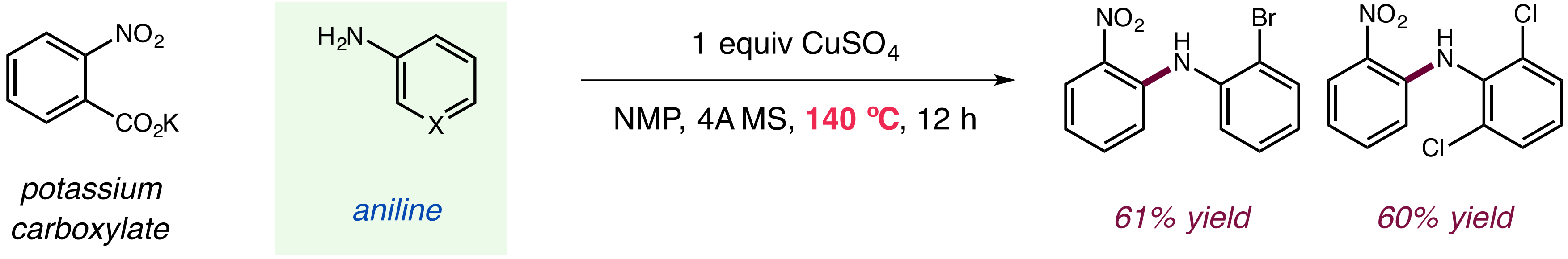
20 mol% $CuCl_2$, 20 mol% Phen
2 equiv $NaHCO_3$, O_2

anisole, 4A MS, **170 ℃**, 14 h

73% yield

60% yield

With aniline



potassium carboxylate

aniline

1 equiv $CuSO_4$

NMP, 4A MS, **140 ℃**, 12 h

61% yield

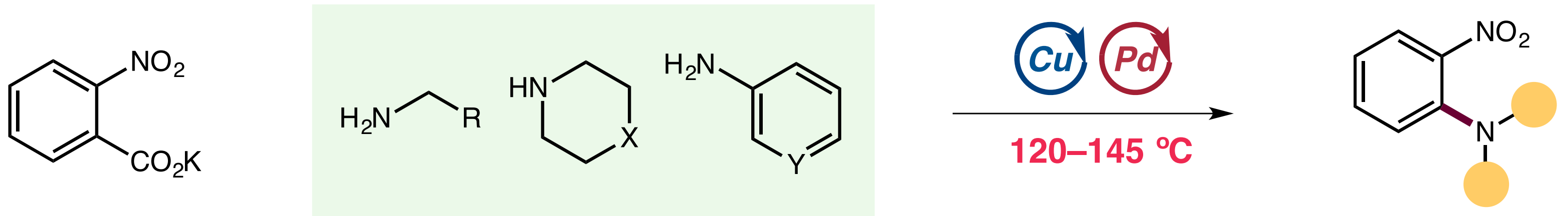
60% yield

Zhang, Y.; Patel, S.; Mainolfi, N. *Chem. Sci.* **2012**, *3*, 3196–3199

Sheng, W.-J.; Ye, Q.; Yu, W.-B.; Liu, R.-R.; Xu, M.; Gao, J.-R.; Jia, Y.-X. *Tetrahedron Lett.* **2015**, *56*, 599–601

Decarboxylative C–N Coupling

■ A recent example via bimetallic Cu/Pd system

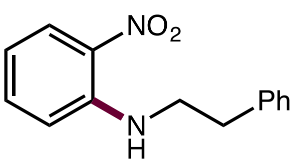


potassium carboxylate

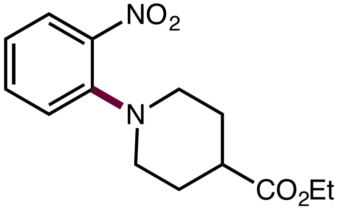
1°, 2° amine, electron-rich aniline

120–145 °C

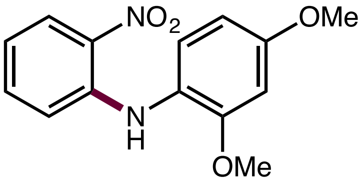
N-aryl product



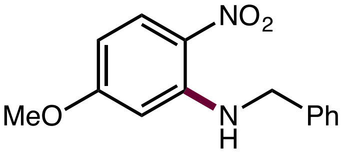
63% yield



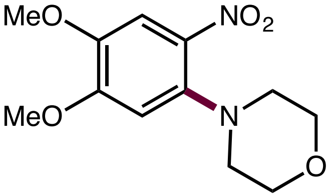
70% yield



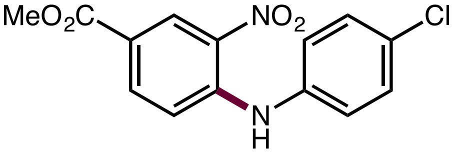
84% yield



77% yield



74% yield

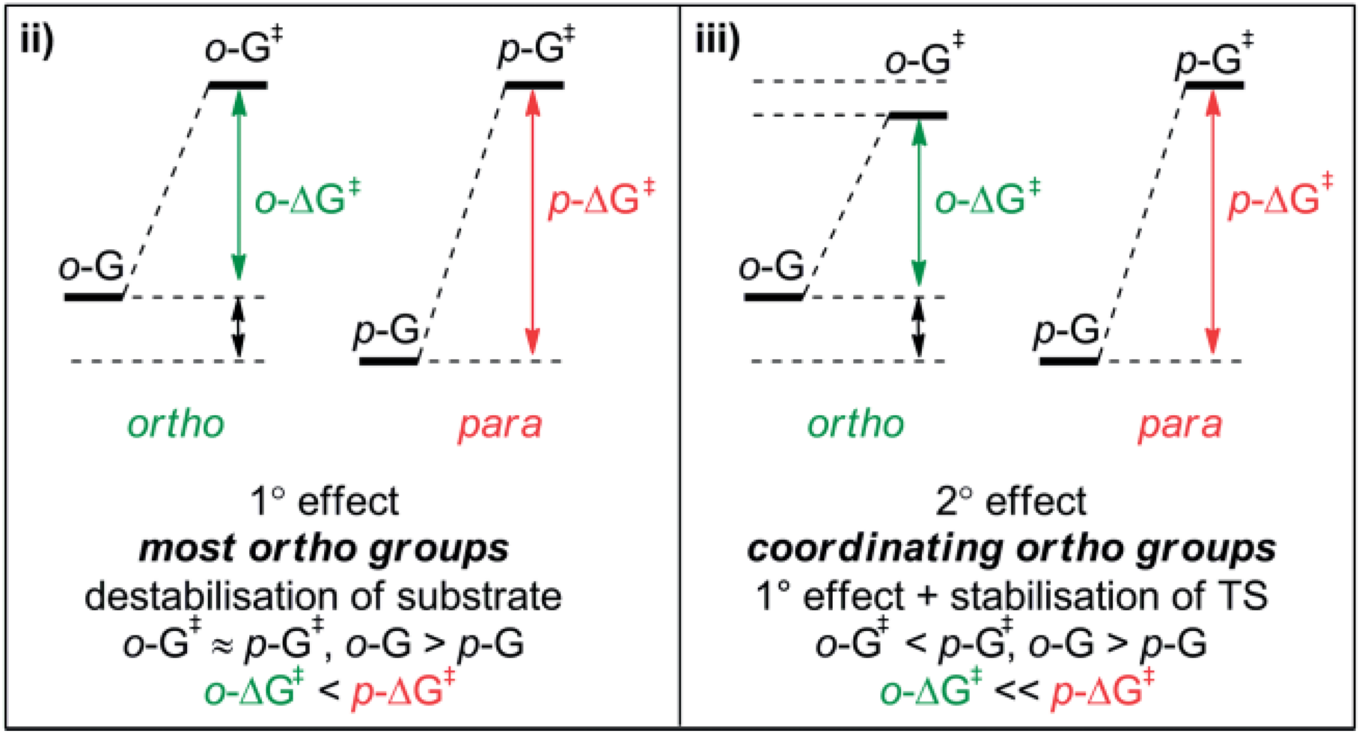


70% yield

Drapeau, M. P.; Bahri, J.; Lichte, D.; Goossen, L. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 892–896

Decarboxylative Couplings: Computational and Mechanistic Studies

Ortho effect in decarboxylation step

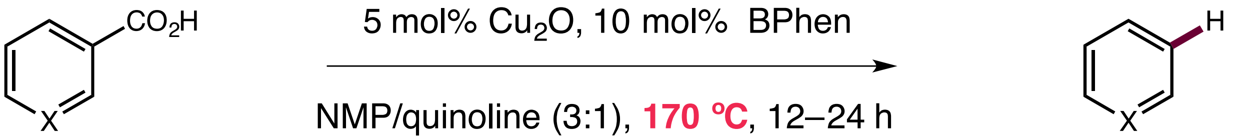


- Most groups at *ortho* positions can destablize substrates (steric effect)
- Coordinating groups at *ortho* positions can stablize TS (electronic effect)

Perry, G. J. P.; Larrosa, I. *Eur J. Org. Chem.* **2017**, 3517–3527

Protodecarboxylation via Copper-Catalysis

A general platform for protodecarboxylation

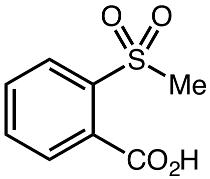


5 mol% Cu_2O, 10 mol% BPhen

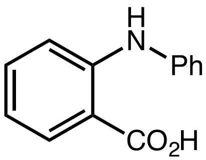
NMP/quinoline (3:1), **170 °C**, 12–24 h

aryl acid

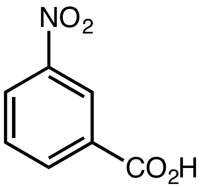
arene



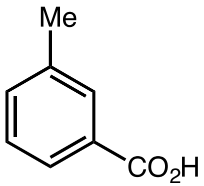
60% yield



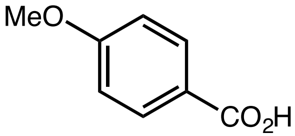
82% yield



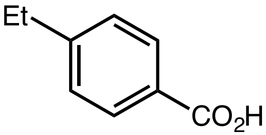
89% yield



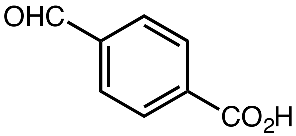
60% yield



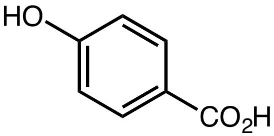
80% yield



92% yield



65% yield

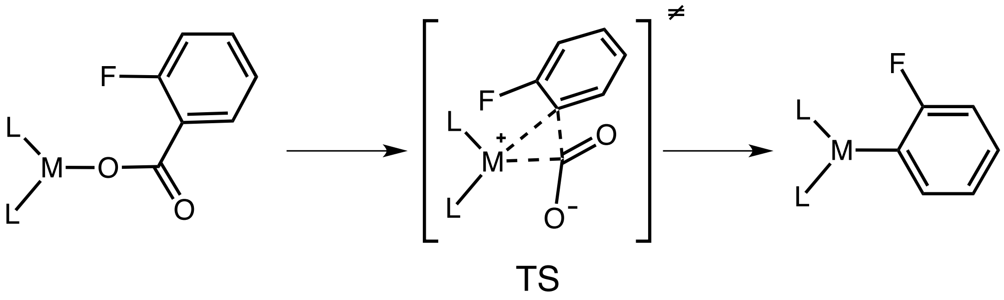


75% yield

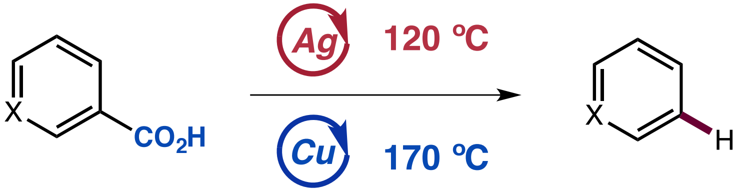
Goosen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007,** *349*, 2241–2246

Decarboxylative Couplings: Efforts toward Lower-Temperature Decarboxylation

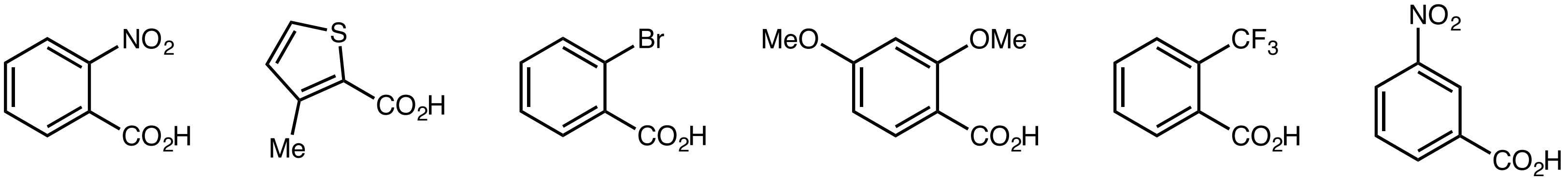
Comparisons of Cu and Ag-catalyzed systems



M	L	$\Delta G^{\neq}_{393}$
Cu	phen	31.3 kcal/mol
Ag	phen	29.5 kcal/mol
Ag	NMP	**29.2 kcal/mol**



- Very good for *ortho*-substituted acids
- Not applicable to *meta* and *para*-acids

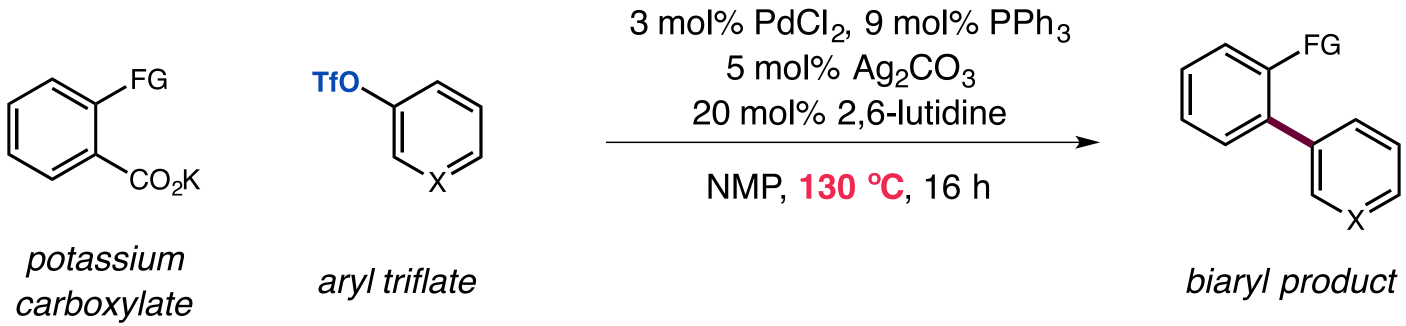


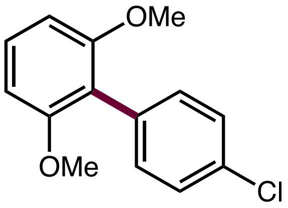
92% yield	*78% yield*	*76% yield*	*89% yield*	*91% yield*	*0% yield*
87% yield	*73% yield*	*0% yield*	*0% yield*	*22% yield*	*89% yield*

Goossen, L. J.; Rodriguez, N.; Linder, C.; Lange, P. P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430–442

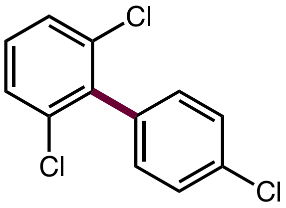
Decarboxylative Couplings: Efforts toward Lower-Temperature Decarboxylation

Biaryl synthesis based on bimetallic Ag/Pd system

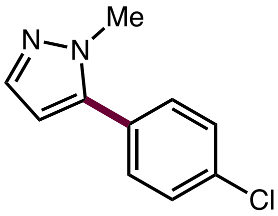




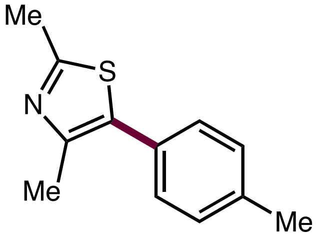
74% yield



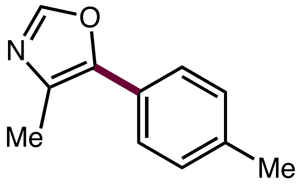
76% yield



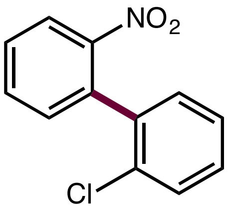
60% yield



75% yield



89% yield



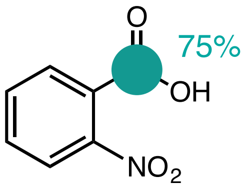
36% yield

Goossen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906–3909

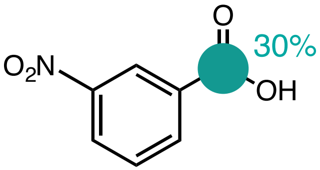
Decarboxylative Couplings: A Recent Example

■ Dynamic Carbon Isotope Exchange with Labeled CO_2

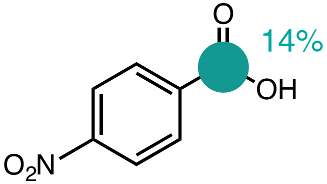
$[^{14}C]CO_2$ can also be applied



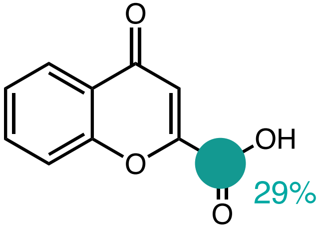
50% yield



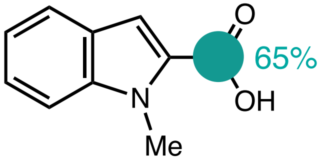
88% yield



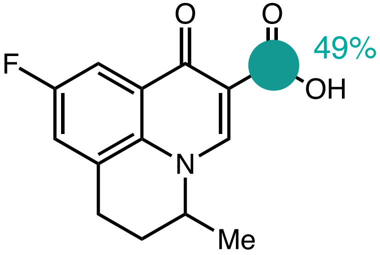
65% yield



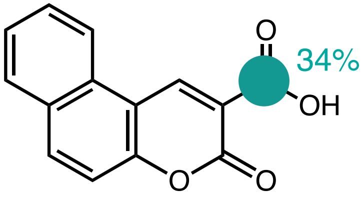
72% yield



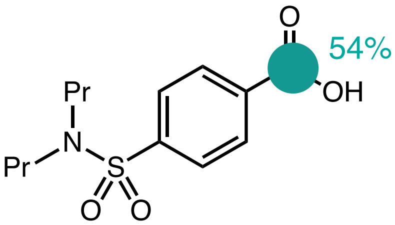
35% yield



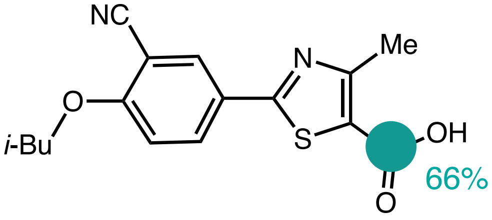
42% yield



26% yield



50% yield

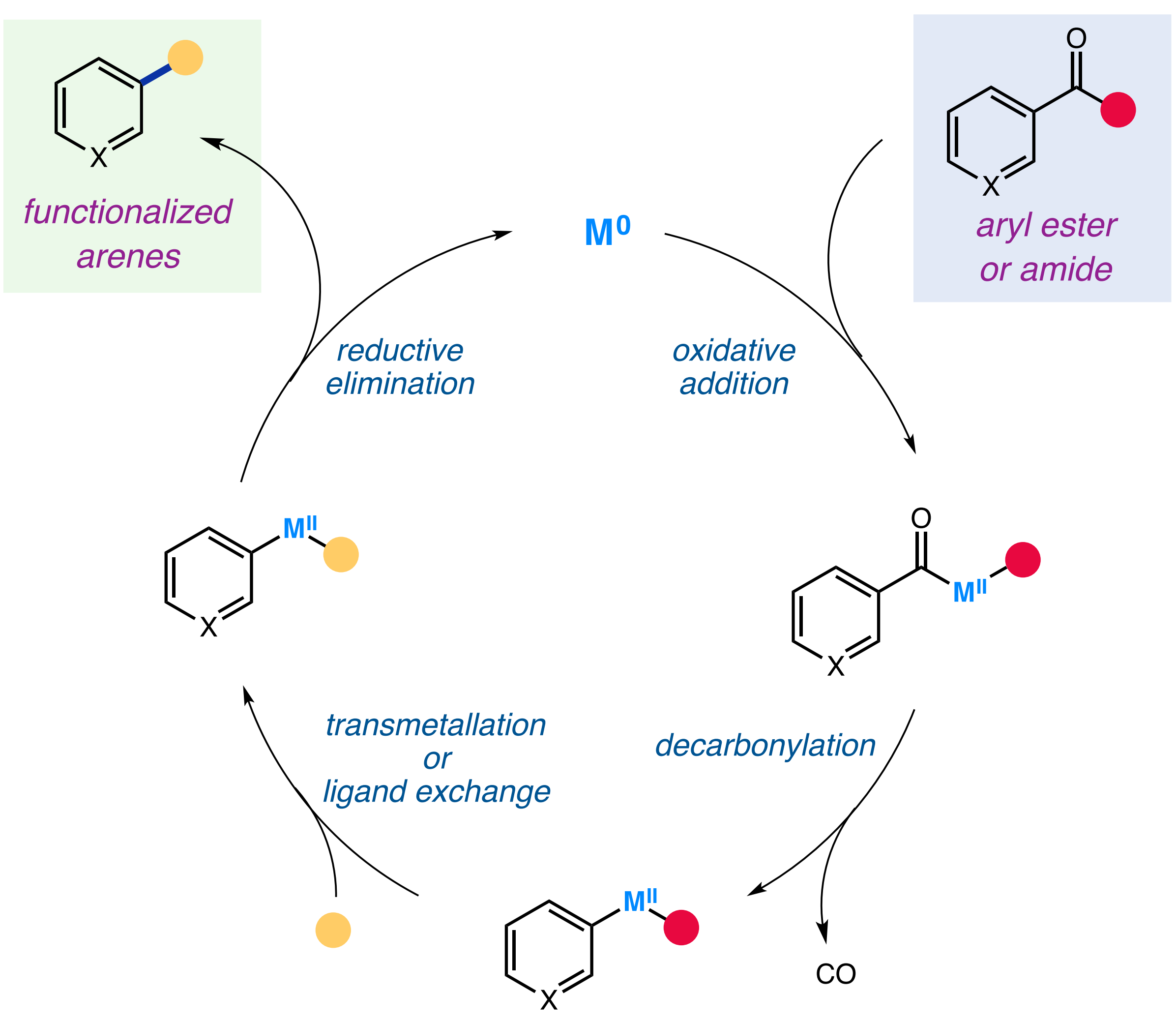


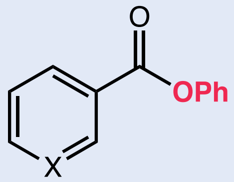
10% yield

Destro, G.; Loreau, O.; Marcon, E.; Taran, F.; Cantat, T.; Audisio, D. *J. Am. Chem. Soc.* **2019**, *141*, 780–784

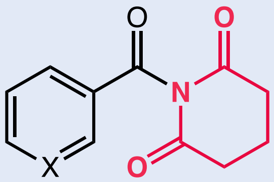
Decarbonylative Couplings of Aryl Amides and Esters: Overview

General ideas of mechanistic hypothesis





activated ester

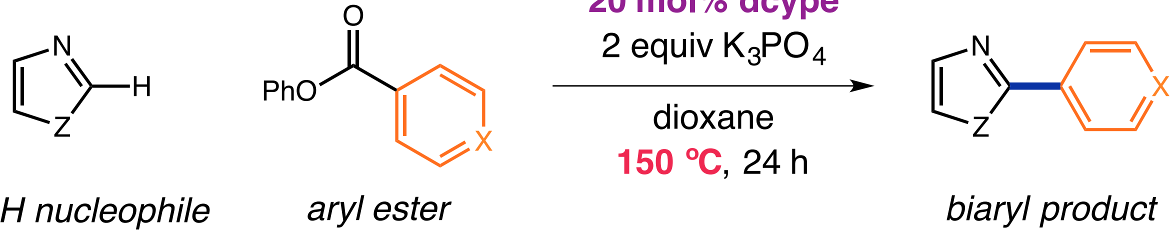


twisted amide

- Monometallic system
- Pd^0/Pd^{II} or Ni^0/Ni^{II} cycles
- Decarbonylative step needs high T
- When Ni is used, sometimes the scope is only limited to extended-π substrates

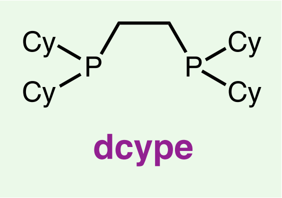
Decarbonylative Couplings for C–C Bond Formation

■ From activated esters: coupling with C–H nucleophiles

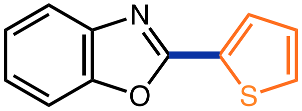


10 mol% Ni(COD)$_2$
20 mol% dcype
2 equiv K_3PO_4

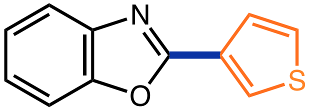
dioxane
150 ºC, 24 h



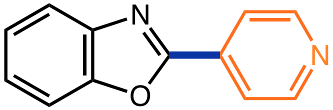
dcype



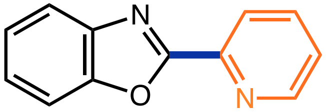
96% yield



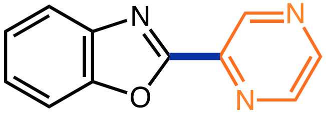
96% yield



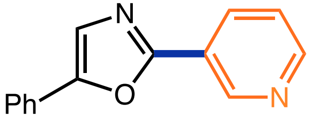
92% yield



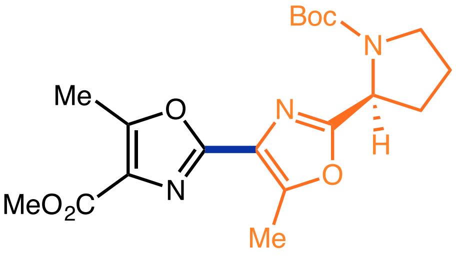
57% yield



52% yield



96% yield

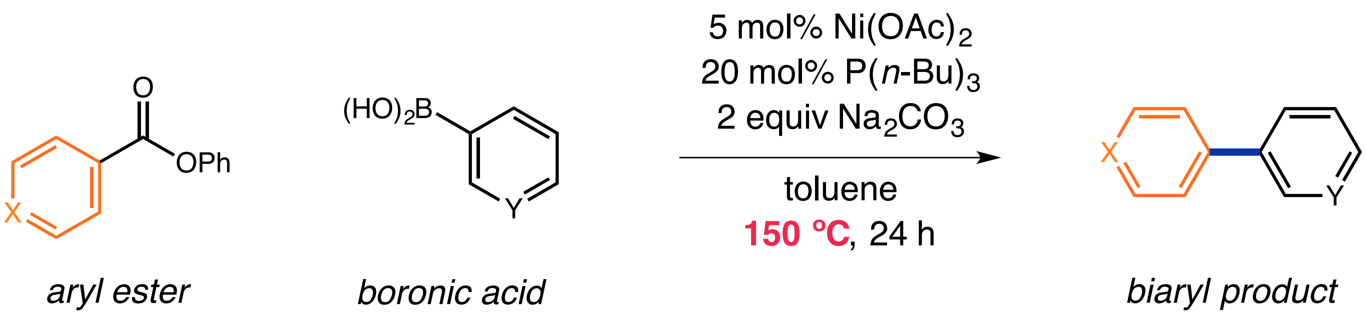


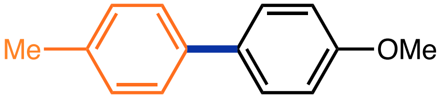
39% yield

Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573–13576

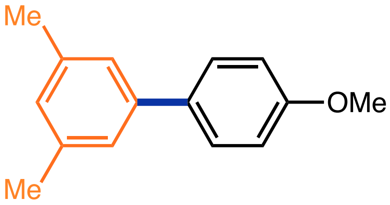
Decarbonylative Couplings for C–C Bond Formation

■ From activated esters: coupling with aryl boronic acids

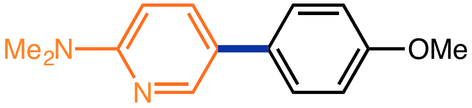




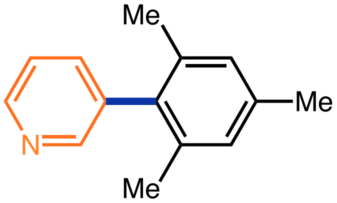
89% yield



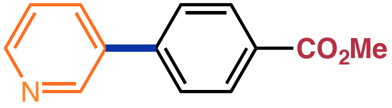
75% yield



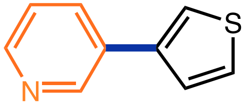
63% yield



66% yield



72% yield



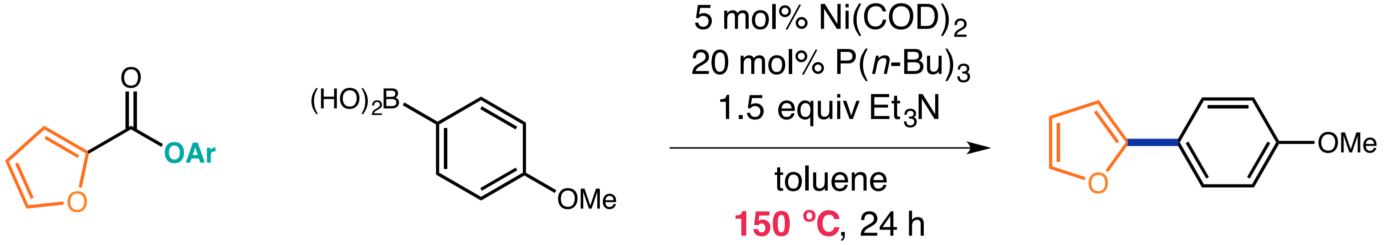
64% yield

Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508

A Pd-catalyzed version using azincarboxylates: Muto, K.; Hatakeyama, T.; Itami, K.; Yamaguchi, J. *Org. Lett.* **2016**, *18*, 5106–5109

Decarbonylative Couplings for C–C Bond Formation

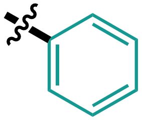
Coupling with aryl boronic acids: the effect of ester aryl groups



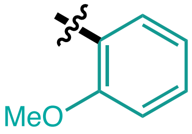
5 mol% $Ni(COD)_2$
20 mol% $P(n\text{-}Bu)_3$
1.5 equiv Et_3N

toluene
150 °C, 24 h

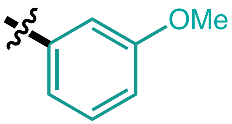
aryl ester *boronic acid* *biaryl product*



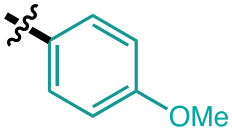
50% yield



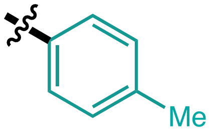
20% yield



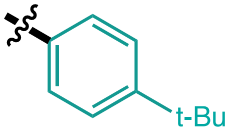
14% yield



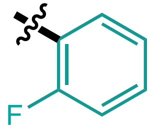
53% yield



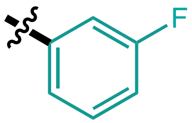
20% yield



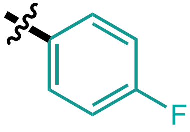
17% yield



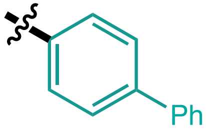
15% yield



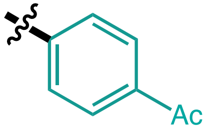
30% yield



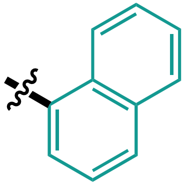
50% yield



20% yield



3% yield



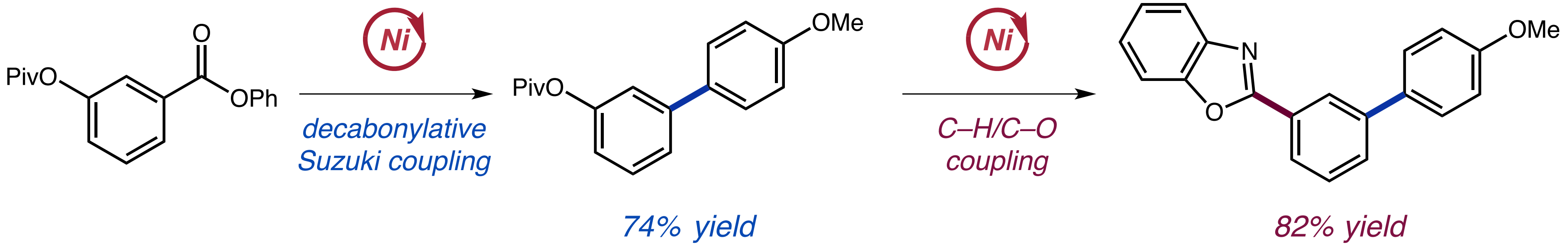
17% yield

- Alkyl esters don't work
- Possible role of phenyl ring: coordination with Ni(0) to facilitate oxidative addition

Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508

Decarbonylative Couplings for C–C Bond Formation

■ Coupling with aryl boronic acids: applications

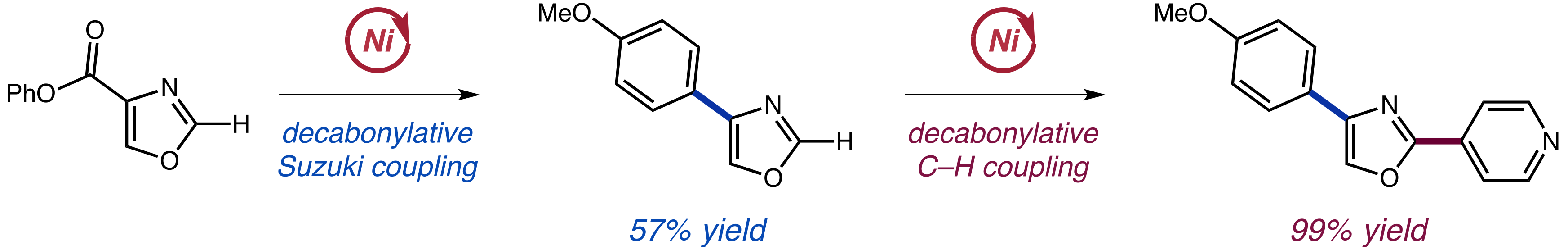


decabonylative Suzuki coupling

74% yield

C–H/C–O coupling

82% yield

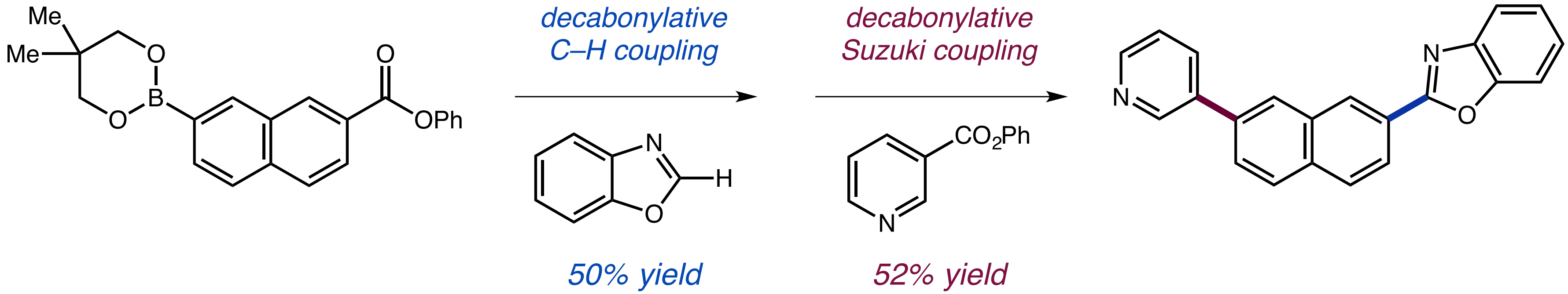


decabonylative Suzuki coupling

57% yield

decabonylative C–H coupling

99% yield



decabonylative C–H coupling

50% yield

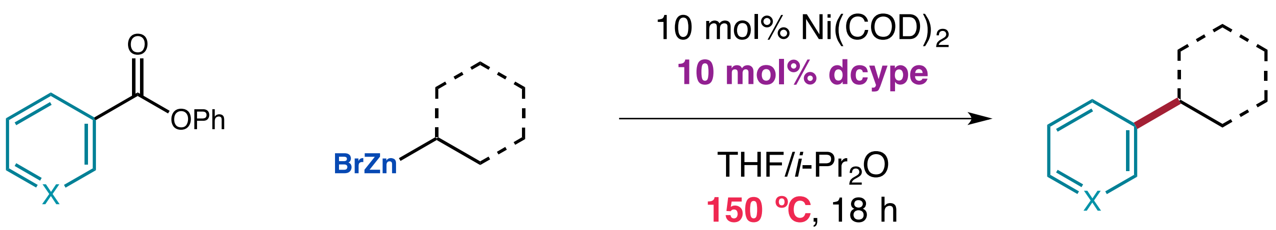
decabonylative Suzuki coupling

52% yield

Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508

Decarbonylative Couplings for C–C Bond Formation

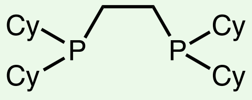
From activated esters: coupling with alkyl zinc reagents



10 mol% Ni(COD)$_2$
10 mol% dcype

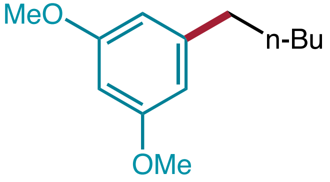
THF/*i*-Pr$_2$O
150 ºC, 18 h

aryl ester *alkylzinc reagent* *alkylated arene*

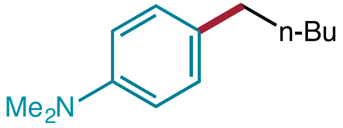


dcype

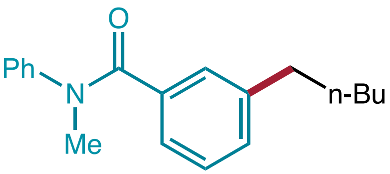
- extended-π substrates



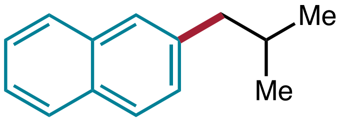
50% yield



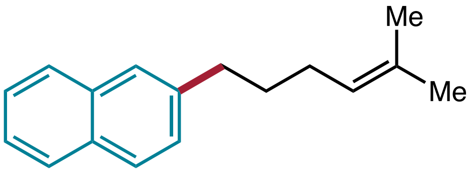
42% yield



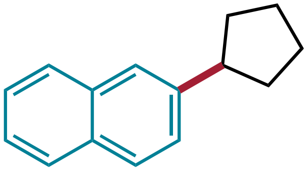
68% yield



72% yield



57% yield

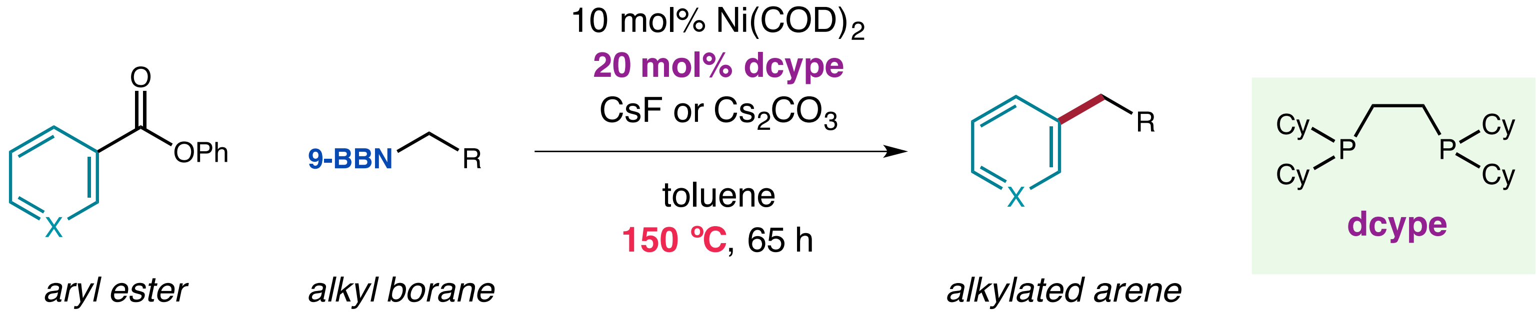


71% yield

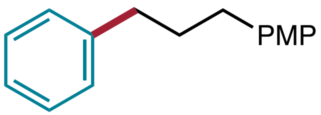
Liu, X.; Jia, J.; Rueping, M. *ACS Catal.* **2017**, *7*, 4491–4496

Decarbonylative Couplings for C–C Bond Formation

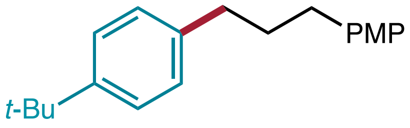
■ From activated esters: coupling with alkyl boranes



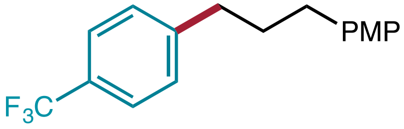
■ Switch ligand to PBu_3 or PCy_3 can lead to ketone products



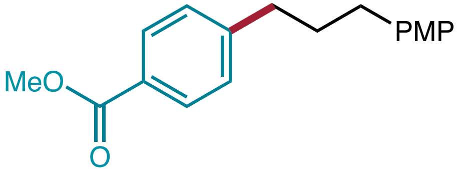
82% yield



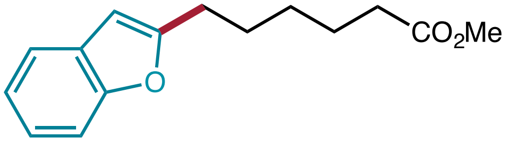
84% yield



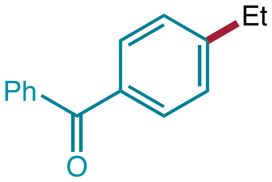
62% yield



43% yield



81% yield

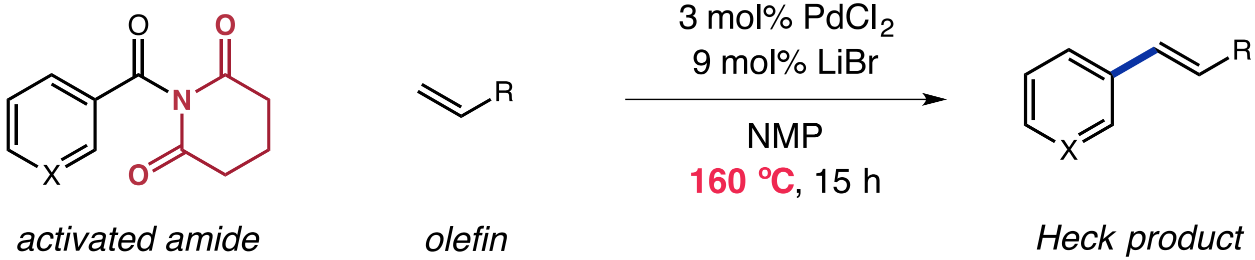


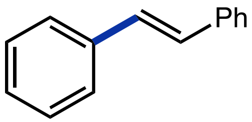
71% yield
with BEt_3

Chatupheeraphat, A.; Liao, H.-H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M. *JACS* **2018**, *140*, 3724

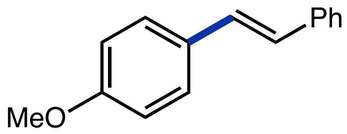
Decarbonylative Couplings for C–C Bond Formation

■ From activated amides: Heck reaction

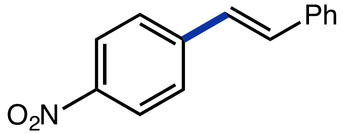




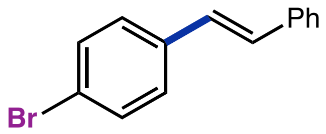
86% yield



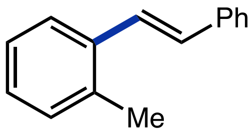
81% yield



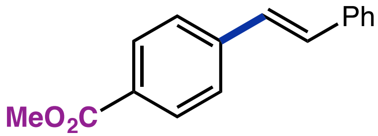
76% yield



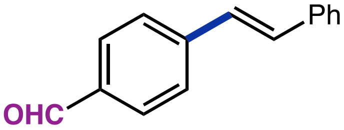
71% yield



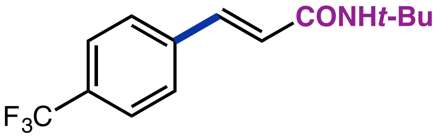
91% yield



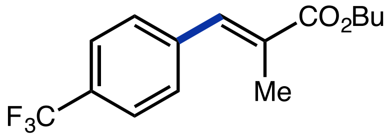
65% yield



75% yield



86% yield

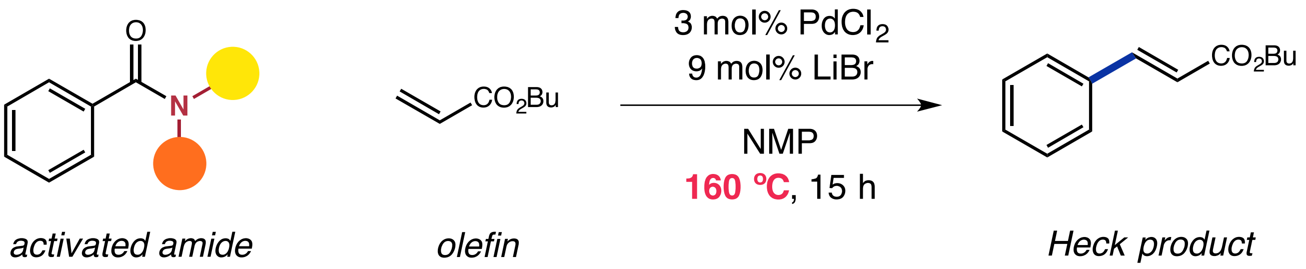


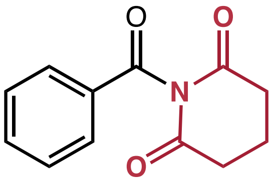
80% yield

Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518–14522

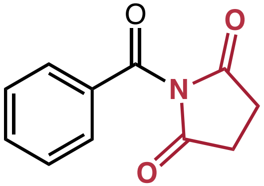
Decarbonylative Couplings for C–C Bond Formation

■ From activated amides: Heck reaction, amide structure effect

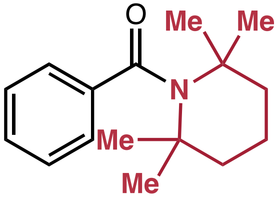




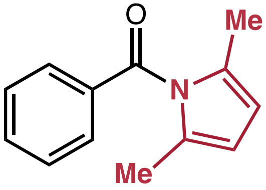
95% yield



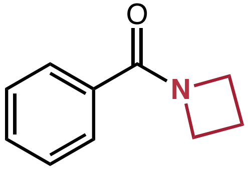
<5% yield



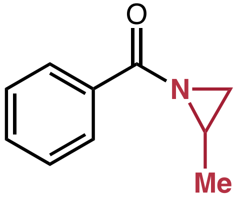
<5% yield



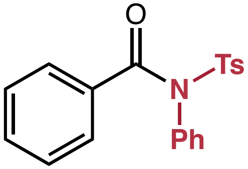
<5% yield



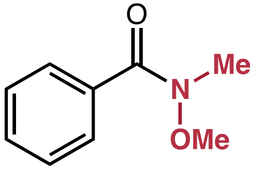
<5% yield



<5% yield



<5% yield

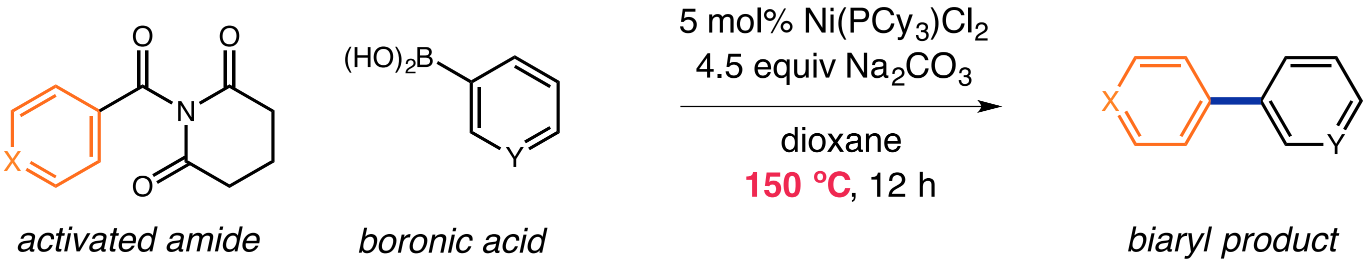


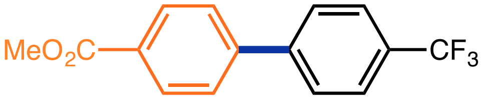
<5% yield

Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518–14522

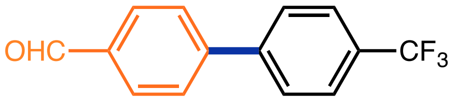
Decarbonylative Couplings for C–C Bond Formation

■ From activated amides: Suzuki coupling

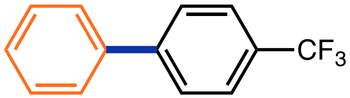




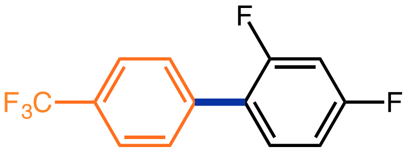
81% yield



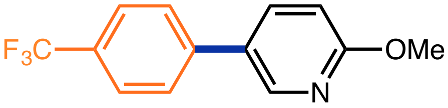
46% yield



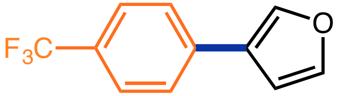
80% yield



74% yield



74% yield

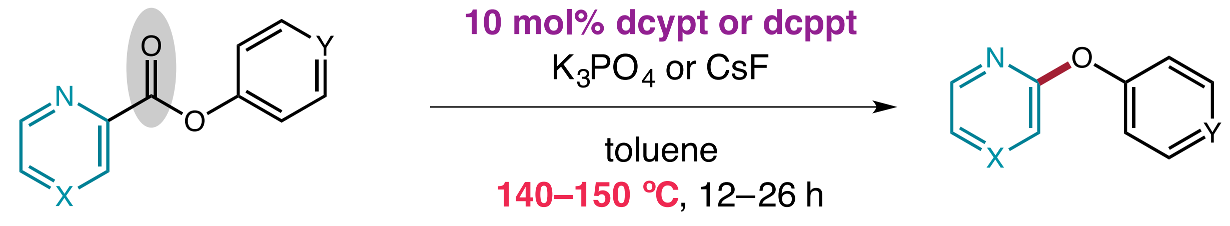


52% yield

Shi, S.; Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959–6963

Decarbonylative Couplings for C–Heteroatom Bond Formation

■ C–O formation from ester: unimolecular reaction

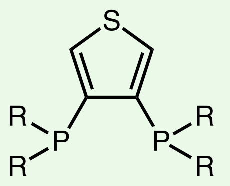


5 mol% $Ni(COD)_2$ or $Pd(OAc)_2$
10 mol% dcypt or dcppt
K_3PO_4 or CsF

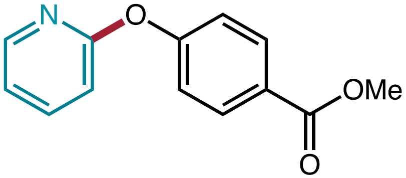
toluene
140–150 ℃, 12–26 h

2-azine ester

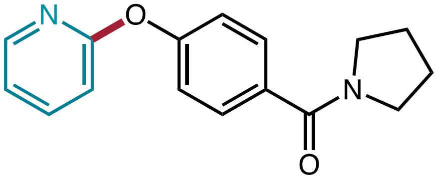
diaryl ether



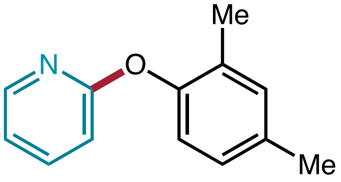
dcypt, R = Cy
dcppt, R = Cyp



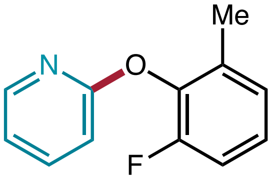
64% yield
Ni



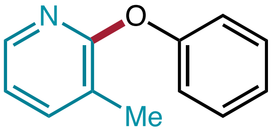
72% yield
Ni



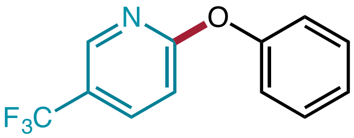
80% yield
Ni



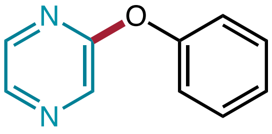
54% yield
Ni



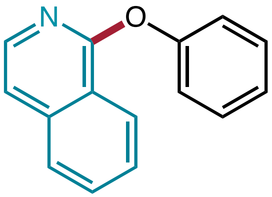
72% yield
Pd



75% yield
Ni



50% yield
Ni



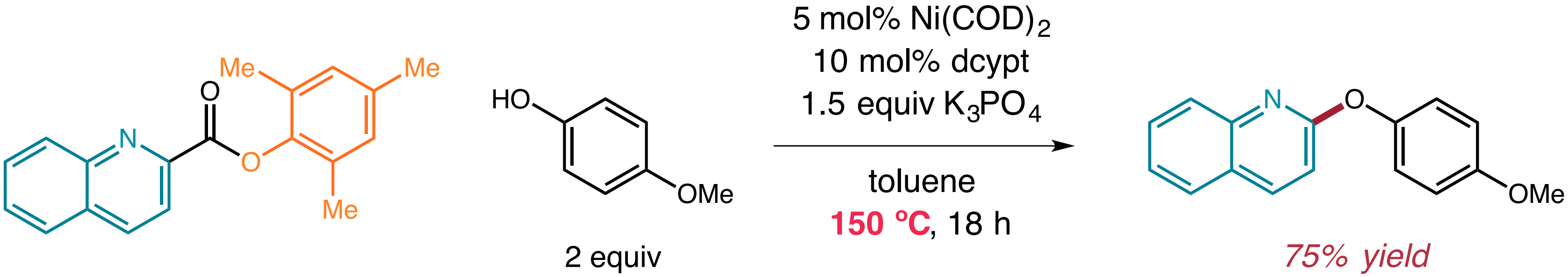
93% yield
Pd

Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340–3343

Decarbonylative Couplings for C–Heteroatom Bond Formation

■ C–O formation from ester: applications

intermolecule C–O formation



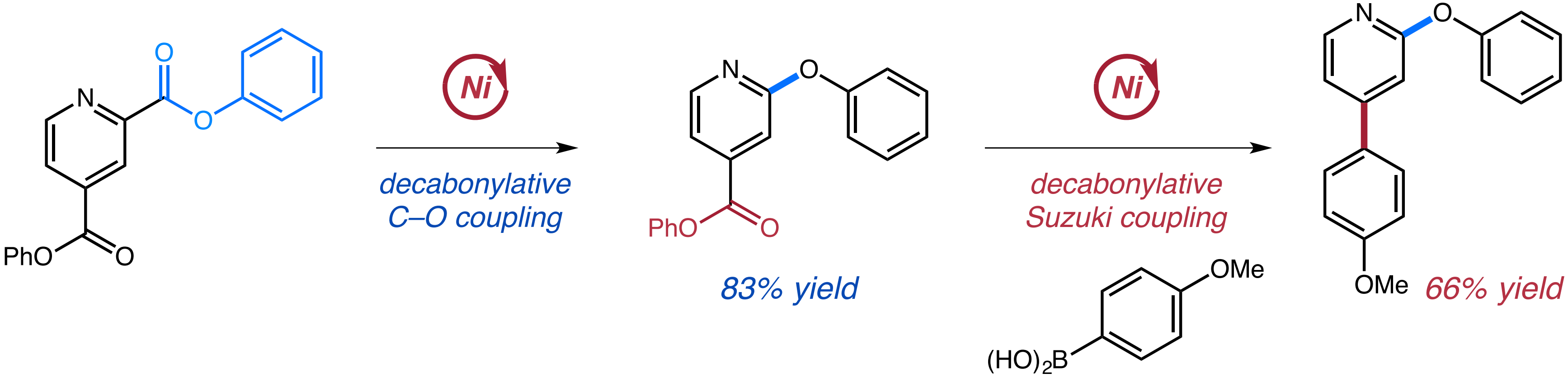
2 equiv

5 mol% $Ni(COD)_2$
10 mol% dcypt
1.5 equiv K_3PO_4

toluene
150 °C, 18 h

75% yield

sequential chemoselective decarbonylation



decabonylative C–O coupling

83% yield

decabonylative Suzuki coupling

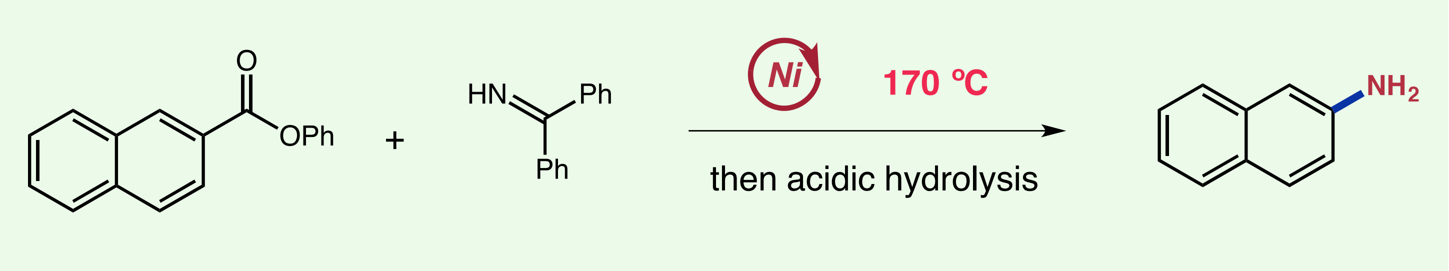
66% yield

Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340–3343

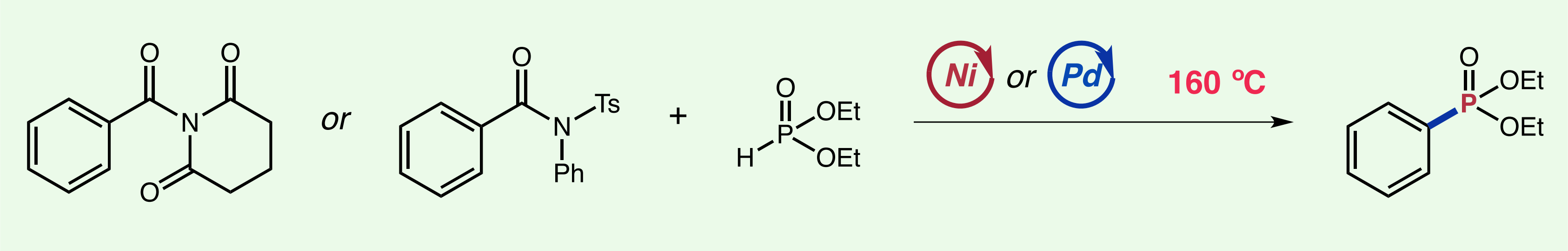
Decarbonylative Couplings for C–Heteroatom Bond Formation

■ C–N, C–P and C–H formation from activated esters and amides

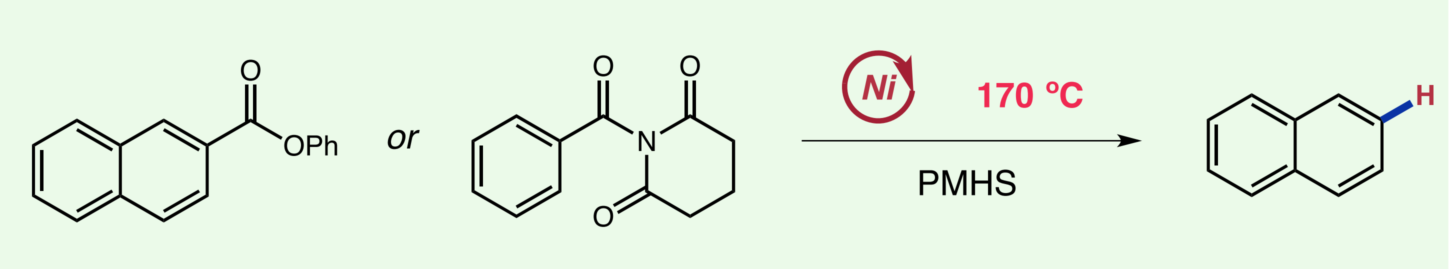
C–N formation Magnus Rueping et al., *Angew. Chem. Int. Ed.* **2017**, *56*, 4282–4285



C–P formation Michal Szostak et al., *Angew. Chem. Int. Ed.* **2017**, *56*, 12718–12722

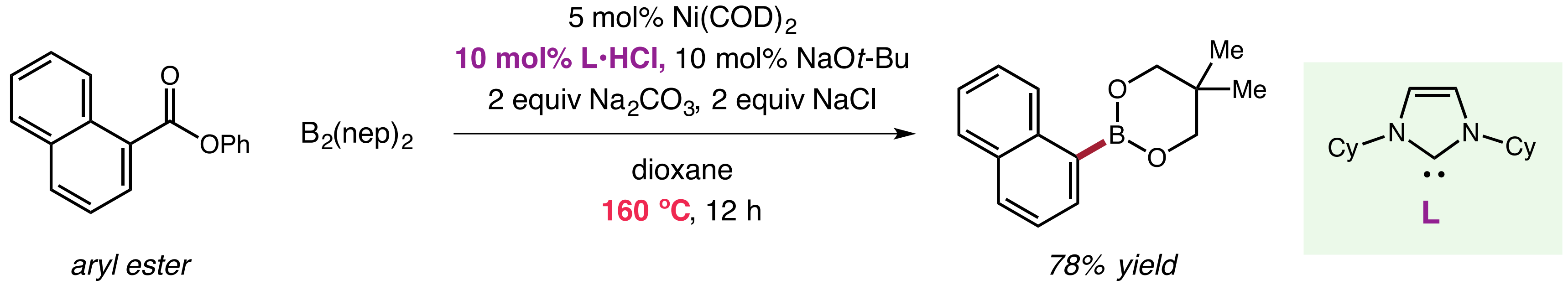


C–H formation Magnus Rueping et al., *Angew. Chem. Int. Ed.* **2017**, *56*, 3972–3976



Decarbonylative Couplings for C–Heteroatom Bond Formation

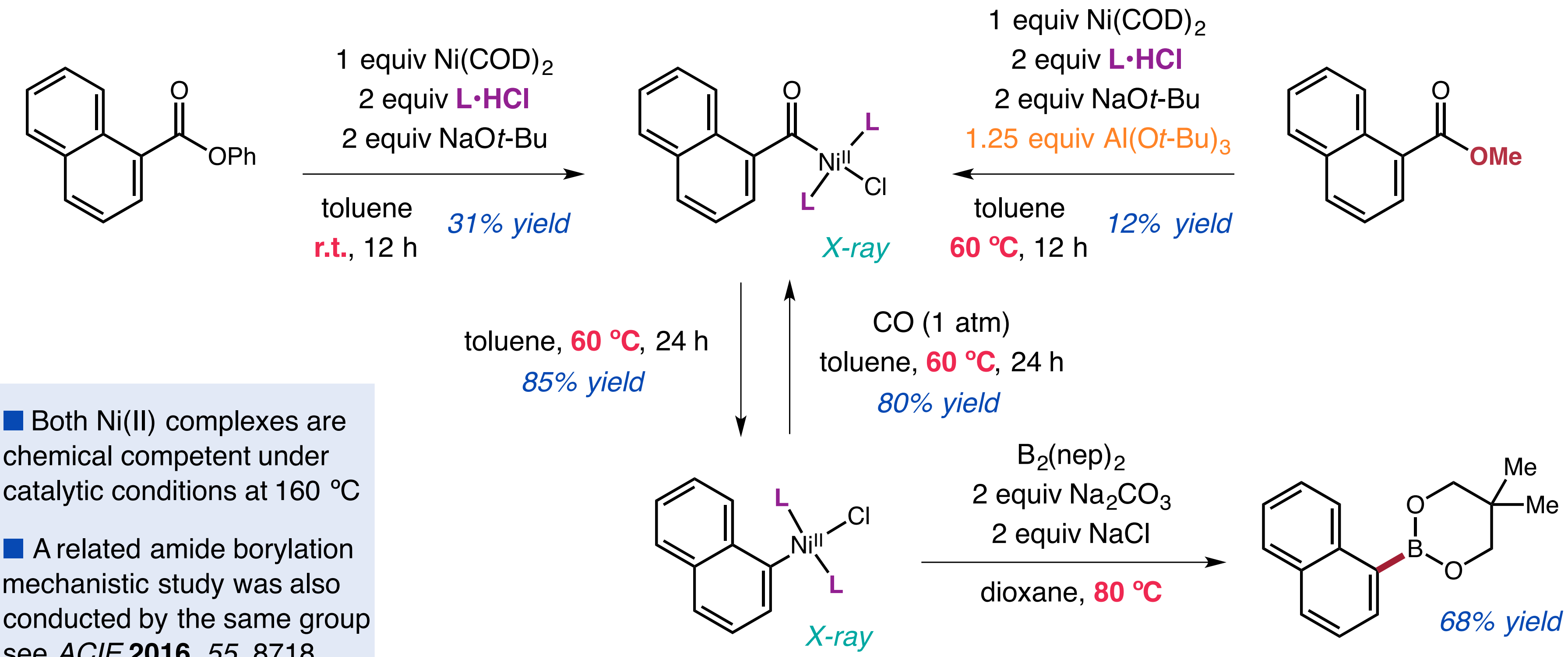
■ Mechanistic study: from ester to Ar–Bnep



5 mol% $Ni(COD)_2$
10 mol% L•HCl, 10 mol% NaO*t*-Bu
2 equiv Na_2CO_3, 2 equiv NaCl
dioxane
160 °C, 12 h

aryl ester

78% yield



1 equiv $Ni(COD)_2$
2 equiv **L•HCl**
2 equiv NaO*t*-Bu
toluene
r.t., 12 h
31% yield

1 equiv $Ni(COD)_2$
2 equiv **L•HCl**
2 equiv NaO*t*-Bu
1.25 equiv Al(O*t*-Bu)$_3$
toluene
60 °C, 12 h
12% yield

X-ray

toluene, **60 °C**, 24 h
85% yield

CO (1 atm)
toluene, **60 °C**, 24 h
80% yield

X-ray

$B_2(nep)_2$
2 equiv Na_2CO_3
2 equiv NaCl
dioxane, **80 °C**

68% yield

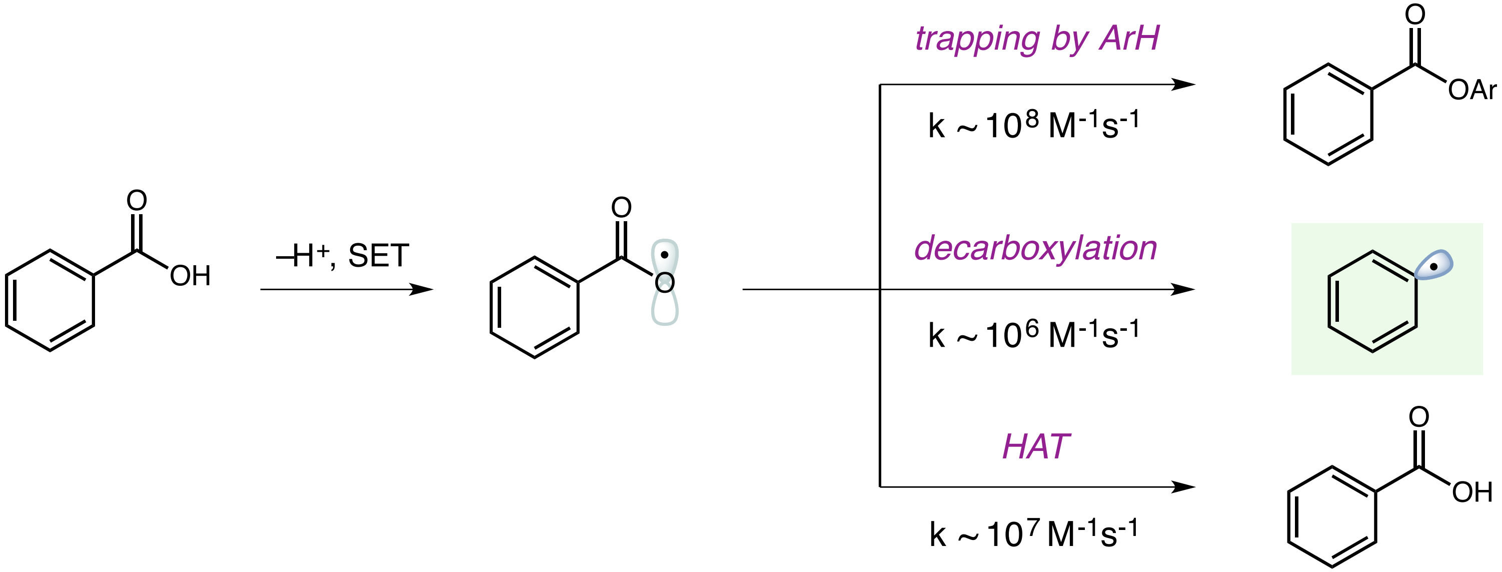
- Both Ni(II) complexes are chemical competent under catalytic conditions at 160 °C

- A related amide borylation mechanistic study was also conducted by the same group see *ACIE* **2016**, *55*, 8718

Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. *ACS Catal* **2016**, *6*, 6692–6698

Decarboxylation Coupling: Radical Pathway

General consideration: decarboxylation is a kinetically less favoured pathway



trapping by ArH

k ~ $10^8\ M^{-1}s^{-1}$

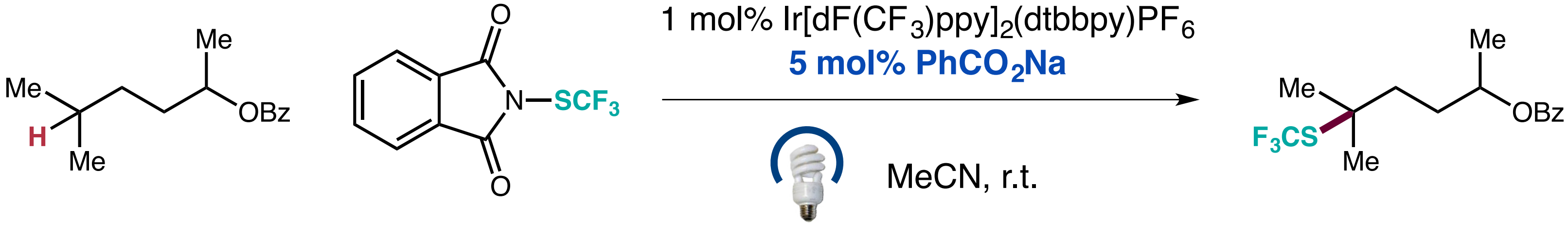
decarboxylation

k ~ $10^6\ M^{-1}s^{-1}$

HAT

k ~ $10^7\ M^{-1}s^{-1}$

Using aryl carboxylic acid as HAT reagent in photoredox catalysis



1 mol% Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6

5 mol% $PhCO_2Na$

MeCN, r.t.

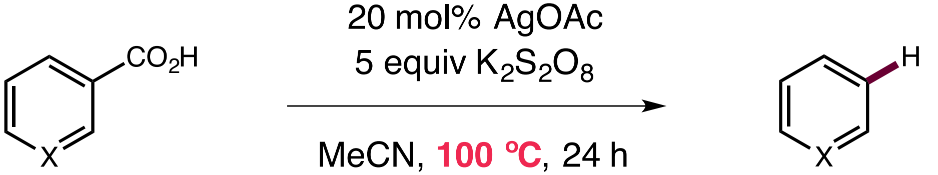
96% yield

Candish, L.; Freitag, M.; Gensch, T.; Glorius, F. *Chem. Sci.* **2017**, *8*, 3618–3622

Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 16200–16203

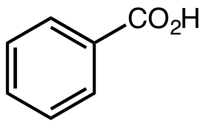
Decarboxylation Coupling: Radical Pathway

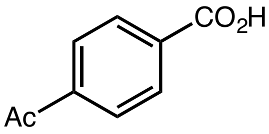
■ Protodecarboxylation platform using Ag/persulfate

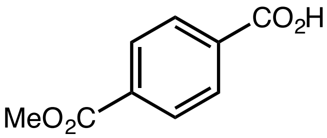

20 mol% AgOAc

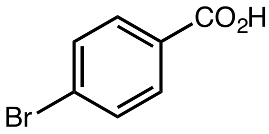
5 equiv $K_2S_2O_8$

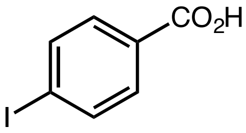
MeCN, 100 °C, 24 h

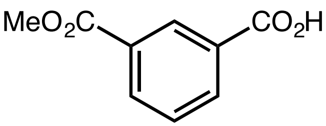

52% yield

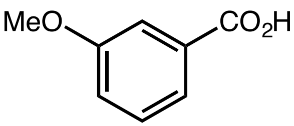

78% yield

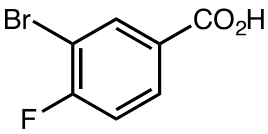

82% yield

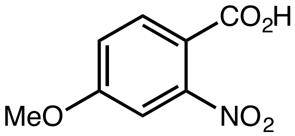

67% yield

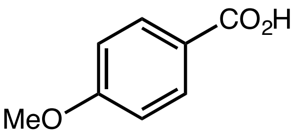

40% yield

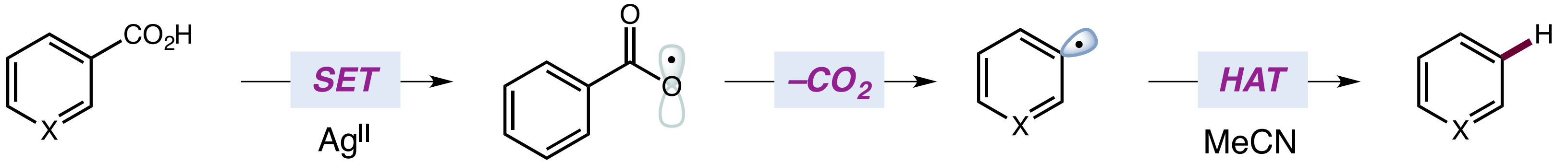

81% yield


45% yield


74% yield


58% yield


34% yield


SET

Ag^{II}

–CO₂

HAT

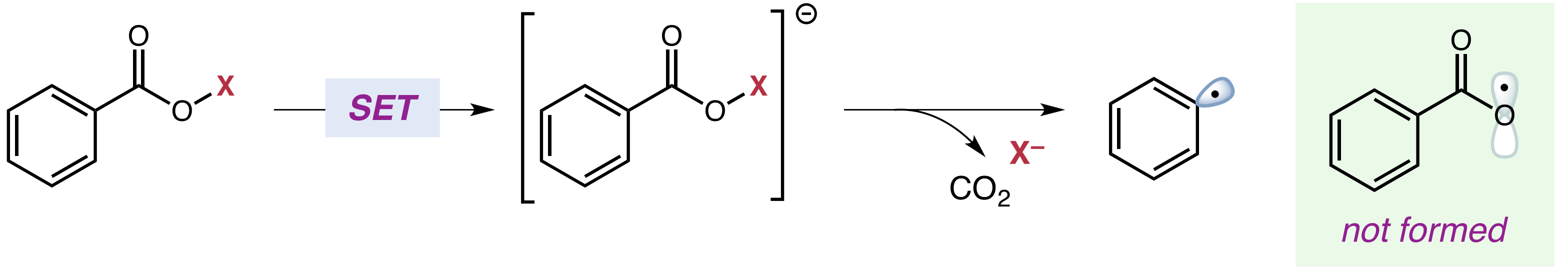
MeCN

Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2012**, *48*, 8270–8272

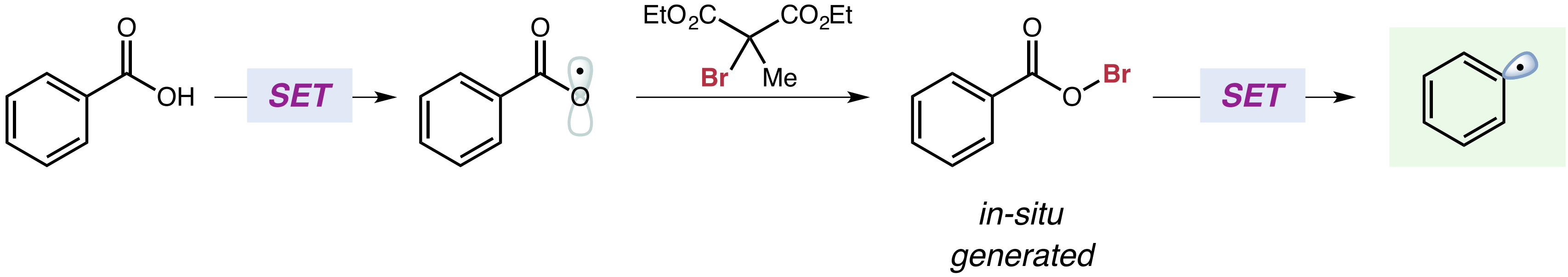
Quenching the radical with arenes: Kan, J.; Huang, S.; Lin, J.; Zhang, M.; Su, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 2199–2203

Decarboxylation Coupling: Radical Pathway

An alternative strategy: avoid generating oxygen-center radical



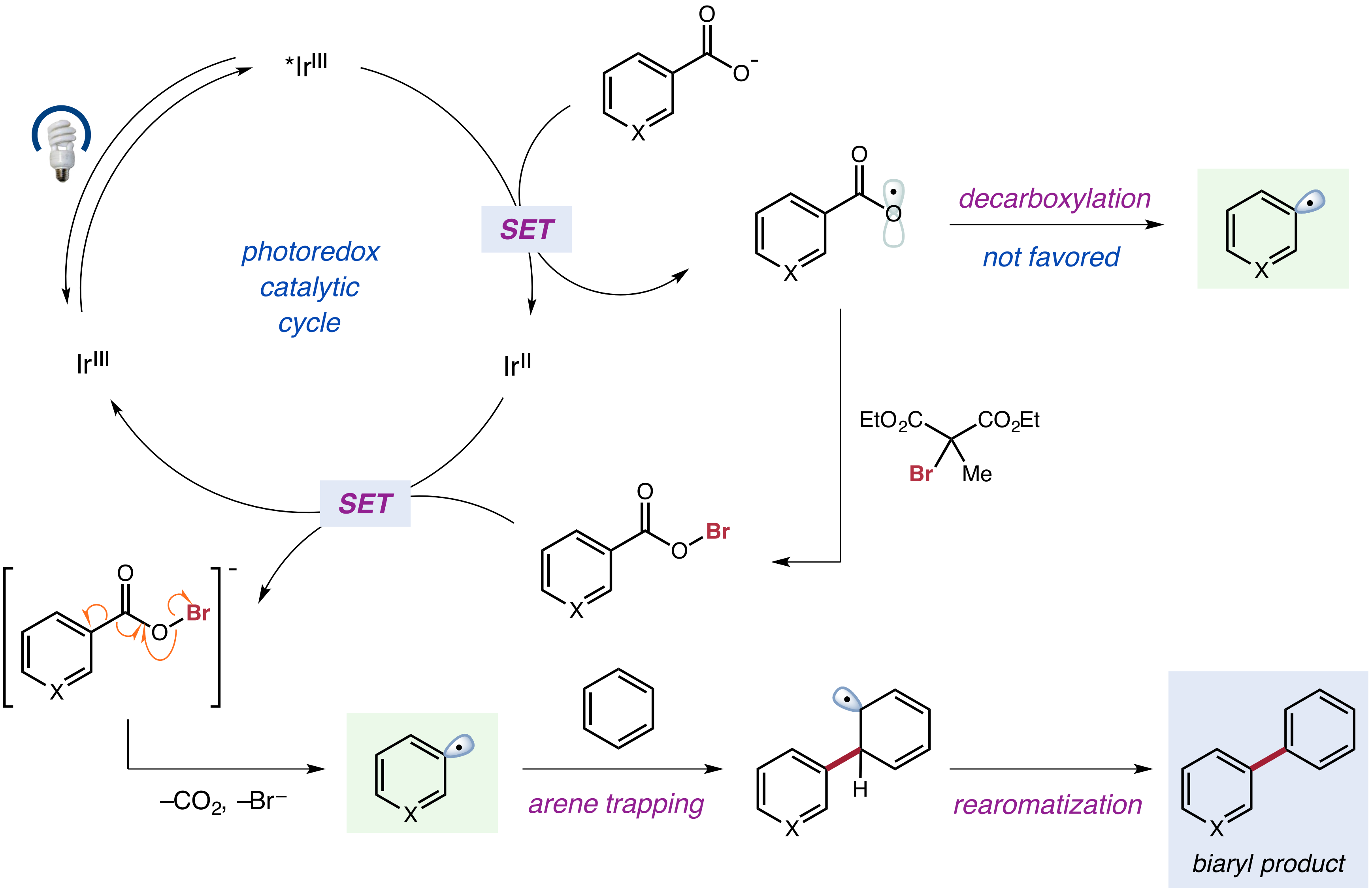
Benzoyl hypohalites as intermediates



Candish, L.; Freitag, M.; Gensch, T.; Glorius, F. *Chem. Sci.* **2017**, *8*, 3618–3622

Decarboxylation Coupling: Radical Pathway

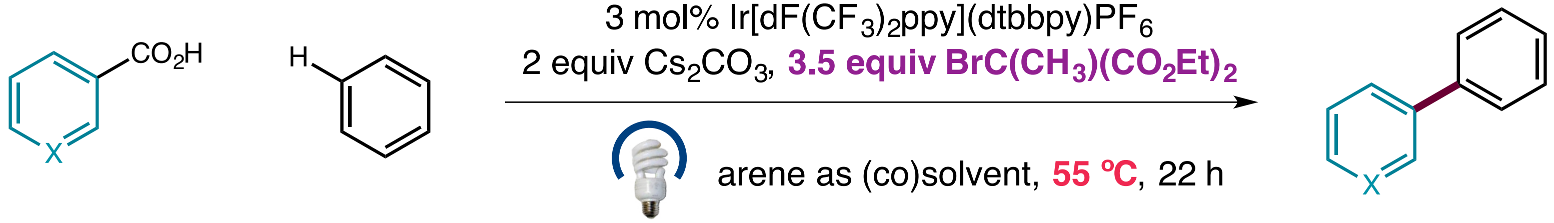
■ Proposed mechanism: decarboxylative arylation with arenes



Candish, L.; Freitag, M.; Gensch, T.; Glorius, F. *Chem. Sci.* **2017**, *8*, 3618–3622

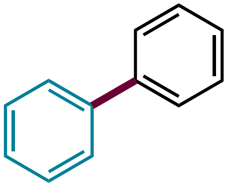
Decarboxylation Coupling: Radical Pathway

Decarboxylative C–H coupling via radical decarboxylation

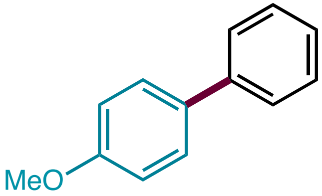


3 mol% $Ir[dF(CF_3)_2ppy](dtbbpy)PF_6$
2 equiv Cs_2CO_3, **3.5 equiv $BrC(CH_3)(CO_2Et)_2$**
arene as (co)solvent, **55 °C**, 22 h

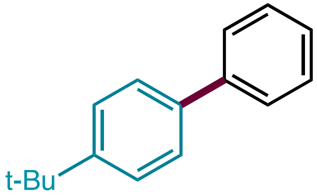
aryl acid *arene* *biaryl product*



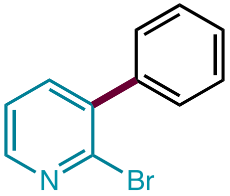
52% yield



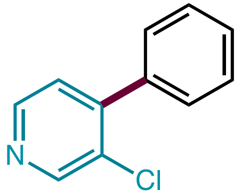
68% yield



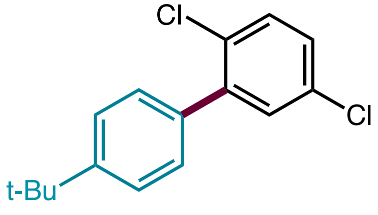
57% yield



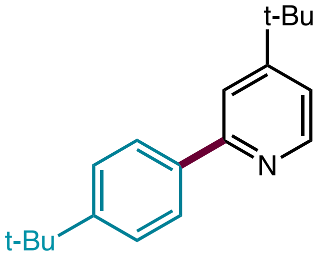
78% yield



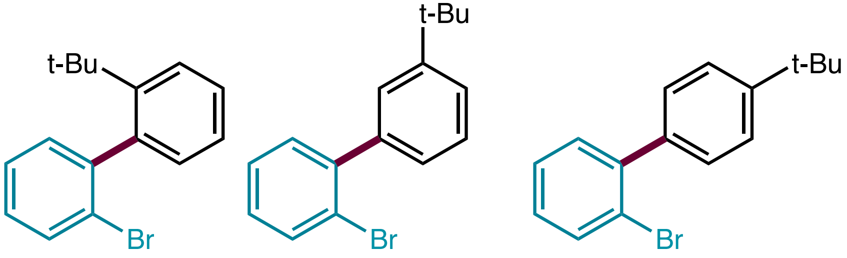
67% yield



56% yield



59% yield

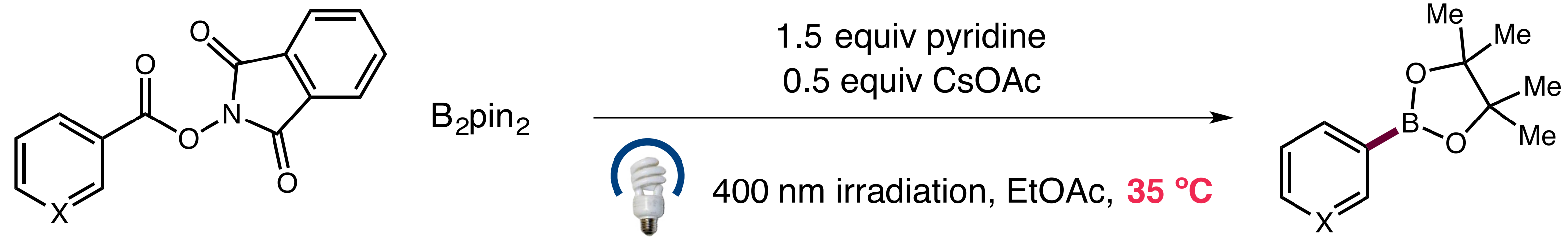


79% yield
21:50:29

Candish, L.; Freitag, M.; Gensch, T.; Glorius, F. *Chem. Sci.* **2017**, *8*, 3618–3622

Decarboxylation Coupling: Radical Pathway

■ Using redox ester: decarboxylative borylation under mild condition

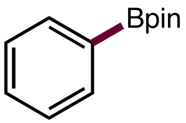


1.5 equiv pyridine
0.5 equiv CsOAc

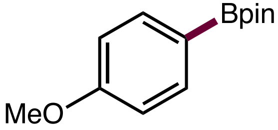
400 nm irradiation, EtOAc, **35 °C**

aryl redox ester

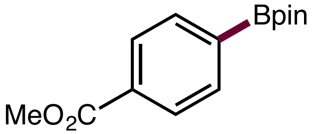
aryl boronic ester



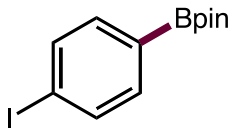
84% yield



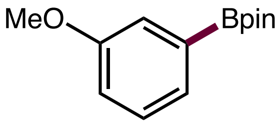
72% yield



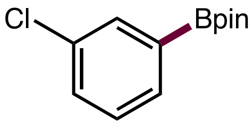
61% yield



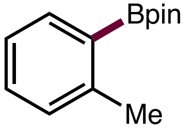
52% yield



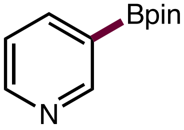
72% yield



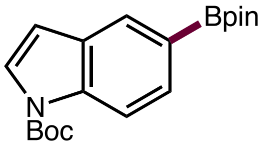
35% yield



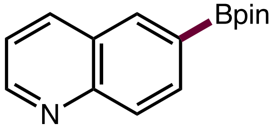
34% yield



78% yield



59% yield

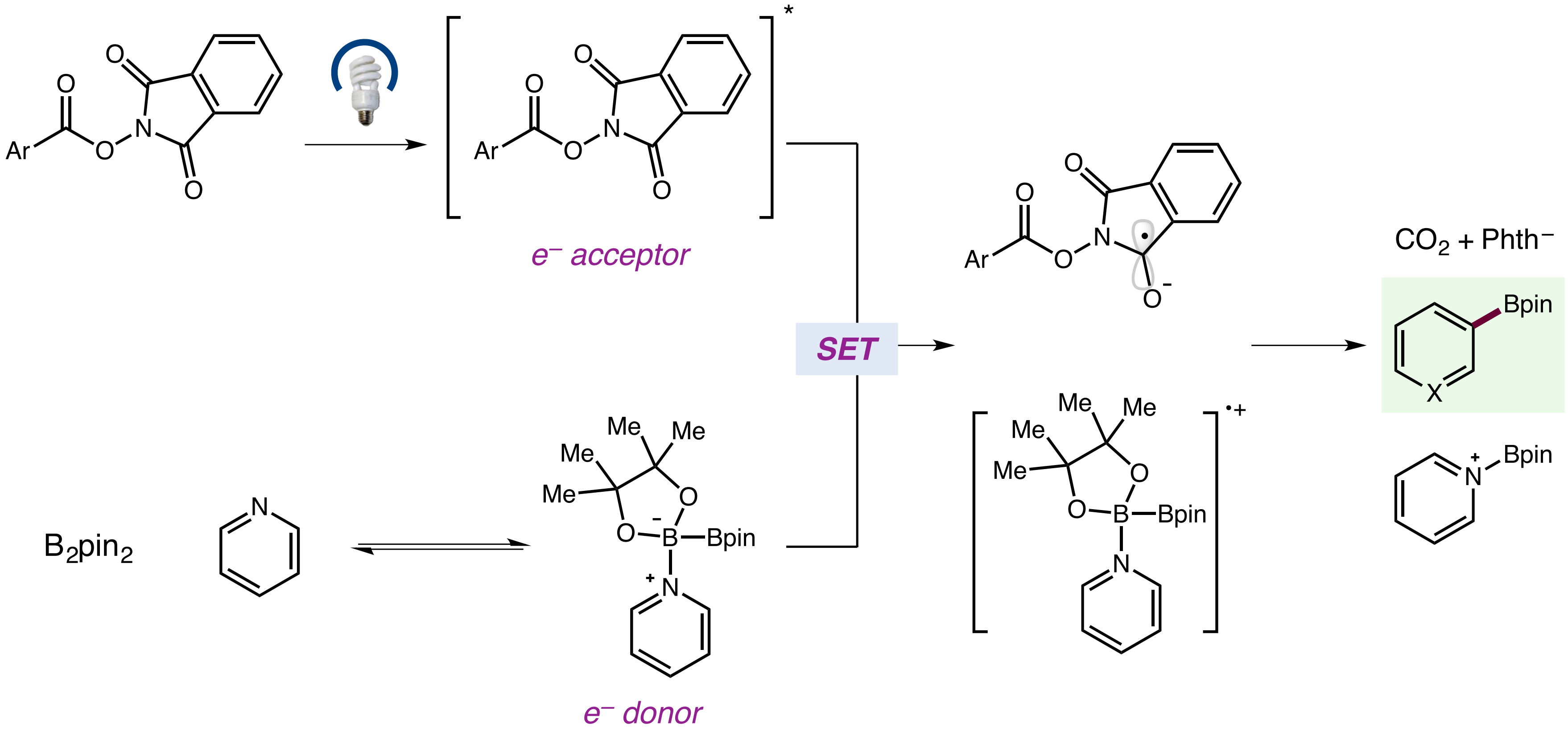


66% yield

Candish, L.; Teders, M.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 7440–7443

Decarboxylation Coupling: Radical Pathway

Mechanistic hypothesis



Candish, L.; Teders, M.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 7440–7443