Cross-Coupling of Amides by N–C Activation

25 March, 2020

ACS Spring 2020 National Meeting
Paper no. ORGN 593

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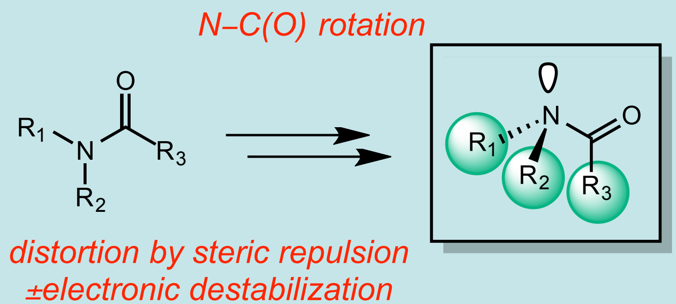
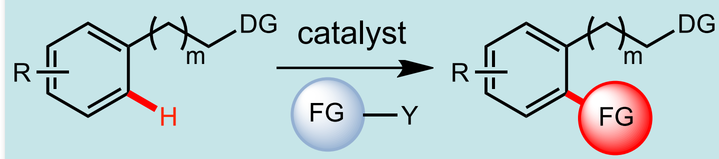
New Metal-Catalyzed Methods for Carbon-Carbon Bond Construction

■ Chemistry of Amide Bonds: N–C Activation



•N–C(O) activation, R–NC(O) activation, N as directing group, electrophilic activation

■ C–H Activation using Sustainable Metals

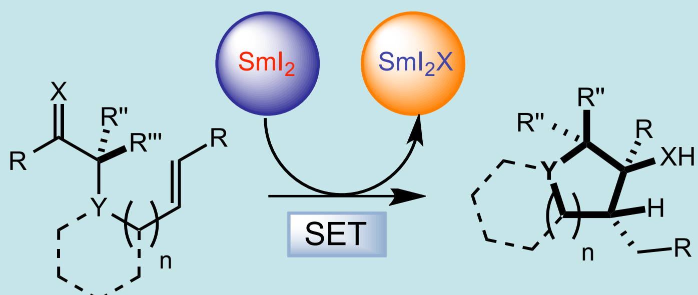


FG = Ar, CF_3, NH_2

DG = OH, NH_2

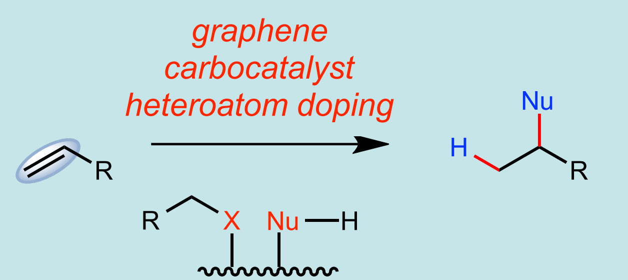
•abundant, benign, inexpensive metal catalyst [metal = Ru, Co, Fe, Cu, Mn]

■ Metal-Mediated Radical Reactions



•complexity-generating radical reactions [lanthanides, Cp_2TiCl, photoredox]

■ Carbocatalysis by Engineered Carbon Surface



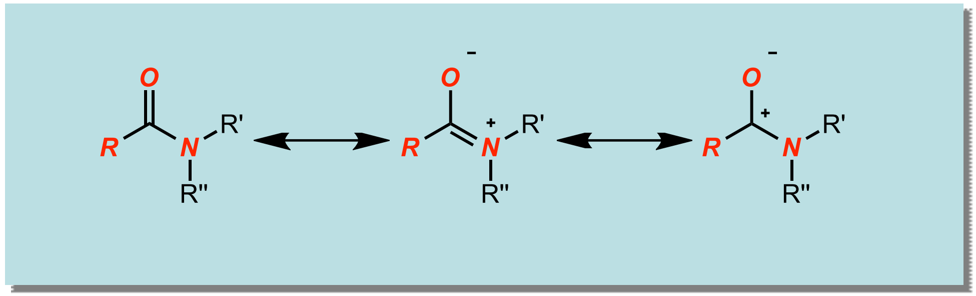
[π–system = olefin, alkyne, allene, diene, arene] [nucleophile = Ar, N, O, CH_2]

■ Iron-catalyzed cross-coupling (*ACIE* **2018**, *57*, 11116; *GC* **2017**, *19*, 5361; *ChemCatChem* **2019**, *11*, 5733)

Amide Bonds

Fundamental functional group of synthetic and biological significance

- Amide bond resonance: ***15-20 kcal/mol*** (Pauling, 1935)



amide resonance:

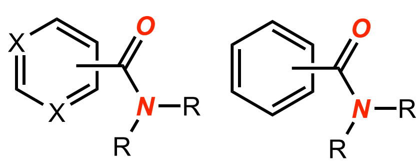
planar amide = 40% double bond

Greenberg, A.; Breneman, C. M.; Liebman, J. F. The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science; Wiley-VCH: New York, 2003.

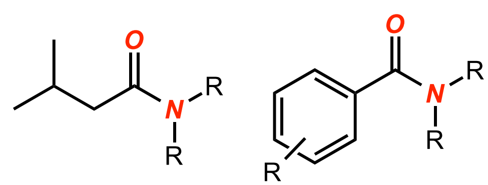
- ***Synthetic*** and ***biological*** importance of amides

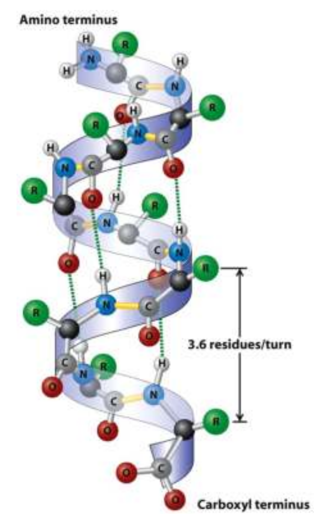
amides = peptides, proteins, pharmaceuticals

- abundant feedstock

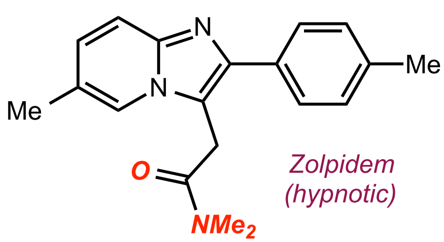


- bench-stable intermediates



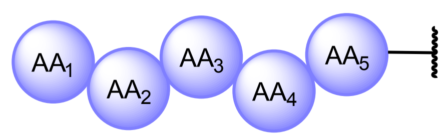


- pharmaceuticals



Zolpidem (hypnotic)

- biomolecules

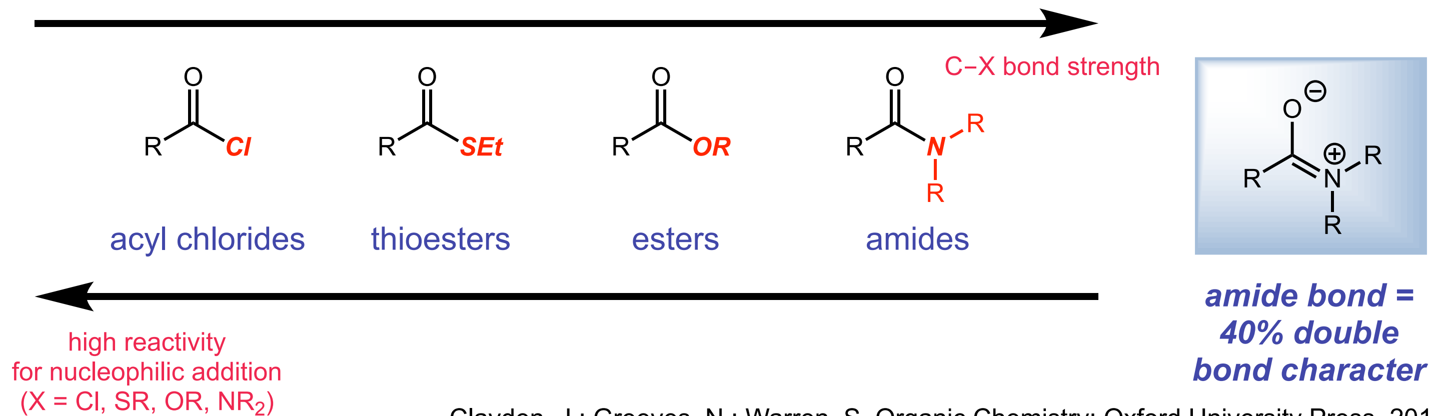


Lodish, H. Molecular Cell Biology; Freeman: New York, 2008.
Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.
Amide-based polymers: Marchildon, K. *Macromol. React. Eng.* **2011**, *5*, 22.

Electrophilic Reactivity of Amide Bonds

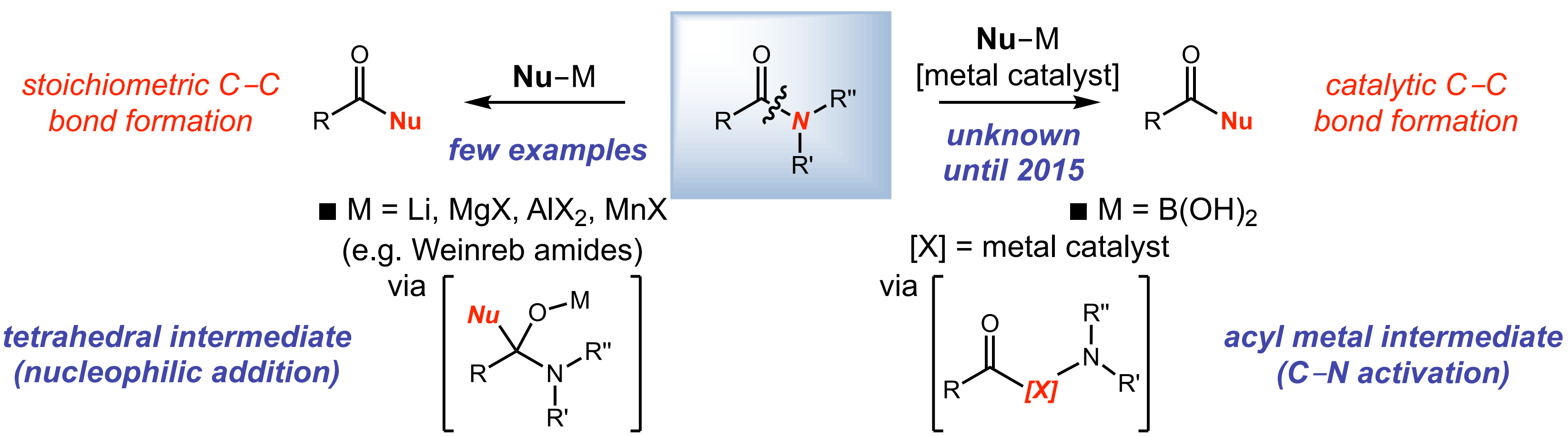
Activation of inert N–C bonds in amides

■ Reactivity of carboxylic acid derivatives: nucleophilic addition



Clayden, J.; Greeves, N.; Warren, S. Organic Chemistry; Oxford University Press, 2012.

■ General reactivity pathways in nucleophilic addition to amides



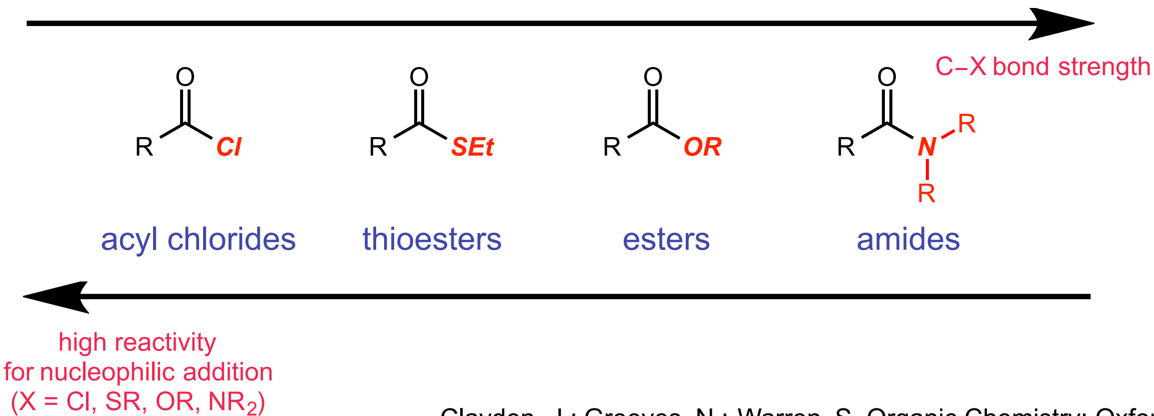
■ broadly applicable catalytic mode

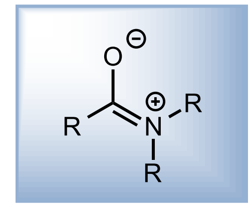
Amides: until 2015 completely unexplored in transition metal catalysis: *low reactivity due to* $n_N \rightarrow \pi^*_{CO}$ *conjugation*

Electrophilic Reactivity of Amide Bonds

Activation of inert N–C bonds in amides

■ Reactivity of carboxylic acid derivatives: nucleophilic addition

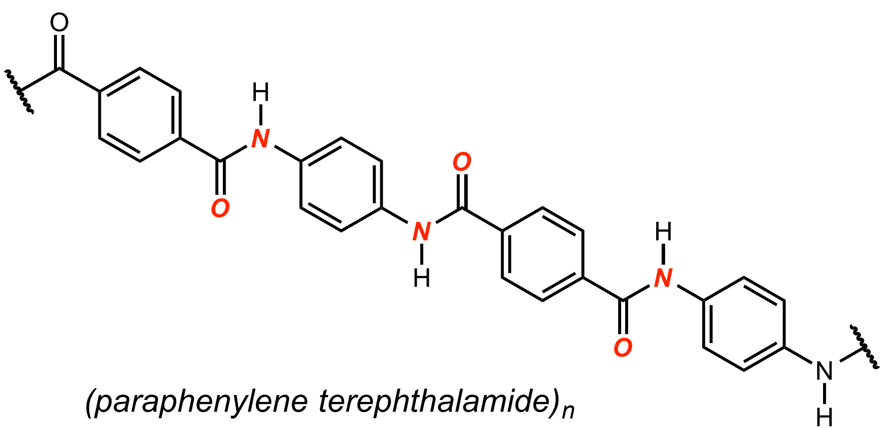




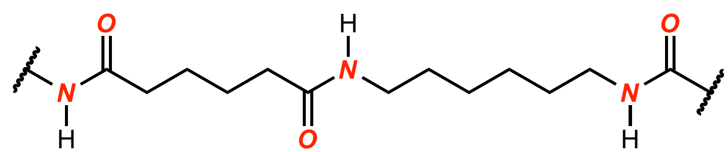
amide bond = 40% double bond character

Clayden, J.; Greeves, N.; Warren, S. Organic Chemistry; Oxford University Press, 2012.

■ Synthetic fibers and plastics Kevlar and Nylon 66 represent polyamide monomers



(paraphenylene terephthalamide)$_n$



(hexamethylenediamine/adipic acid)$_n$

Kwolek, S.; Mera, H.; Takata, T. High-Performance Fibers In Ullmann's Encyclopedia of Industrial Chemistry; Wiley, 2002.

Amides: until 2015 completely unexplored in transition metal catalysis: *low reactivity due to $n_N \rightarrow \pi^*_{CO}$ conjugation*

General Strategy for Amide N–C Bond Activation

Exploiting amide bond ground-state-destabilization

- **Three-pronged approach to highly chemoselective amide bond activation**

*1. New catalytic **transformations** of amides by N–C activation*

*2. New **classes** of amides that partake in cross-coupling manifolds*

*3. Mechanistic **understanding** of amide bond distortion at the fundamental level*

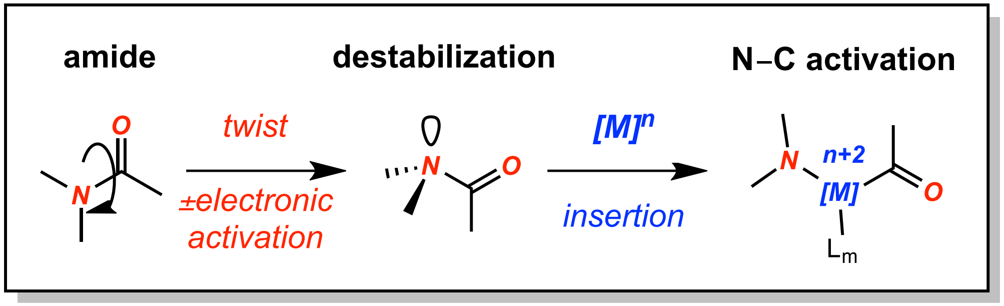
Hypothesis: due to unique geometric features amides can participate in highly tunable reaction manifolds unavailable to other functions by selective N–C metal insertion

General Strategy for Amide N–C Bond Activation

Exploiting amide bond ground-state-destabilization

■ Our group: ***New strategies for activation of amide N–C bonds via ground-state destabilization***

■ steric
and/or
■ electronic

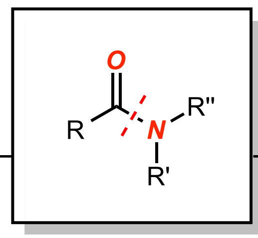


bring down
amide resonance:
15-20 kcal/mol

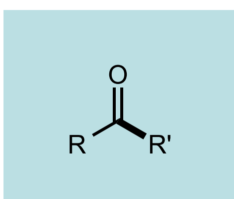
Greenberg, A.; Breneman, C. M.; Liebman, J. F. The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science; Wiley-VCH: New York, 2003.

■ Previously elusive ***transition metal catalyzed*** mode of reactivity of inert amide N–C bonds of ***biological importance***

amides = peptides, proteins, pharmaceuticals
bench-stable acyl/aryl equivalents



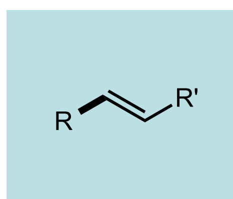
metal catalysis:
Nobel Prize 2010



Suzuki, Negishi

Meng, Szostak *Org. Lett.* **2015**, *17*, 4364.

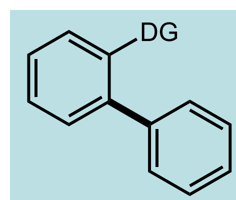
Pd, Ni



Heck

Meng, Szostak *Angew. Chem. Int. Ed.* **2015**, *54*, 14518.

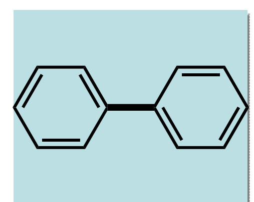
Pd



C–H activation

Meng, Szostak *Org. Lett.* **2016**, *18*, 796.

Rh



Suzuki

Shi, Meng, Szostak *Angew. Chem. Int. Ed.* **2016**, *55*, 6959.

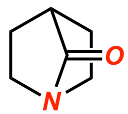
Ni

Since 2015, in total >10 distinct previously unknown reactions of amides via catalytic transformations

General Strategy for Amide N–C Bond Activation

Bridged lactams as models for N–C cross-coupling

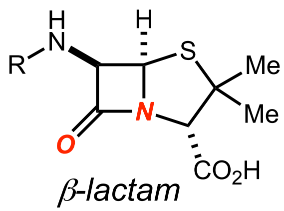
■ Bridged lactams as models for disrupting amidic resonance: ***amino-ketone reactivity of amides***



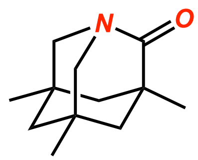
proposed

1938
Lukes

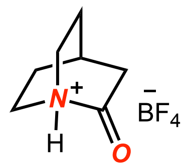
synthesized in 2016
(Stolz, *JACS* **2016**, *138*, 969)



1941
Woodward

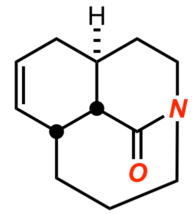


1998
Kirby



2006
Stoltz

perpendicularly twisted
(τ = 90°, χN = 60°)



2005
Aubé

medium bridged
(τ = 50°; χN = 35°)

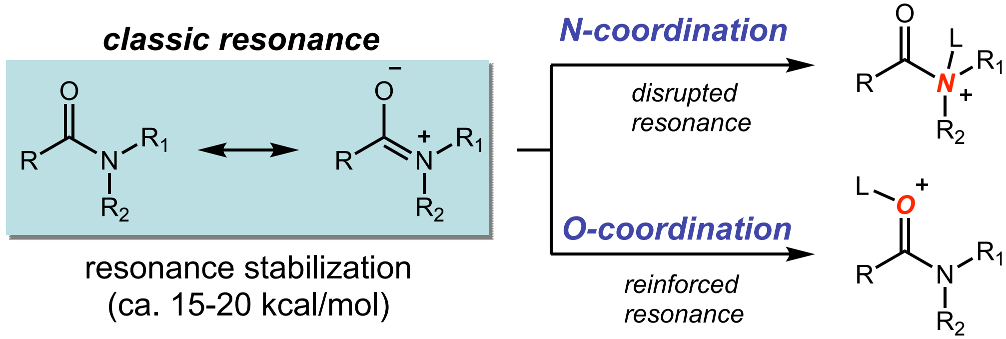
■ excellent models for rotated amide bonds

■ hydrolytically unstable

■ N-protonation

Reviews on bridged lactams: Szostak, M.; Aubé, J. *Chem. Rev.* **2013**, *113*, 5701.
Hall, H. K., Jr.; El-Shekeil, A. *Chem. Rev.* **1983**, *83*, 549. Yamada, S. *Rev. Heteroat. Chem.* **1999**, *19*, 203.
Classic computational studies on bridged lactams: Greenberg, A. *JACS* **1993**, *115*, 6951; *JACS* **1996**, *118*, 8658.

■ Activation of amide bonds by switchable N-/O-coordination



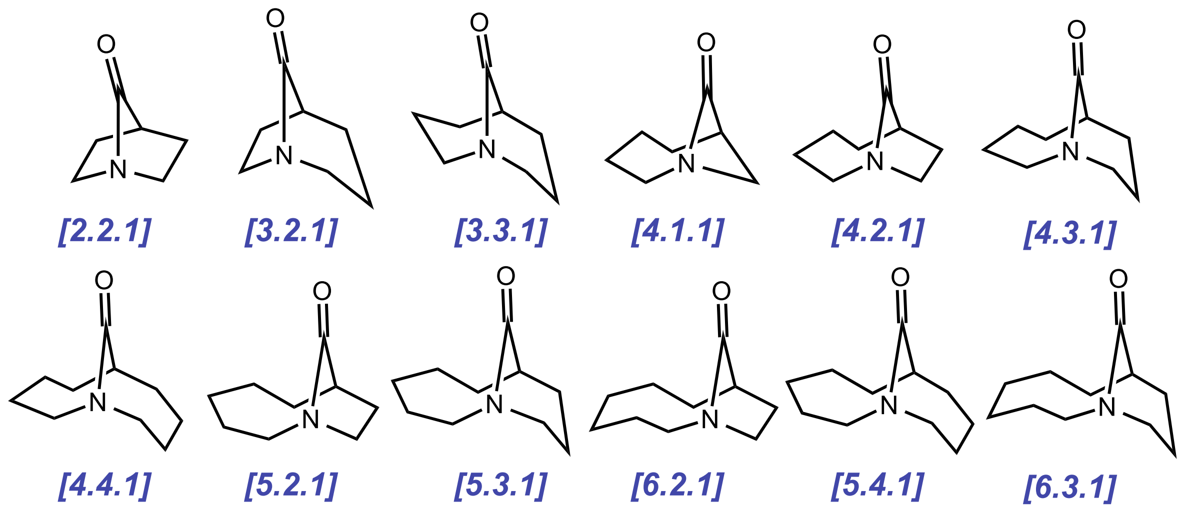
■ N-coordination is preferred when (τ + χ_N) = 50° → new amide bond reactivity

Szostak, R.; Aubé, J.; Szostak, M. *Chem. Commun.* **2015**, *51*, 6395.
Full account: Szostak, R.; Aubé, J.; Szostak, M. *J. Org. Chem.* **2015**, 80, 7905.
For structures of N-alkylated twisted amides, see: Hu, F.; Lalancette, R.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 5062.

General Strategy for Amide N–C Bond Activation

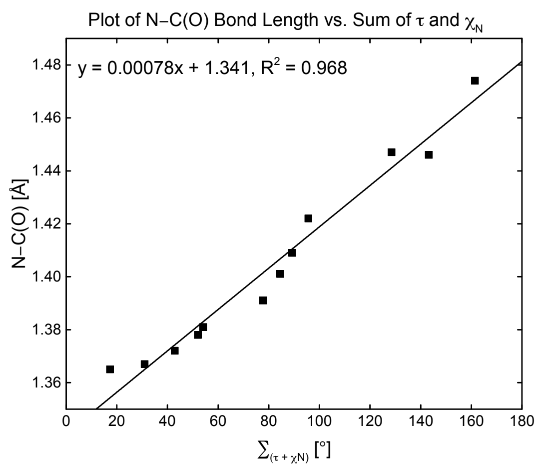
Bridged lactams as models for N–C cross-coupling

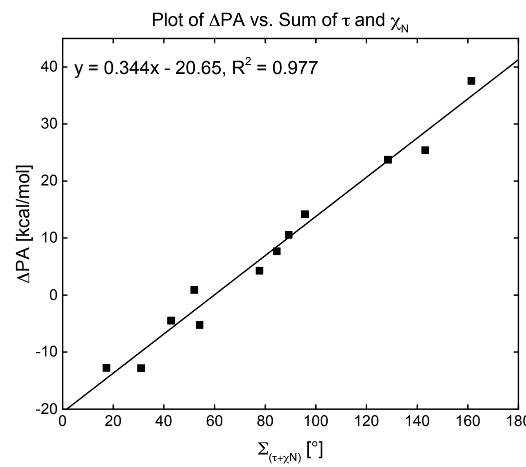
- Model one-carbon bridged lactams used to predict N-/O-coordination aptitude: ***amide distortion: ($\tau + \chi_N$) = 20° to 150°***



Calculated using
MP2/6-311++G(d,p)

- ***Additive*** Winkler-Dunitz distortion paramter and excellent ***ΔPA vs. geometry*** correlation



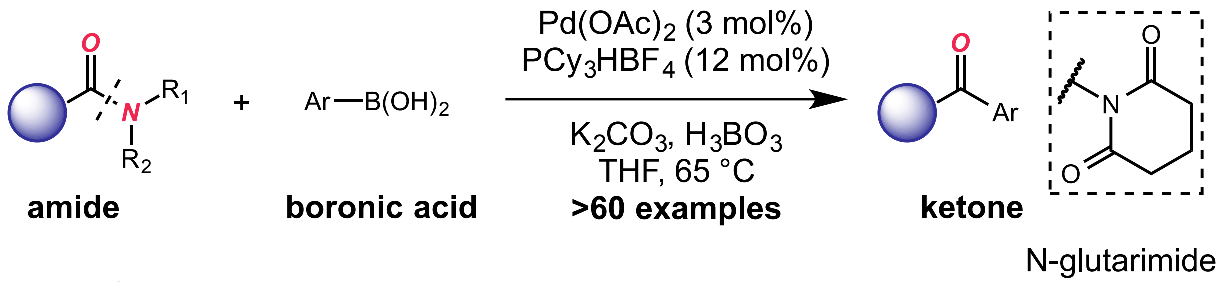


Szostak, R.; Aubé, J.; Szostak, M. *Chem. Commun*. **2015**, *51*, 6395.
Full account: Szostak, R.; Aubé, J.; Szostak, M. *J. Org. Chem.* **2015**, 80, 7905.

General Strategy for Amide N–C Bond Activation

Acyl-amide cross-coupling

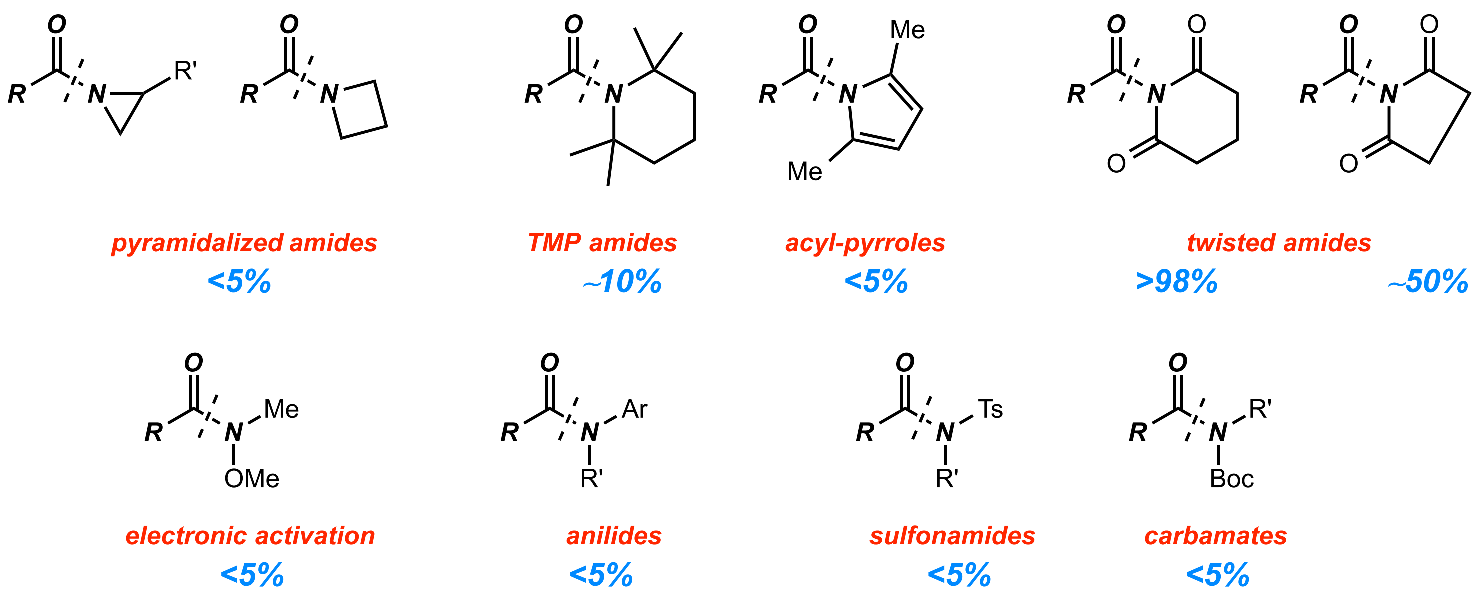
■ Suzuki-Miyaura cross-coupling of amides by ground-state distortion



■ first results in Oct 2014

Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364.
Meng, G.; Szostak, M. New talent issue, *Org. Biomol. Chem.* **2016**, *14*, 5690.

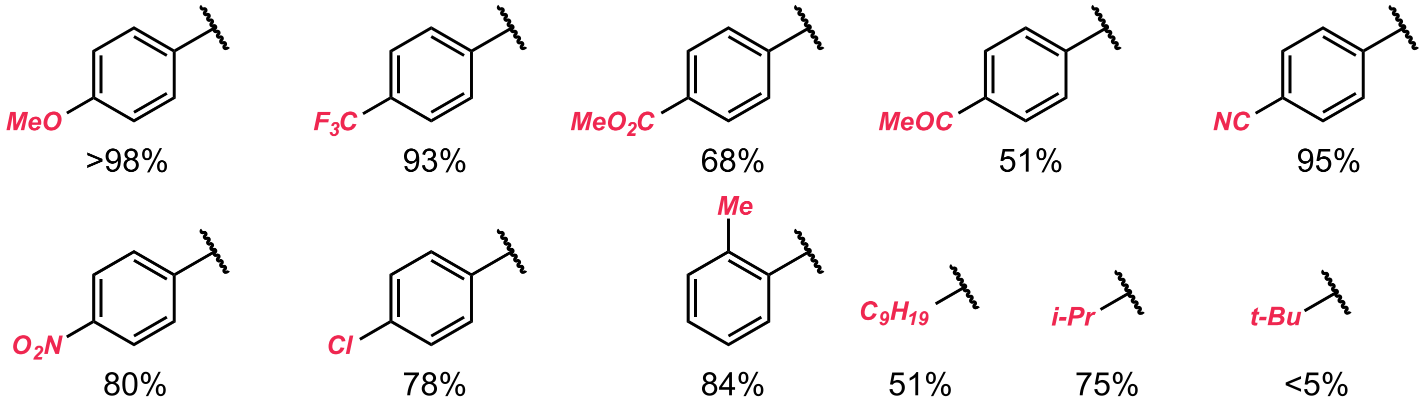
■ High chemoselectivity of N-glutarimide amides in catalytic N–C activation



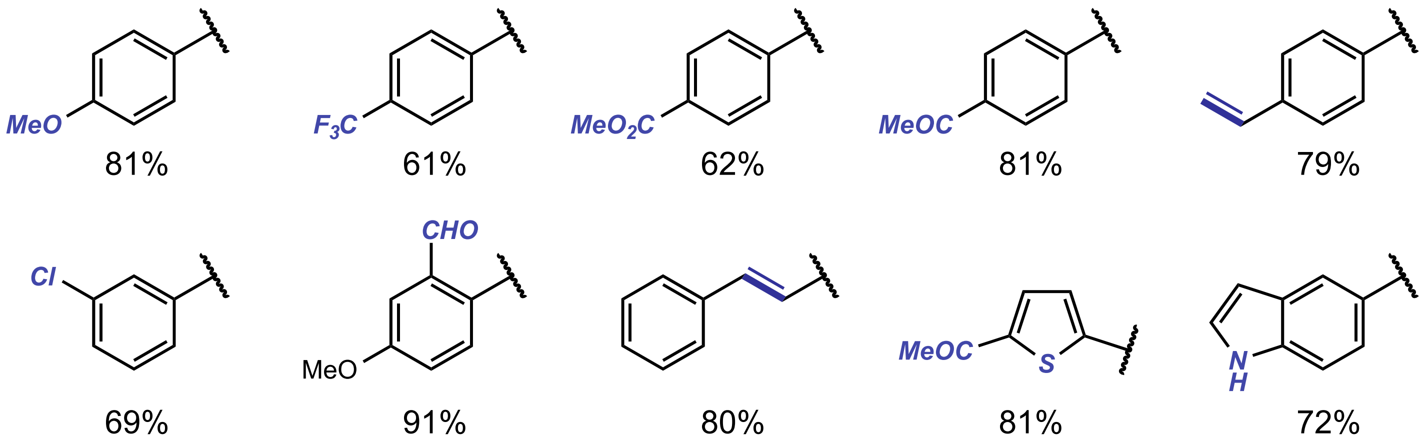
General Strategy for Amide N–C Bond Activation

Acyl-amide cross-coupling

- Suzuki-Miyaura cross-coupling of amides by ground-state distortion: broad substrate scope with bench-stable amides
  - amide scope



  - boronic acid scope



- RT cross-coupling is also possible (93% yield)

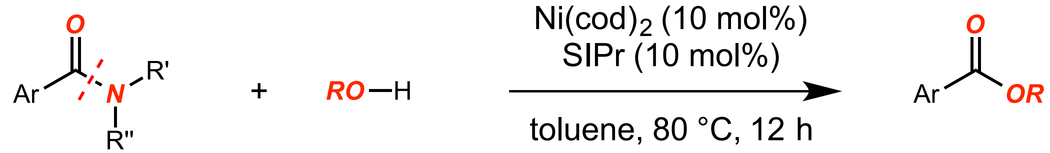
Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364.
Meng, G.; Szostak, M. New talent issue, *Org. Biomol. Chem.* **2016**, *14*, 5690.

General Strategy for Amide N–C Bond Activation

Acyl-amide cross-coupling

- Amide bond cross-coupling in 2015: ***concurrent independent reports***

  - Ni-catalyzed C–O cross-coupling of amides

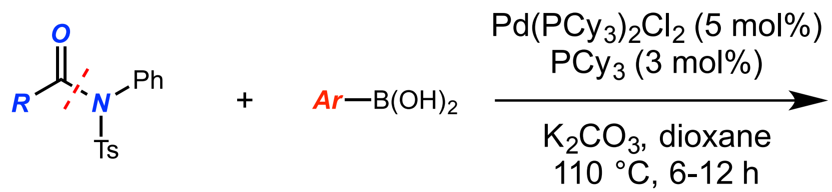


  - R'R'' = Ph,alkyl, Ts,Me, Boc,alkyl

31 examples

Hie, L.; Nathel, N. F. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y. F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79.

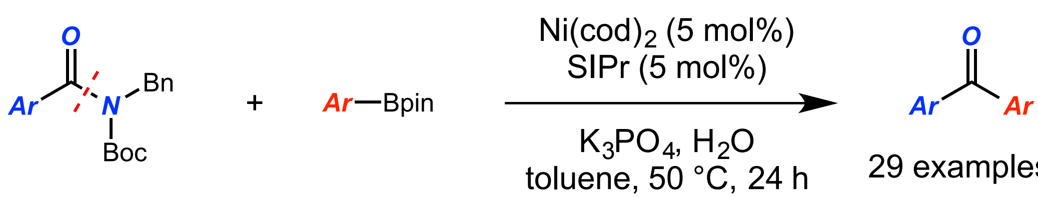
  - Pd-catalyzed Suzuki cross-coupling of amides



32 examples

Li, X.; Zou, G. *Chem. Commun.* **2015**, *51*, 5089.

  - Ni-catalyzed Suzuki cross-coupling of amides



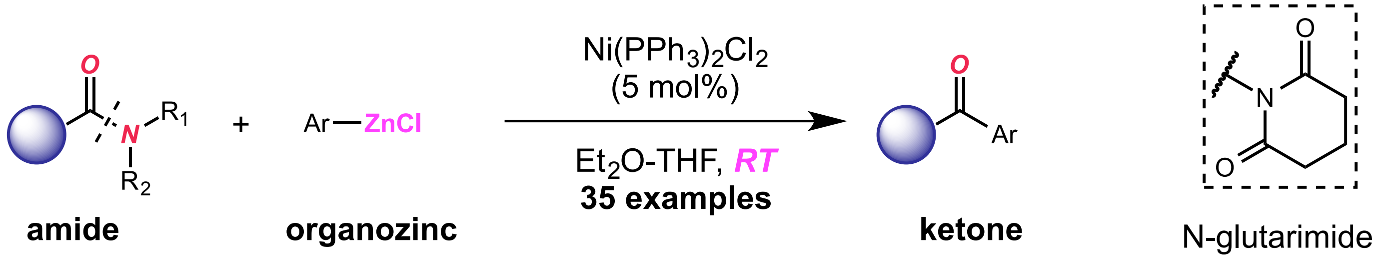
29 examples

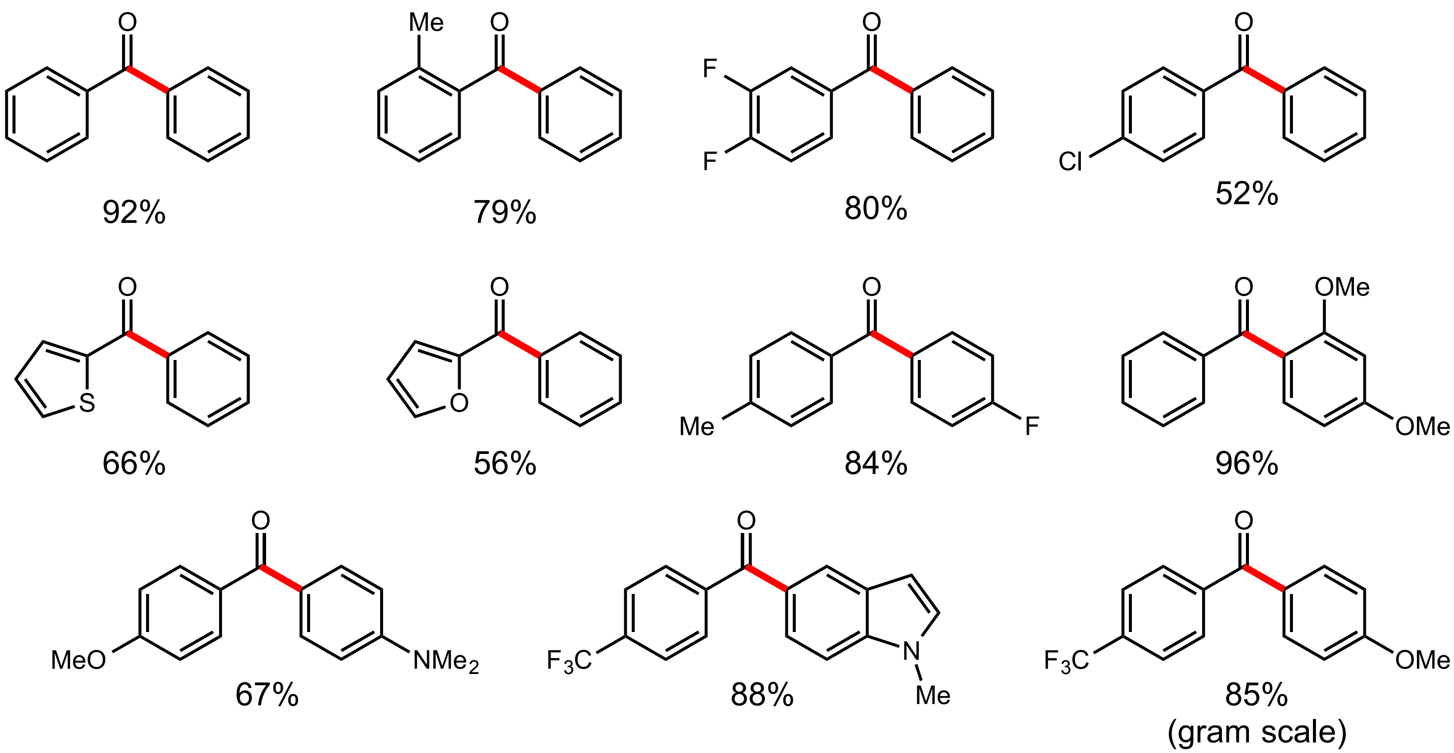
Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem.* **2016**, *8*, 75.

General Strategy for Amide N–C Bond Activation

Acyl-amide cross-coupling

■ Negishi cross-coupling of amides by N–C bond activation at room temperature





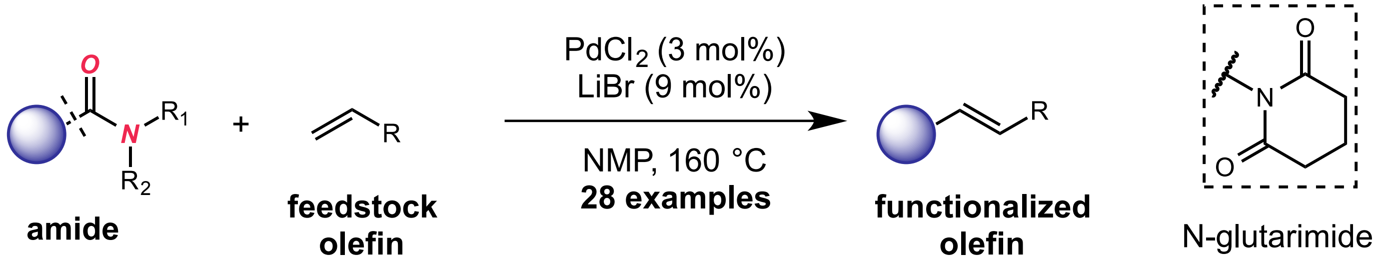
Shi, S.; Szostak, M. *Chem. Eur. J.* **2016**, *22*, 10420.

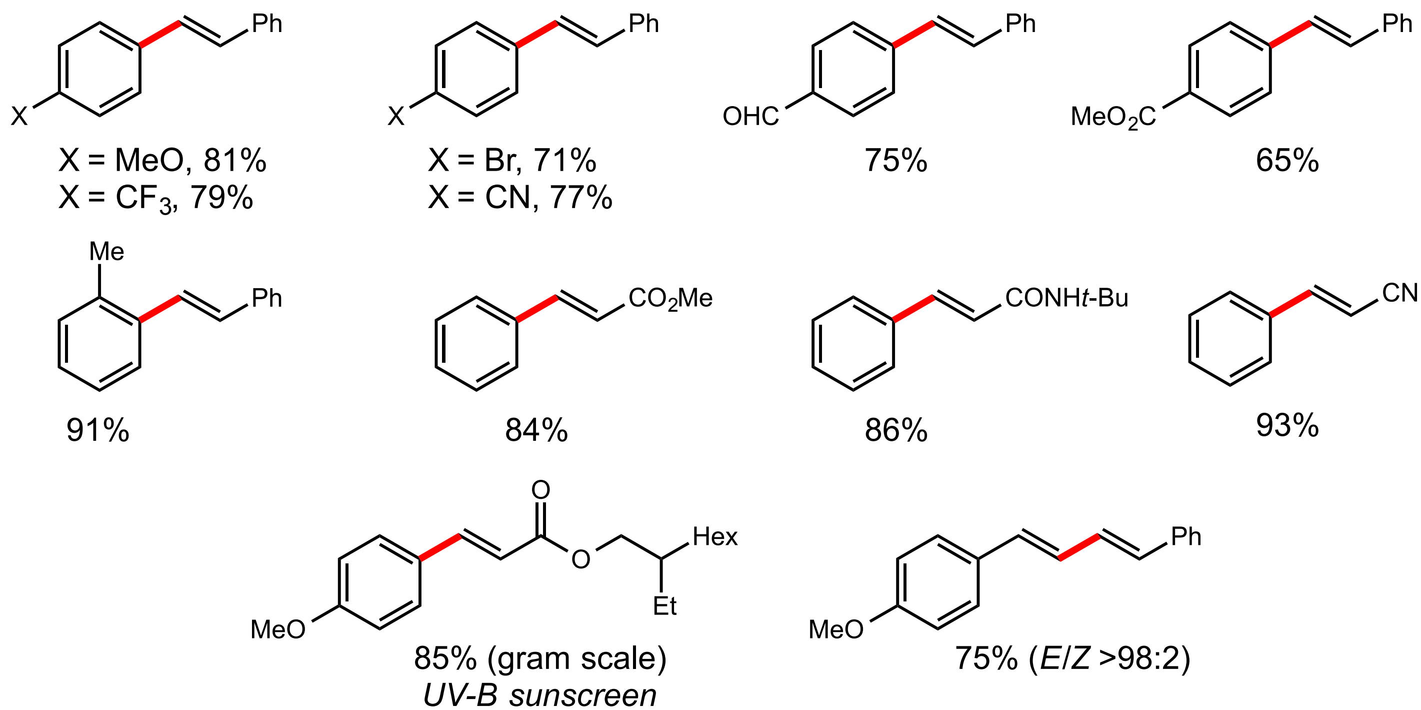
For acyl-alkyl Negishi cross-coupling, see: Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K. *ACS Catal.* **2016**, *6*, 3176.

General Strategy for Amide N–C Bond Activation

Aryl-amide cross-coupling

■ Decarbonylative Heck cross-coupling of amides by N–C bond activation



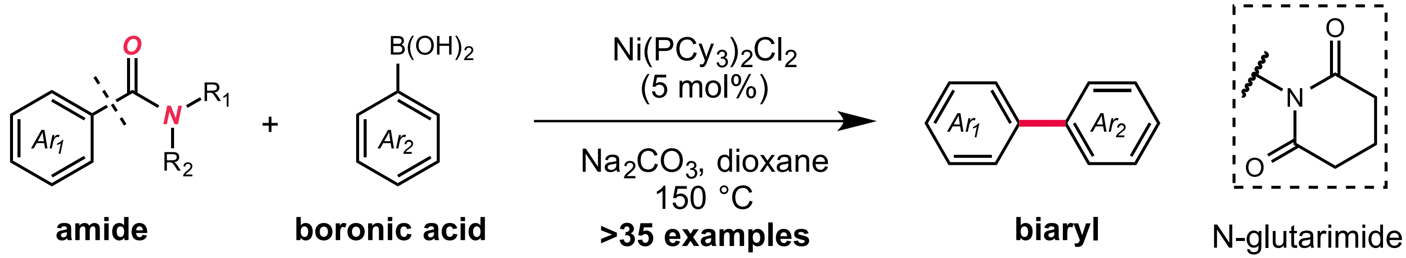


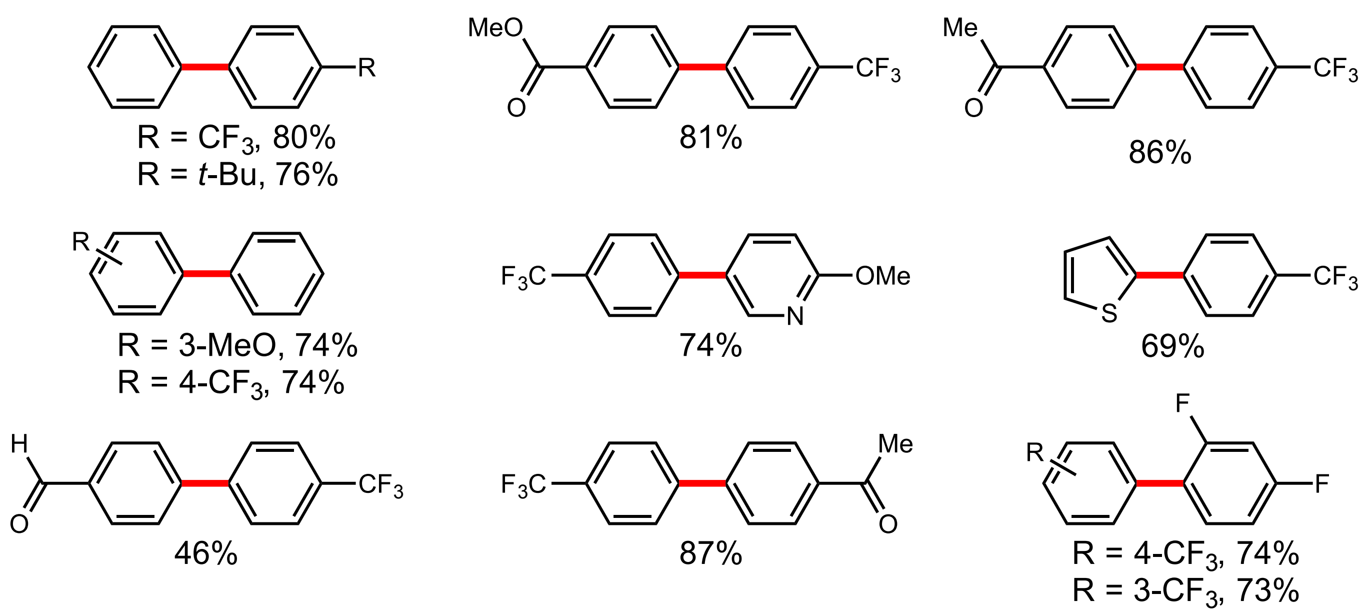
Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518.

General Strategy for Amide N–C Bond Activation

Aryl-amide cross-coupling

■ Decarbonylative Suzuki biaryl cross-coupling of amides by N–C bond activation





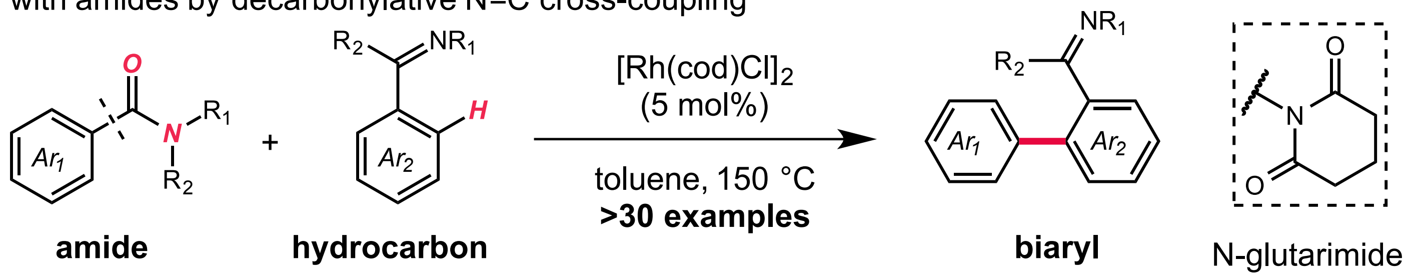
■ the bench-stable Ni-catalyst system shows high selectivity for aryl vs. acyl cross-coupling

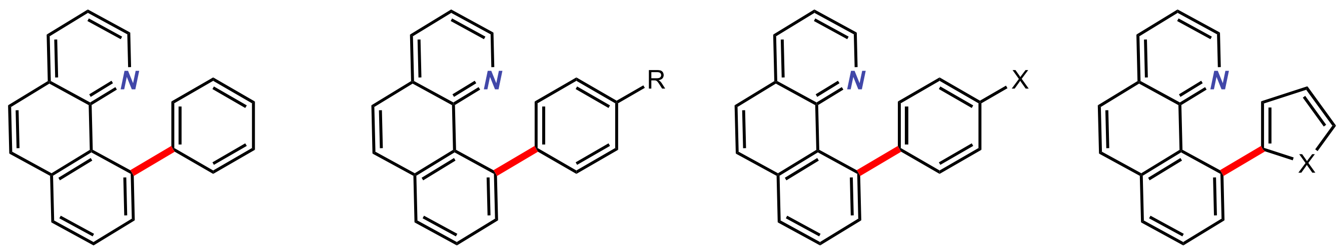
Shi, S.; Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959.

General Strategy for Amide N–C Bond Activation

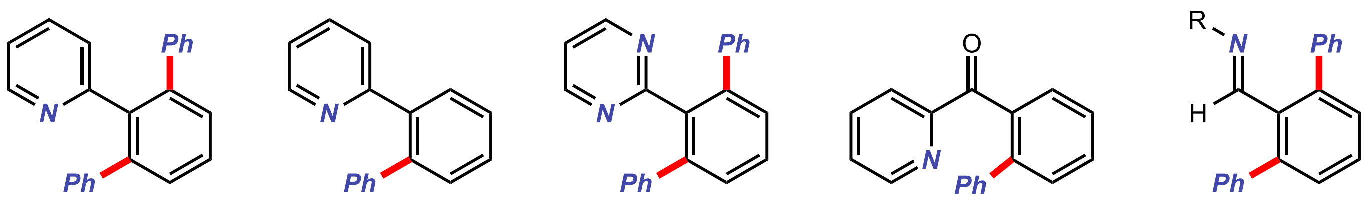
Aryl-amide cross-coupling

- C–H Activation with amides by decarbonylative N–C cross-coupling





91% | R = CO_2Me, 96%; R = CHO, 91% | X = Br, 89%; X = Cl, 92% | X = O, 84%; X = S, 84%



87% | 79% | 96% | 64% | 60%, R = 2,6-*i*-Pr_2-C_6H_3

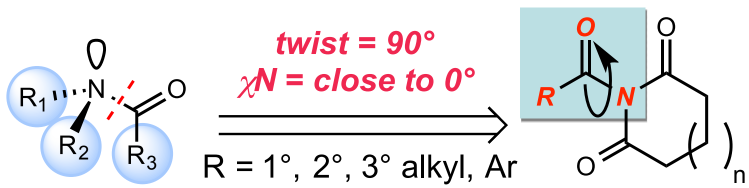
- TON for N–C activation of 1,000
- alkyl- and vinyl-transfer also proceed in high yields

Meng, G.; Szostak, M. *Org. Lett.* **2016**, *18*, 796.

General Strategy for Amide N–C Bond Activation

Structural investigation of amide bond non-planarity

■ Perpendicular distortion of N-glutarimide amides: evidence for ground-state destabilization

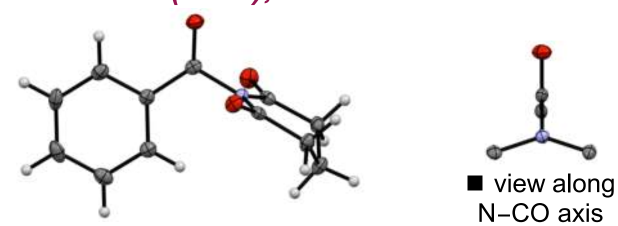


R	N-substituent	τ [°]	χN [°]
Me	glutarimide	90.0	1.0
Ph	glutarimide	90.0	6.0
Me	succinimide	42.2	4.5
Ph	succinimide	68.2	12.1
Me	phthalimide	26.2	4.0
Ph	phthalimide	54.3	15.3

Calculated using B3LYP/6-311++G(d,p).

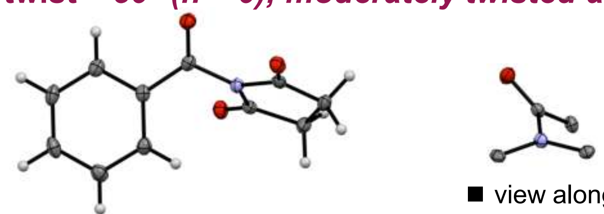
■ high twist irrespective of the α-carbon substituent

■ ***twist = 90° (n = 1), classic twisted amides***



■ view along N–CO axis

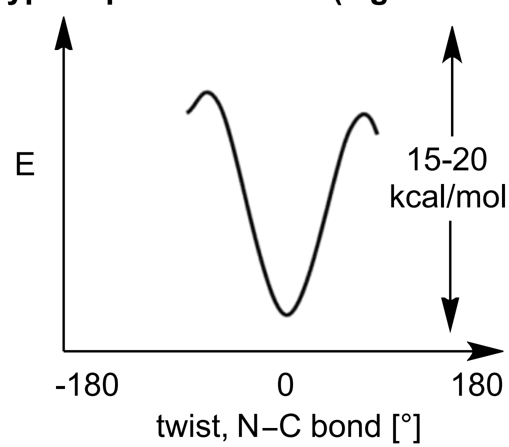
■ ***twist ~ 50° (n = 0), moderately twisted amides***



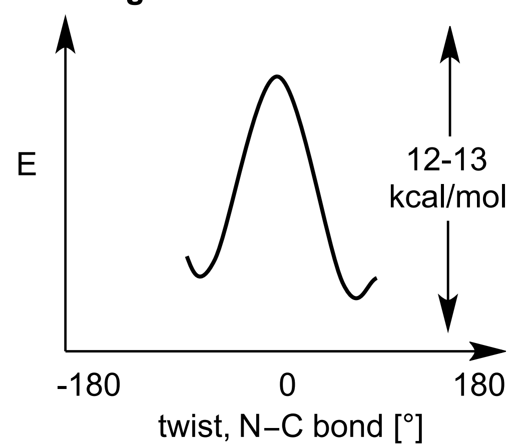
■ view along N–CO axis

■ Inverted rotational profile of N-glutarimide amides: graphical representation

Typical planar amides (e.g. $MeCONMe_2$)



N-glutarimide amides

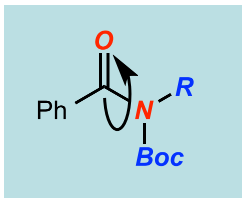


Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *Chem. Eur. J.* **2016**, *22*, 14494.

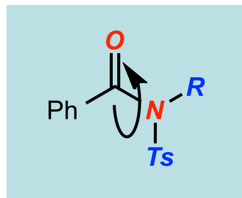
General Strategy for Amide N–C Bond Activation

Structural investigation of amide bond non-planarity

■ Conformational flexibility of N-Boc and N-Ts amides: acyclic twisted amides

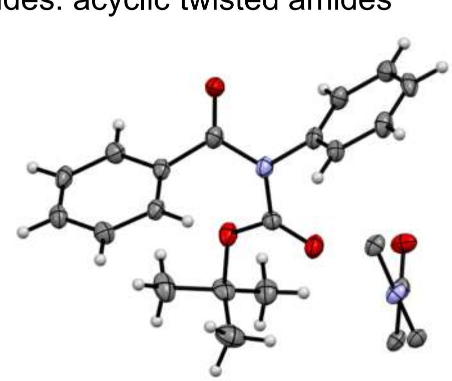


	τ [°]	χN [°]
Me	32.1	17.4
Ph	31.0	15.0



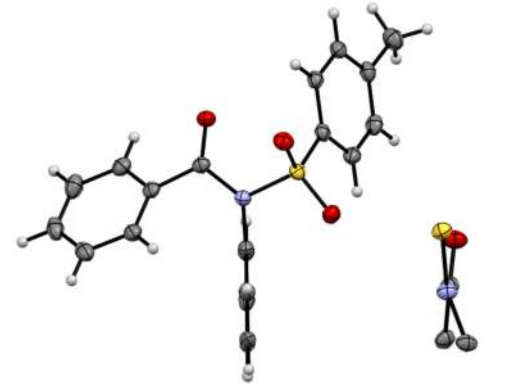
	τ [°]	χN [°]
Me	25.5	12.2
Ph	30.4	22.3

Calculated using B3LYP/6-311++G(d,p).



N = Ph, Boc

■ view along N–CO axis

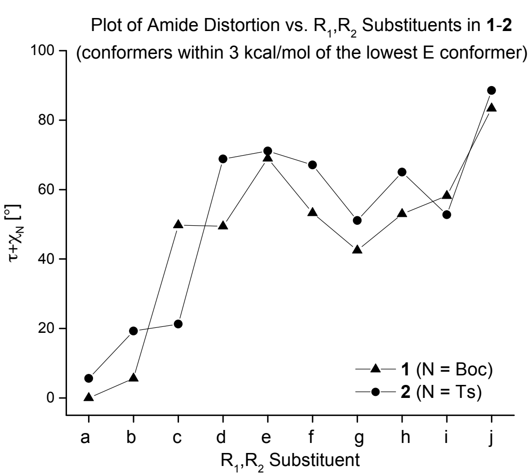


N = Ph, Ts

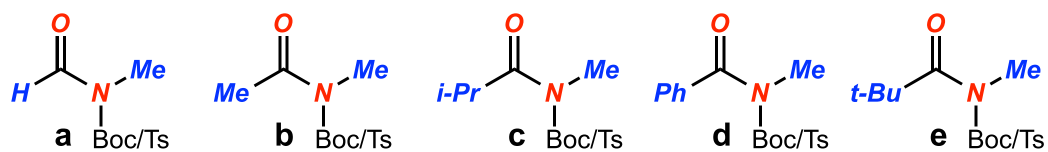
■ view along N–CO axis

■ low E_{rot} ⇒ R/Boc: 6.2-7.2 kcal/mol; R/Ts 8.0-9.7 kcal/mol

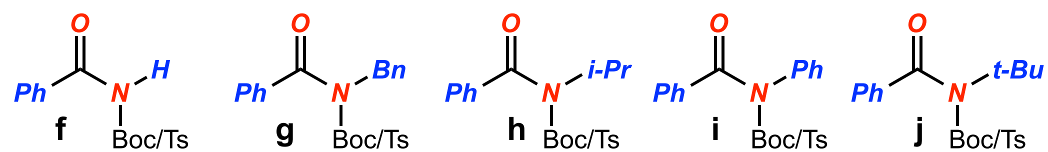
■ Amide bond distortion in N-Boc and N-Ts amides: acyclic twisted amides



■ α-carbon variation



■ N-substituent

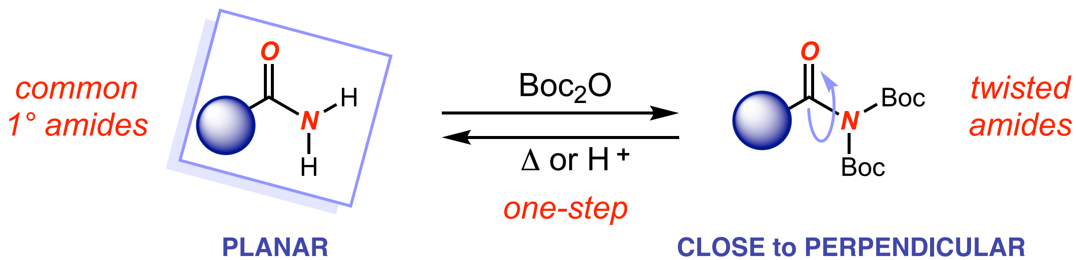


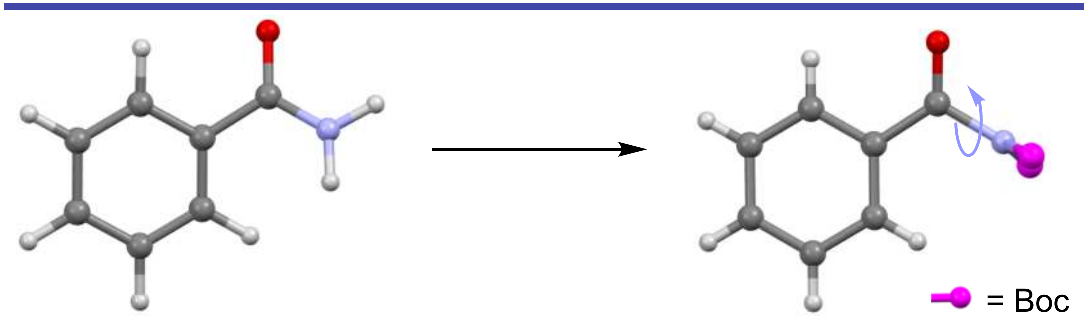
Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, M. *J. Org. Chem.* **2016**, *81*, 8091.

General Strategy for Amide N–C Bond Activation

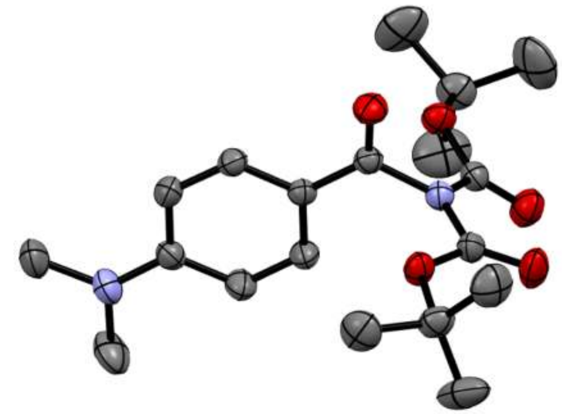
Reversible twisting of primary amides

■ Reversible twisting by ground-state destabilization of primary benzamides

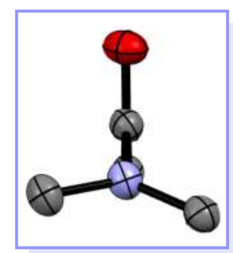




ORTEP: **benzamide** ORTEP: **N,N-Boc$_2$ amide**

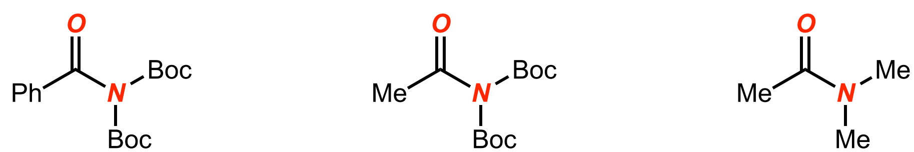


τ = 81.9º
χN = 1.1º
N–C(O) 1.483 Å



the most twisted acyclic amide

■ N,N-Boc$_2$ amides feature significantly decreased amidic resonance



RE = 6.3 kcal/mol *RE = 7.6 kcal/mol* *RE = 18.3 kcal/mol*

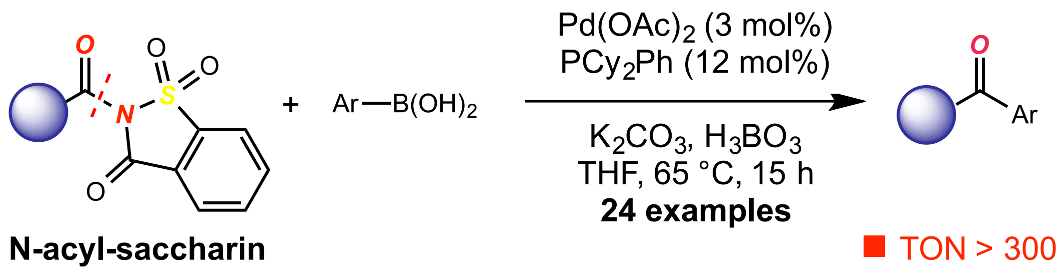
N,N-Boc$_2$-amides: *J. Am. Chem. Soc.* **2018**, *140*, 727.

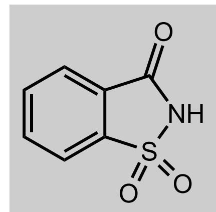
Anilides: *J. Org. Chem.* **2017**, *82*, 6373.
N-Ac-glutarimides: *Org. Lett.* **2018**, *20*, 1342.
N-Ac-hydantoins: *J. Org. Chem.* **2018**, *83*, 14676.
Most twisted N-acylic amides: *Org. Lett.* **2018**, *20*, 7771.

General Strategy for Amide N–C Bond Activation

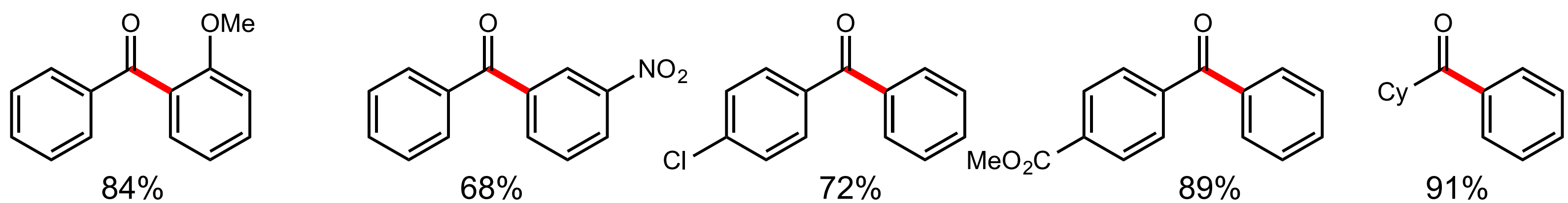
N-acylsaccharins as selective acyl-transfer reagents

■ Suzuki cross-coupling by selective N–C bond cleavage in N-acylsaccharins

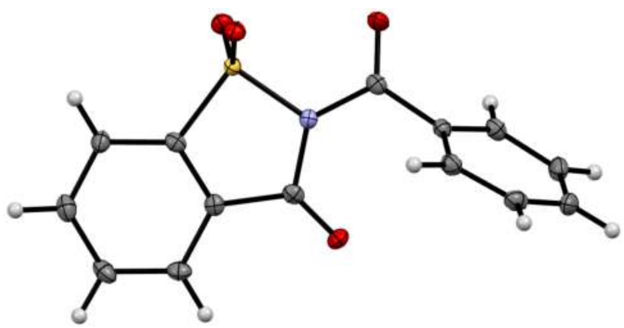




saccharin
- bench-stable solid
- cheap (<0.10$/g)
- benign (sweetener)
- widely-available (>50,000 ton/year)
- tunable reactivity



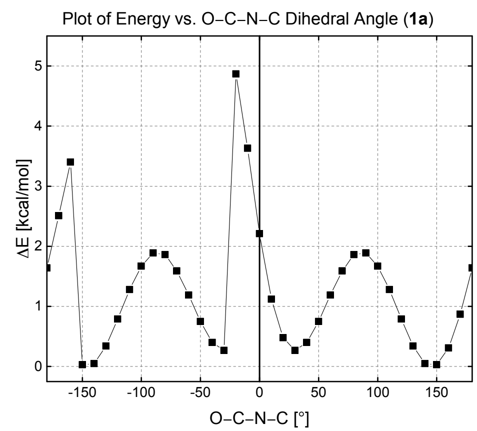
■ Amide distortion in N-acylsaccharins: another class of acyclic twisted amides



$\tau = 23.0°$; $\chi N = 12.5°$

moderate distortion

■ view along N–C axis



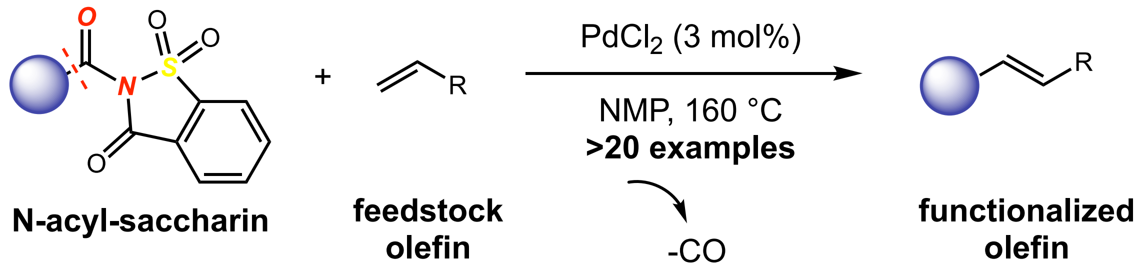
free rotation

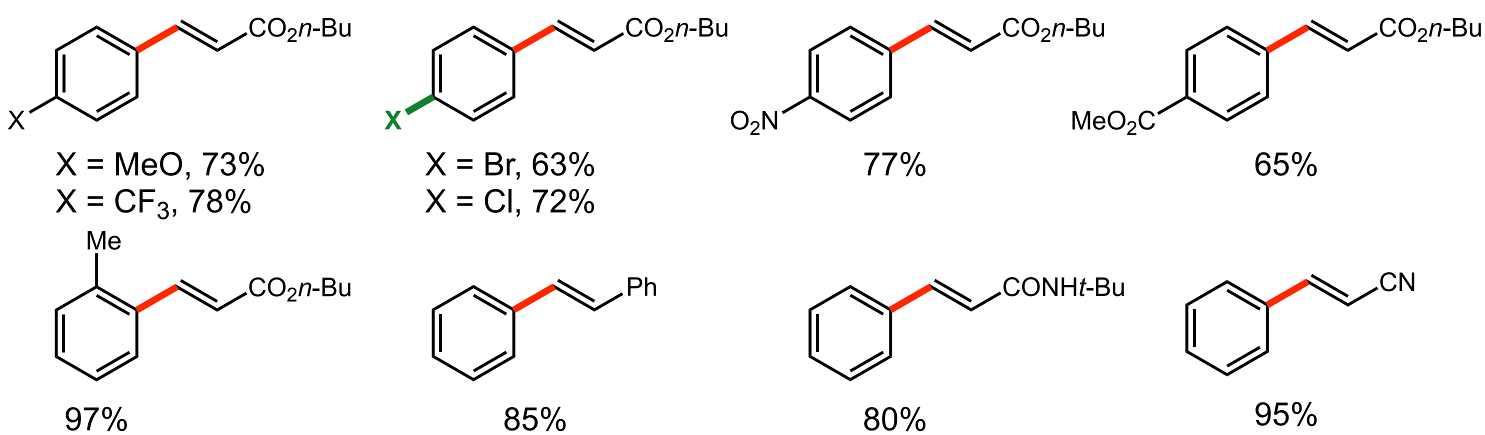
Liu, C.; Meng, G.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. *Org. Lett.* **2016**, *18*, 4194.

General Strategy for Amide N−C Bond Activation

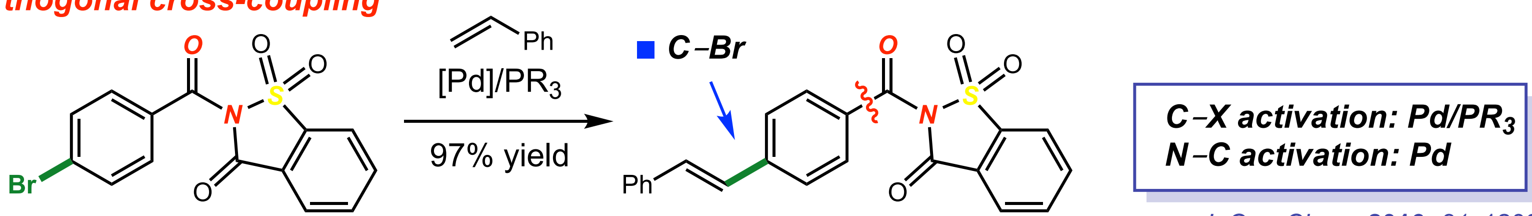
N-acylsaccharins as selective aryl-transfer reagents

■ Decarbonylative Heck cross-coupling by selective N−C bond cleavage in N-acylsaccharins





orthogonal cross-coupling



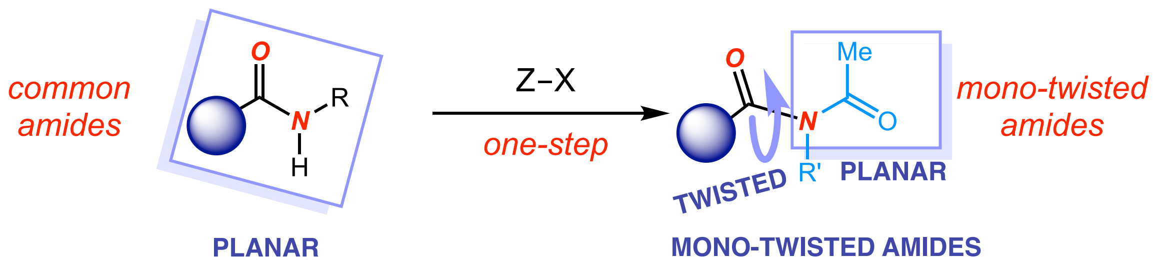
J. Org. Chem. **2016**, *81*, 12023.

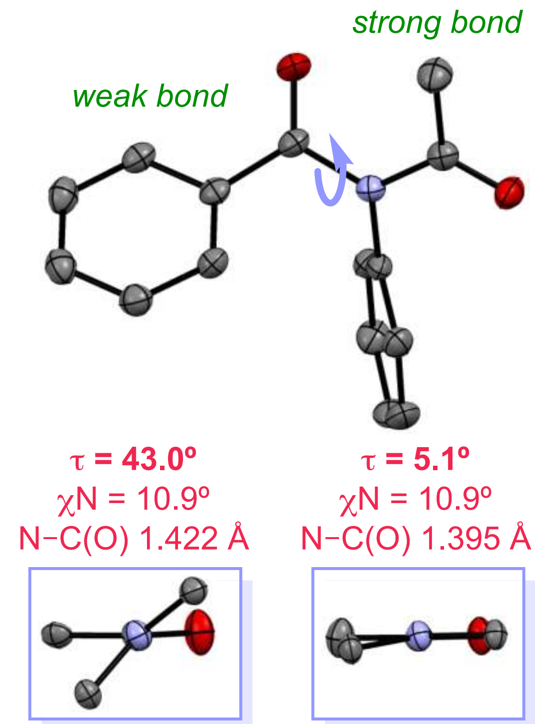
MAPA: *Org. Lett.* **2017**, *19*, 4656.
N-Acylpyrrole/pyrazoles: *Org. Lett.* **2017**, *19*, 3596.
Triflamides: *Org. Lett.* **2019**, *21*, 1253.
N-Mesyl amides: *Org. Lett.* **2017**, *19*, 1434.
N,N-Boc$_2$-amides: *Org. Lett.* **2016**, *18*, 5872.
N-Ac-succinimides: *Synthesis* **2017**, *49*, 3602.

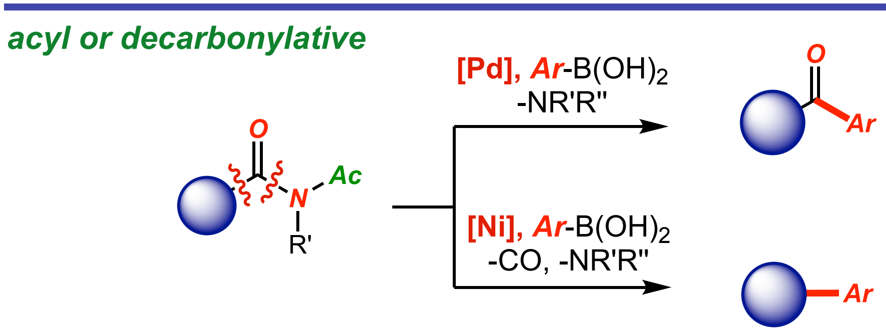
General Strategy for Amide N–C Bond Activation

Decarbonylative and Acyl Cross-Coupling of Common N-Acyclic Amides

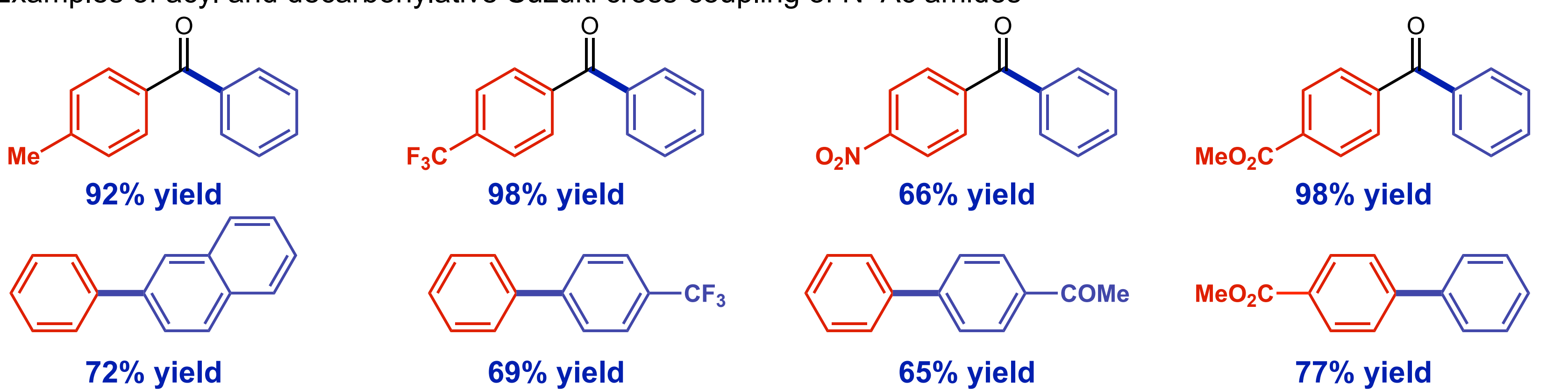
■ Divergent acyl and decarbonylative Suzuki cross-coupling of ***N–Ac amides***







■ Examples of acyl and decarbonylative Suzuki cross-coupling of N–Ac amides



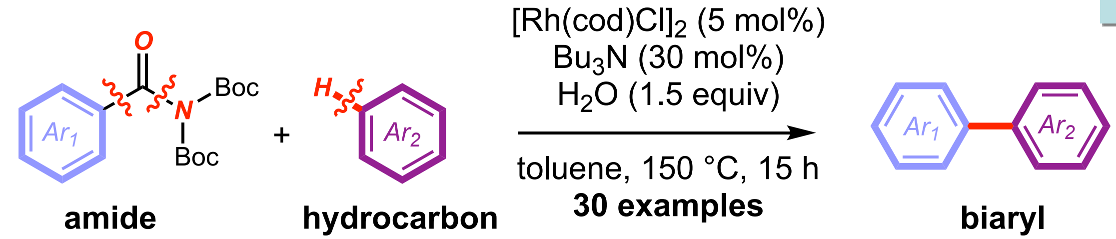
Liu, C.; Li, G.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. *ACS Catal.* **2018**, *8*, 9131.

General Strategy for Amide N–C Bond Activation

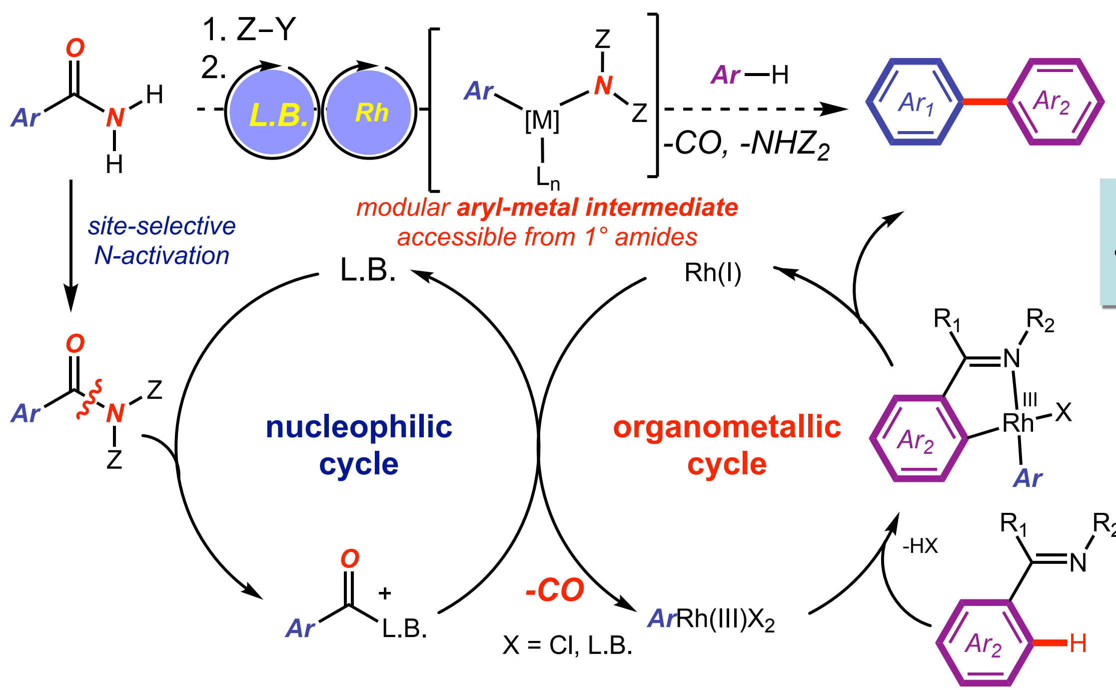
Activation of 1° benzamides

■ Decarbonylative cross-coupling of primary benzamides by ***cooperative catalysis***

common 1° amides as arylating reagents



■ Proposed catalytic cycle



TON up to 480
also works for 2° amides
C–H/N–C/C–C cleavage

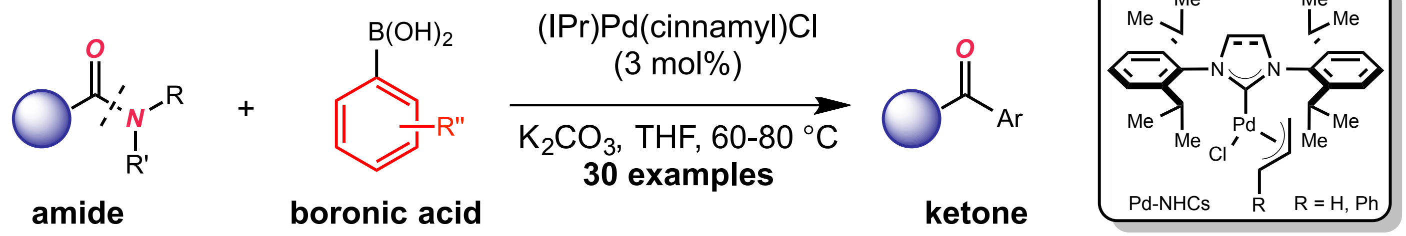
New mode of activation with ubiquitous 1° amides

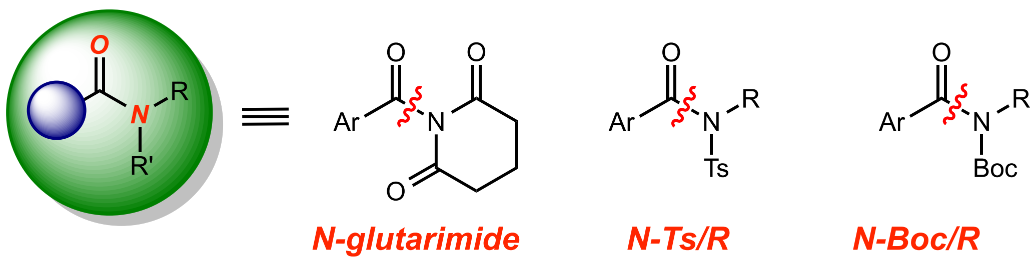
Decarbonylative coupling: Meng, G.; Szostak, M. *ACS Catal.* **2017**, *7*, 7251.
Acyl coupling: Meng, G.; Shi, S.; Szostak, M. *ACS Catal.* **2016**, *6*, 7335.

General Strategy for Amide N–C Bond Activation

Development of general catalytic systems

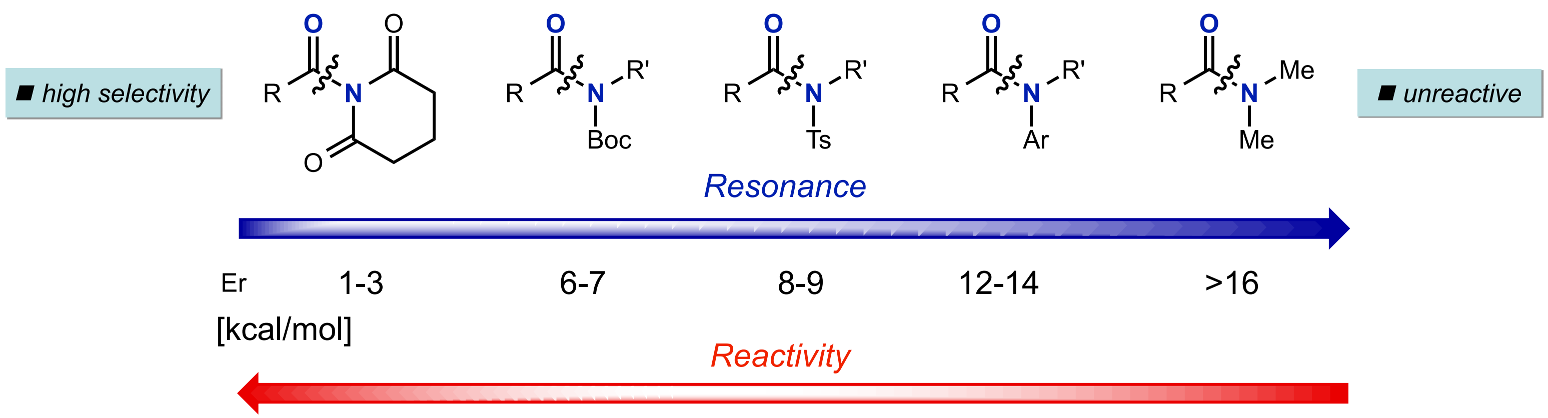
■ Pd-NHCs as general catalysts for Suzuki cross-coupling of amides by N–C bond activation





- TON = 740-850
- FG tolerated: CN, CO_2Me, F, CF_3, OMe, 2-Me, heterocycles
- air- and moisture-stable

■ Reactivity scale in cross-coupling of amides

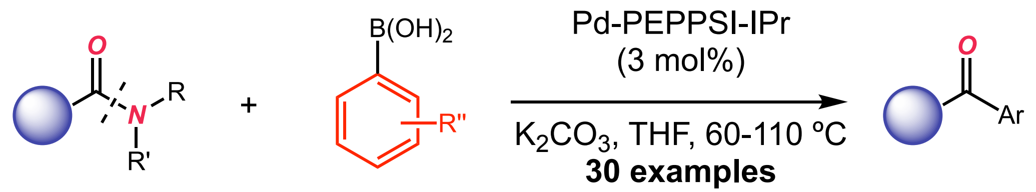


Lei, P.; Meng, G.; Szostak, M. *ACS Catal.* **2017**, *7*, 1960.

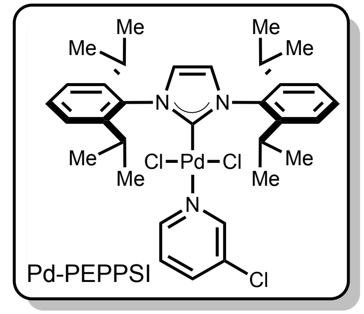
General Strategy for Amide N−C Bond Activation

Development of general catalytic systems

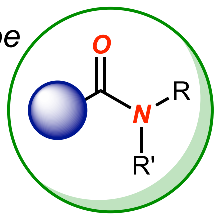
■ Pd-PEPPSI as general catalysts for Suzuki cross-coupling of amides by N−C bond activation



amide **boronic acid** **ketone**



broad scope



≡ ***N-glutarimide***

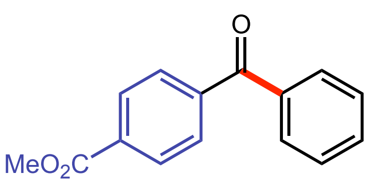
N-Ts/R

N-Boc/R

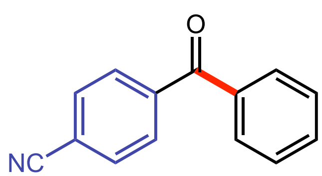
user-friendly catalysts

Pd-PEPPSI ⟹

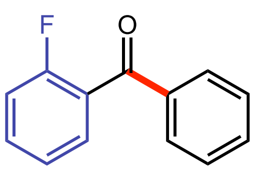
- TON = 480-760
- ***operationally-trivial, single-step synthesis***
- modular catalysts
- air- and moisture-stable



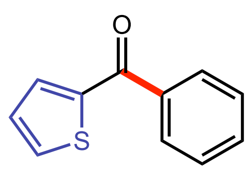
93% yield



82% yield

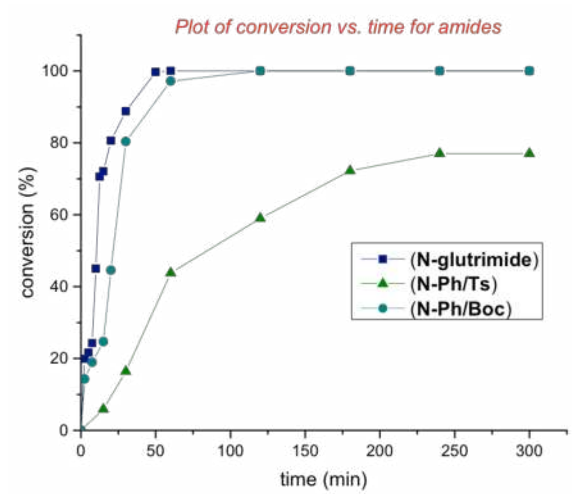


98% yield



76% yield

high reactivity for N-Boc-carbamates

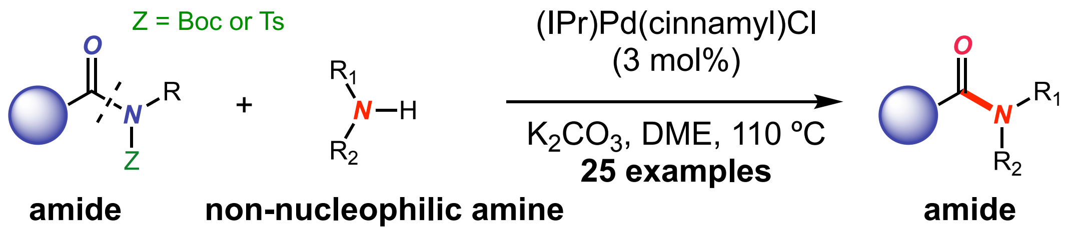


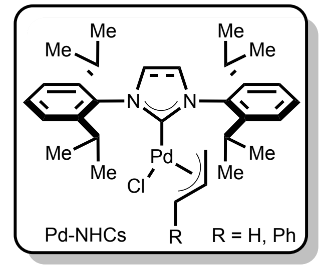
Lei, P.; Meng, G.; Ling, Y.; An, J.; Szostak, M. *J. Org. Chem.* **2017**, *82*, 6638.

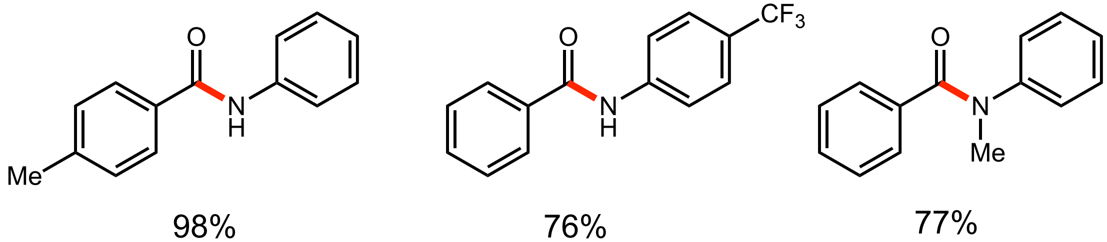
General Strategy for Amide N–C Bond Activation

Development of general catalytic systems

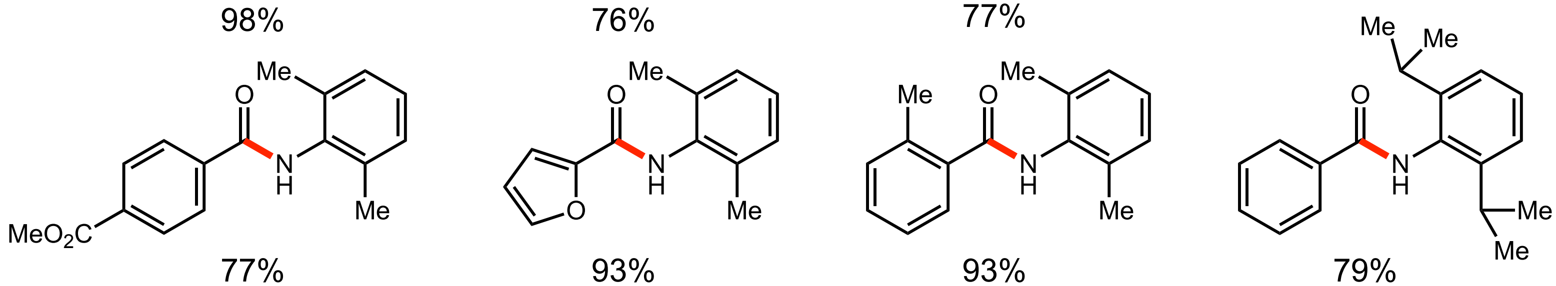
■ Pd-NHCs as general catalysts for Buchwald-Hartwig cross-coupling by acyl N–C activation







- TON = 850
- air-, moisture-stable catalysts
- one-pot N-activation/coupling



Meng, G.; Lei, P.; Szostak, M. *Org. Lett.* **2017**, *19*, 2158.
Ni-catalyzed transamidation: Garg et al. *Nat. Commun.* **2016**, *7*, 11554.

Pd-NHC catalysis:

(*t*-Bu-indenyl)Pd(IPr)(Cl): *Chem. Sci.* **2017**, *8*, 6525.
Acyl Buchwald-Hartwig: *Chem. Commun.* **2017**, *53*, 10584.
Ester cross-coupling: *Organometallics* **2017**, *36*, 3784.
[Pd(μ-OH)Cl(IPr)]$_2$: *Adv. Synth. Catal.* **2018**, *360*, 1538.
RT cross-coupling: *Org. Lett.* **2017**, *19*, 6510.
Mechanism: *ChemCatChem* **2018**, *10*, 3096.
B-Alkyl cross-coupling: *Org. Lett.* **2018**, 20, 6789.
Pd(NHC)(acac)Cl: *Org. Lett.* **2019**, *21*, 3304.

Selected decarbonylative cross-couplings: *Phosphorylation: Angew. Chem. Int. Ed.* **2017**, *56*, 12718. *Thioetherification: Chem. Commun.* **2018**, *54*, 2130. *Cyanation: Org. Lett.* **2017**, *19*, 3095. *Borylation: ACS Omega* **2019**, *4*, 4901.

Amide N–C Bond Activation

■ *Metal-Free Transformations of Amides by Ground-State Destabilization*

Nature Commun. **2018**, *9*, 4165.
JACS **2019**, *141*, 11161.
Org. Lett. **2018**, *20*, 5622.
Chem. Eur. J. **2020**, 26, 611.
Synthesis **2020**, *52*, 1060.

■ *Cross-Coupling of Carboxylic Acid Derivatives*

Angew. Chem. Int. Ed. **2018**, *57*, 16721.
ChemSusChem **2019**, *12*, 2983.
Org. Lett. **2019**, *21*, 9256.
Chem. Sci. **2019**, *10*, 5736.
iScience **2019**, *19*, 749.

■ *Amide Directed C–H Arylation*

Chem. Sci. **2017**, *8*, 3204.
ACS Catal. **2017**, *7*, 5721.
ACS Catal. **2016**, *6*, 4755.

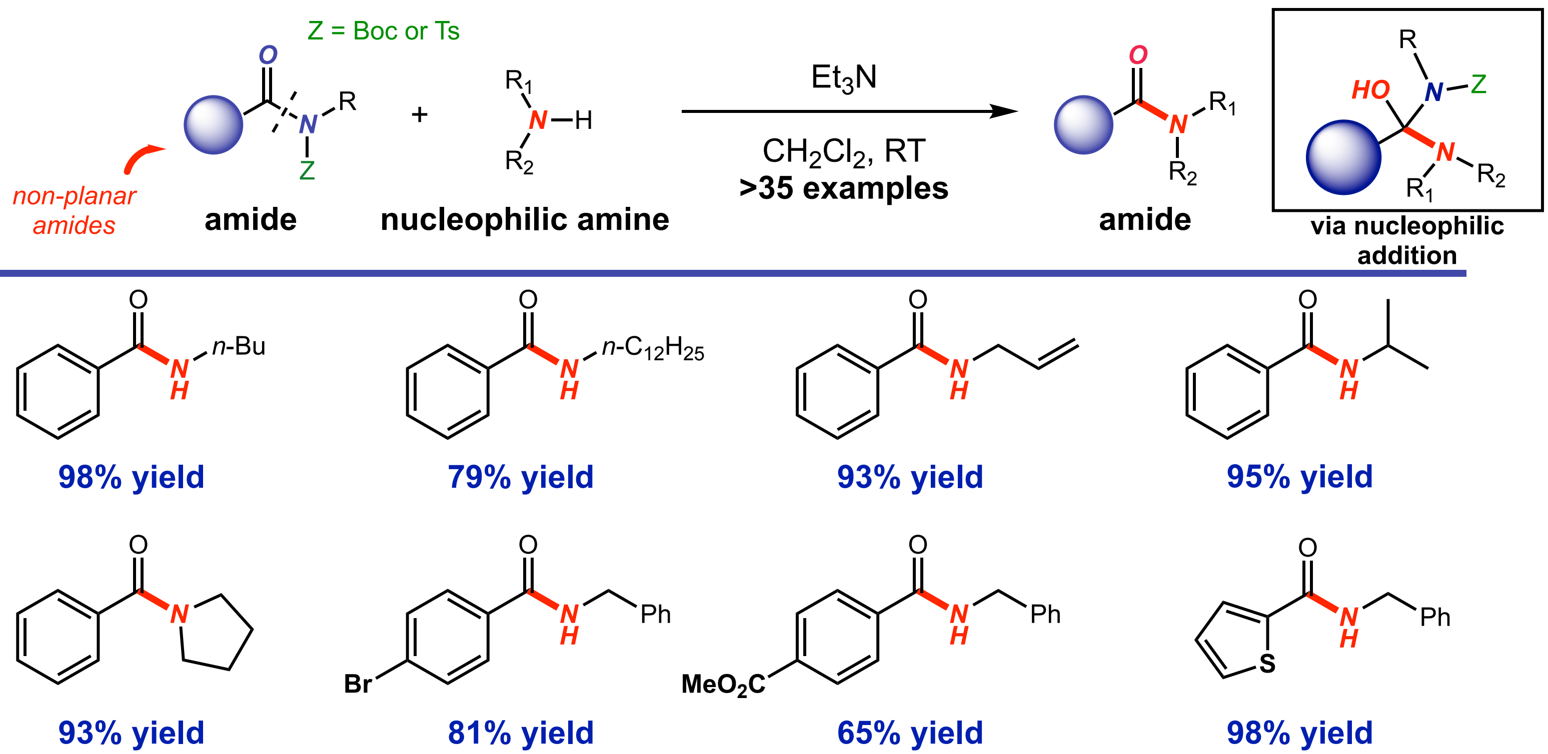
■ *Classic Bridged Lactams as Models for Amide Bond Destabilization*

Org. Lett. **2017**, *19*, 2386.
ACS Catal. **2020**, *10*, 737.
Angew. Chem. Int. Ed. **2016**, *55*, 5062.
Special Issue: Molecules **2019**, *24*, 274.

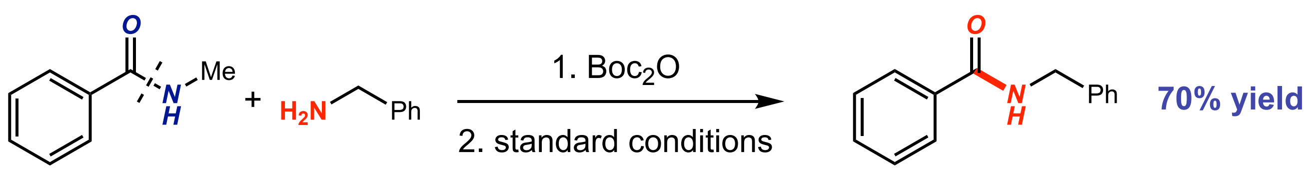
General Strategy for Amide N–C Bond Activation

Metal-free transformations of amides by nucleophilic addition

■ Metal-free transamidation of secondary amides at room temperature



■ One-pot transamidation at room temperature



Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. *Org. Lett.* **2017**, *19*, 1614.

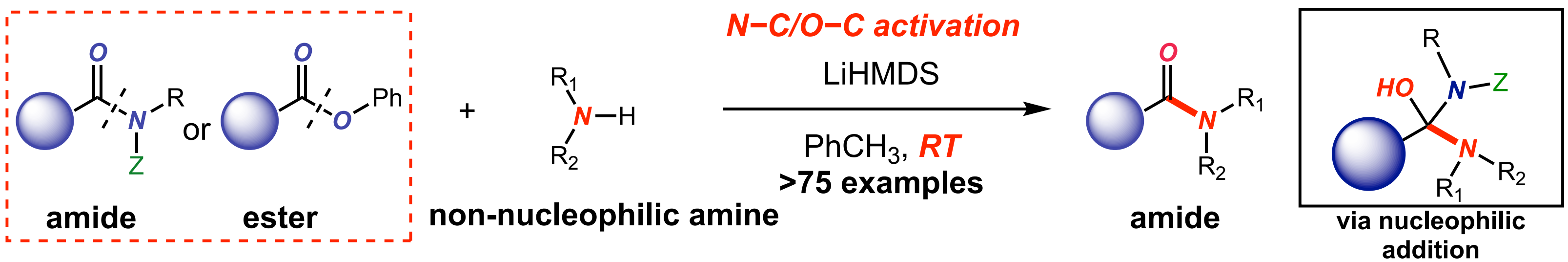
Friedel-Crafts: *Chem. Commun.* **2016**, *52*, 6841. Synthesis of anhydrides: *Org. Biomol. Chem.* **2017**, *15*, 1780. Transamidation of N-acyl-glutarimides: *Org. Biomol. Chem.* **2018**, *16*, 1322. Application in polymer synthesis (free-radical polymerization, polyacrylamides): Hillmyer, *ACS Macro Lett.* **2018**, *7*, 122.

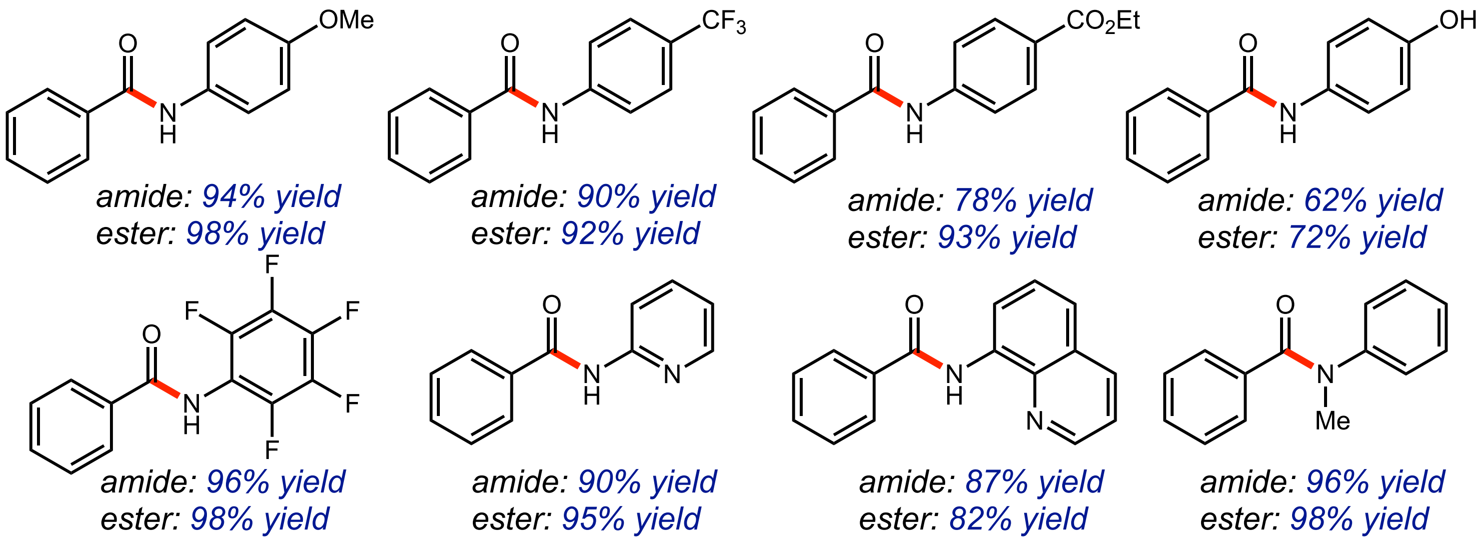
General, additive-free procedure: Rahman, M. M.; Li, G.; Szostak, M. *J. Org. Chem.* **2019**, *84*, 12091.

Selective Activation of Amide and Ester Bonds

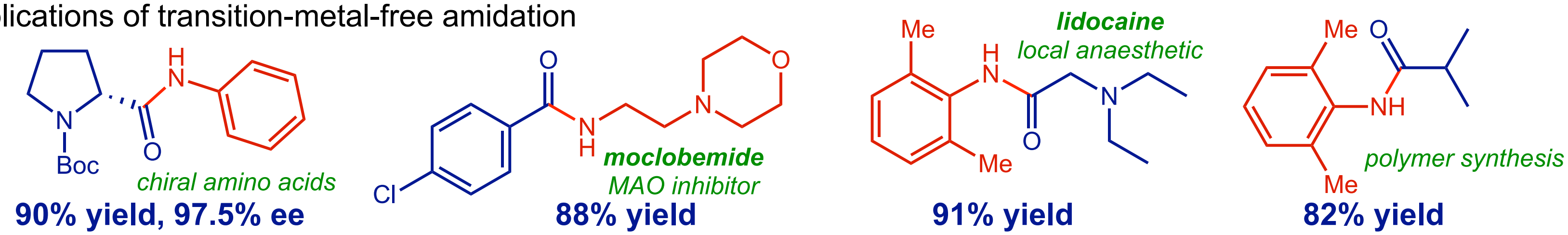
Metal-free amidation with non-nucleophilic amines

■ Transition-metal-free transamidation with non-nucleophilic amines at room temperature





■ Applications of transition-metal-free amidation

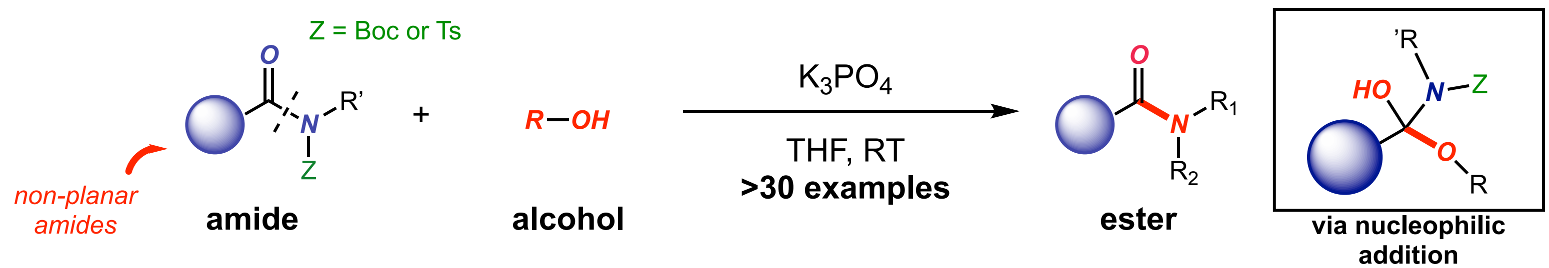


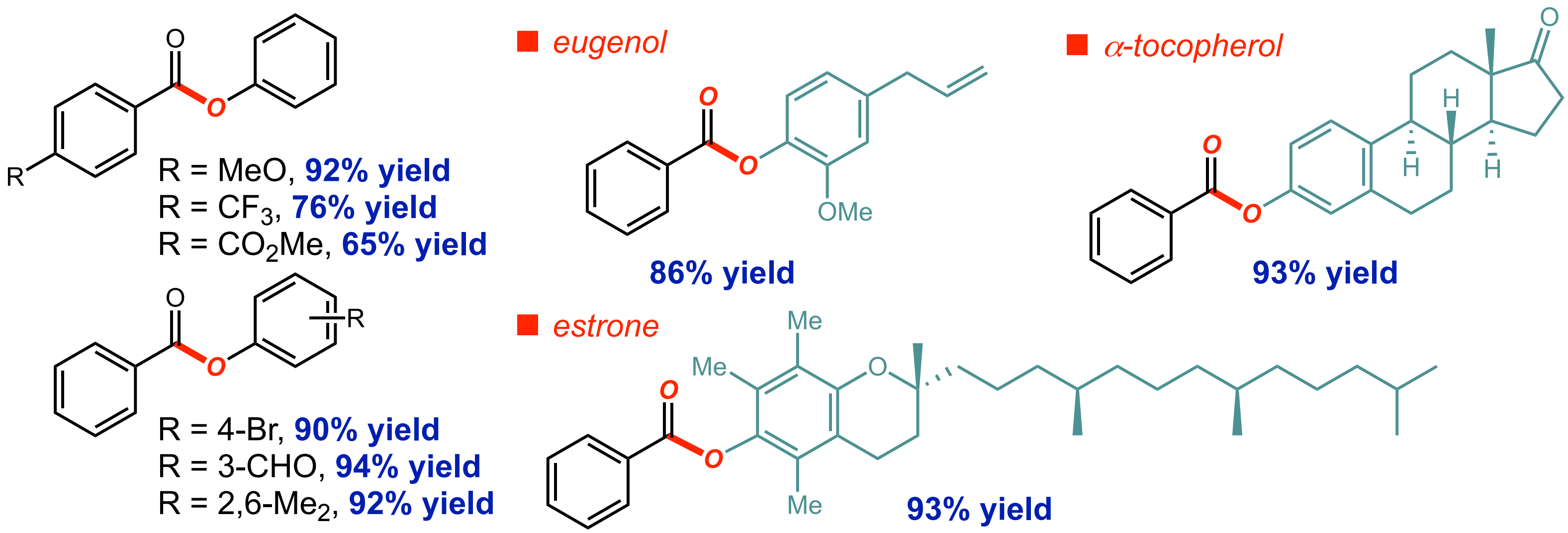
Activated amides and esters: Li, G.; Szostak, M. *Nature Commun.* **2018**, *9*, 4165.
Unactivated amides and esters: Li, G.; Ji, C. L.; Hong, X.; Szostak, M. *J. Am. Chem. Soc.* **2019**, *141*, 11161.

General Strategy for Amide N–C Bond Activation

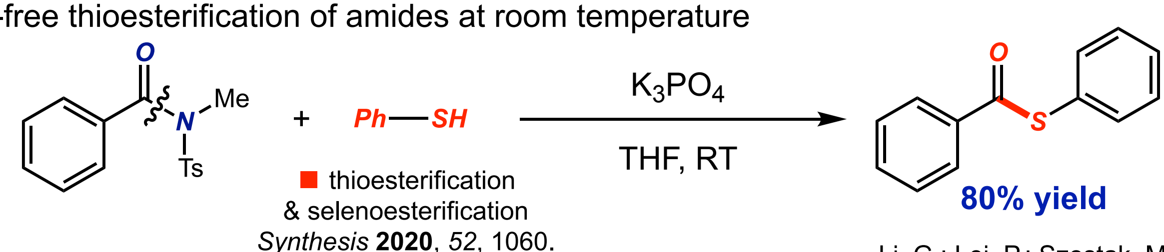
Metal-free esterification of amides by nucleophilic addition

■ Transition-metal-free esterification of secondary amides at room temperature





■ Transition-metal-free thioesterification of amides at room temperature



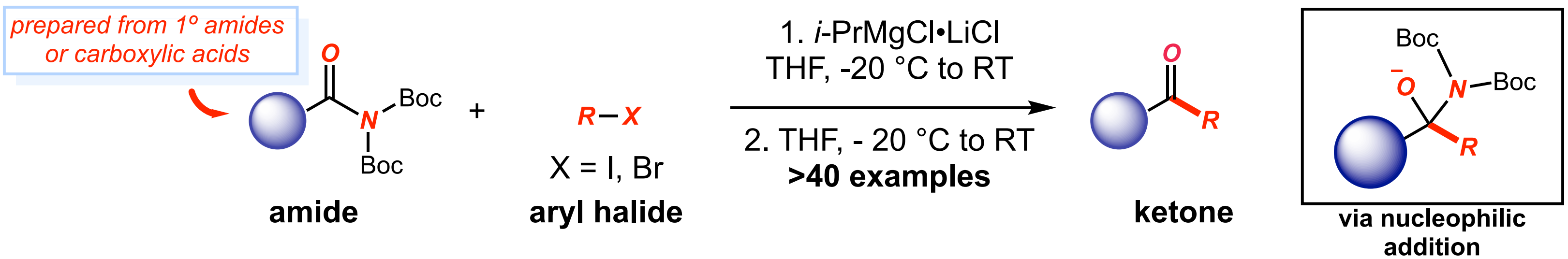
Li, G.; Lei, P.; Szostak, M. *Org. Lett.* **2018**, *20*, 5622.
For metal-catalyzed esterifcation, see: Garg, Houk et al. *Nature* **2015**, *524*, 79.

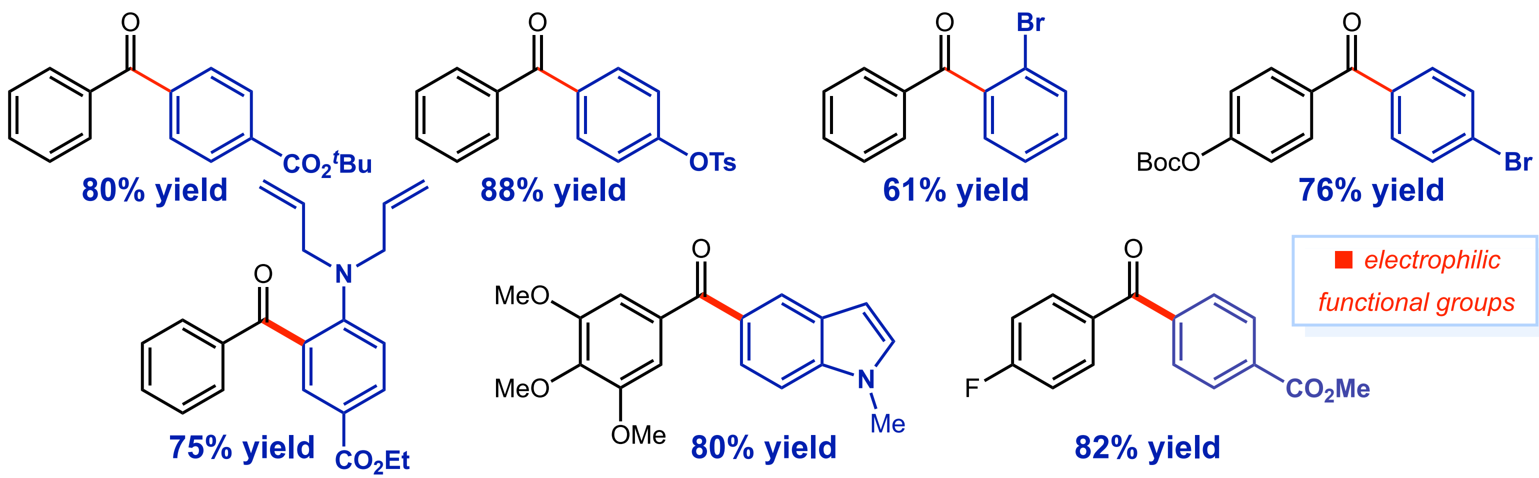
General Strategy for Amide N−C Bond Activation

Metal-free acylation of organometallics with amides by nucleophilic addition

■ works for N-Boc_2, N-Ar/Boc, N-alkyl/Boc

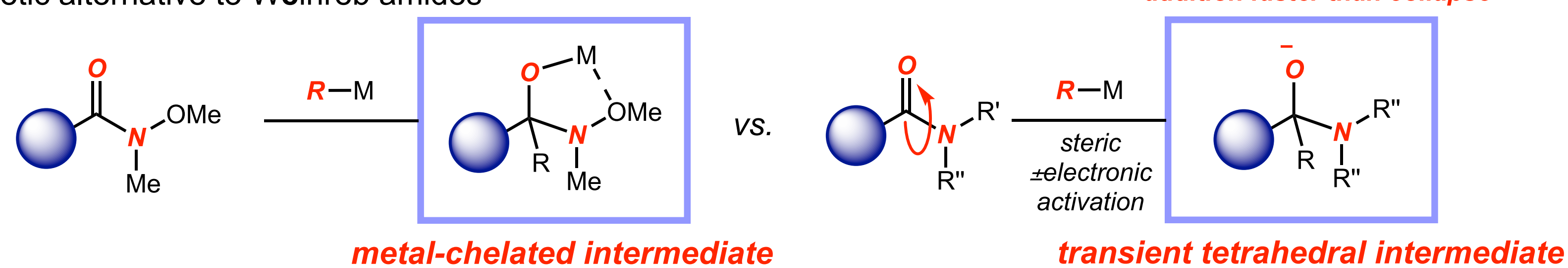
■ Transition-metal-free acylation of functionalized Knochel-type Grignards with amides





■ Kinetic alternative to Weinreb amides

•addition faster than collapse



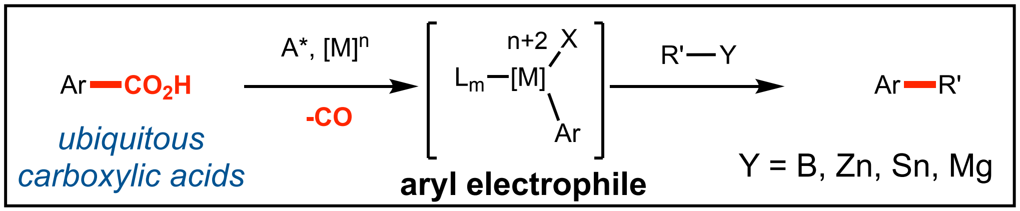
Li, G.; Szostak, M. *Chem. Eur. J.* **2020**, 26, 611.

For a review of transition-metal-free amide bond N−C activation, see: Li, G.; Szostak, M. *Chem. Rec.* **2020**, DOI: 10.1002/tcr.201900072.

For a review on transamidations, see: Li, G.; Szostak, M. *Synthesis* **2020**, in press.

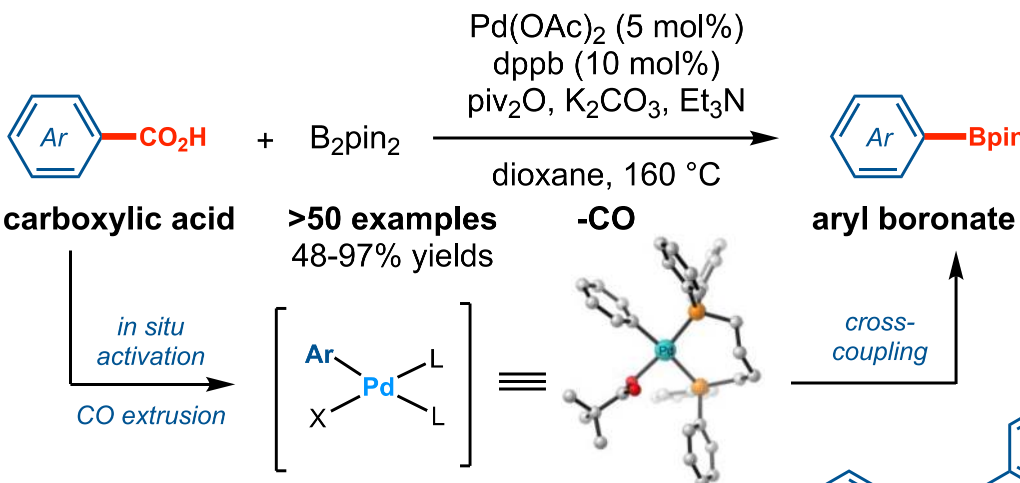
General Strategy for Cross-Coupling of Carboxylic Acids
Development of general catalytic manifolds

■ Carboxylic acids represent highly abundant feedstock materials in organic synthesis



carboxylic acids
ubiquitous
cheap
stable
available
non-toxic
orthogonal

■ Decarbonylative borylation of carboxylic acids: proof of principle

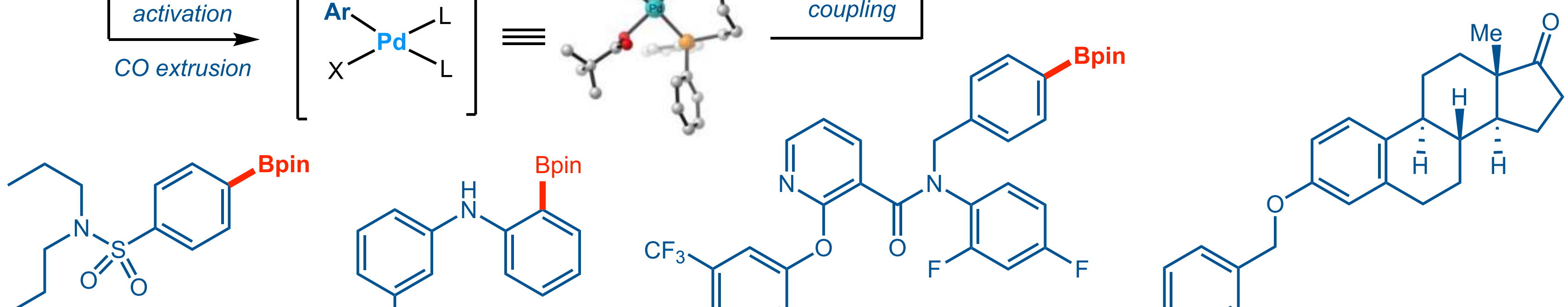


broad scope

FG tolerated: MeO, MeS, CF_3, OCF_3, F, Cl, CN, CHO, CO_2Me, COMe, OAc, OTs, NMe_2, NHBz, OBz, OBn, OH, SO_2NMe_2, 2,6-Me_2, 2-Ph, heterocycles

low catalyst loading

complex substrates



probenecid 91% yield

flufenamic acid 57% yield

diflufenican 95% yield

estrone 71% yield

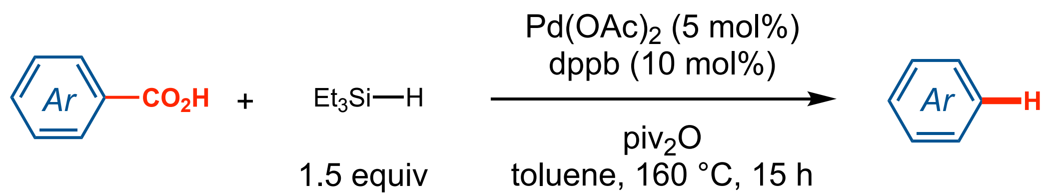
Borylation: Liu, C.; Li, C. L.; Hong, X.; Szostak, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 16721.
Highlight: Zhao, Q.; Szostak, M. *ChemSusChem* **2019**, *12*, 2983.

General Strategy for Cross-Coupling of Carboxylic Acids
Development of general catalytic manifolds

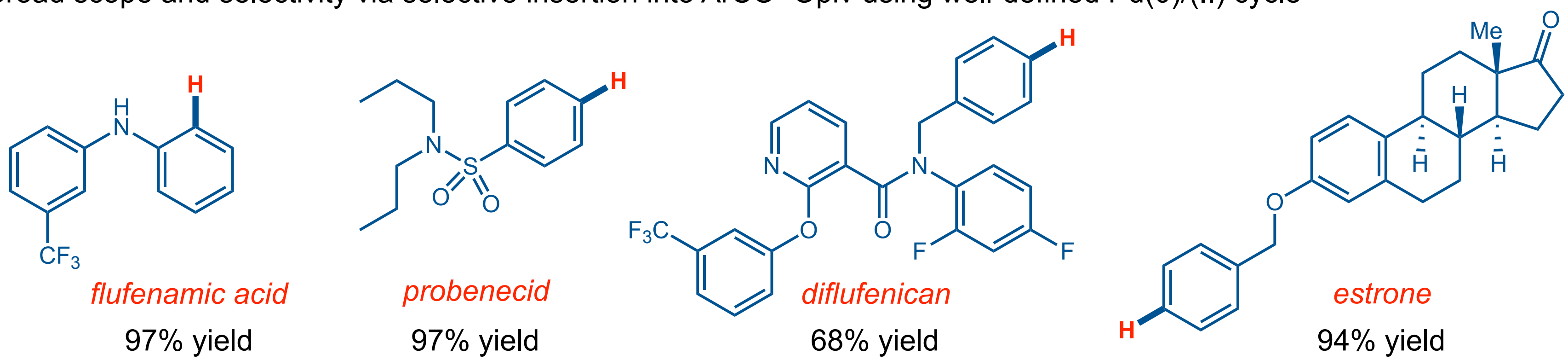
carboxylic acids

traceless directing groups

■ Highly chemoselective step-down reduction of carboxylic acids to aromatic hydrocarbons

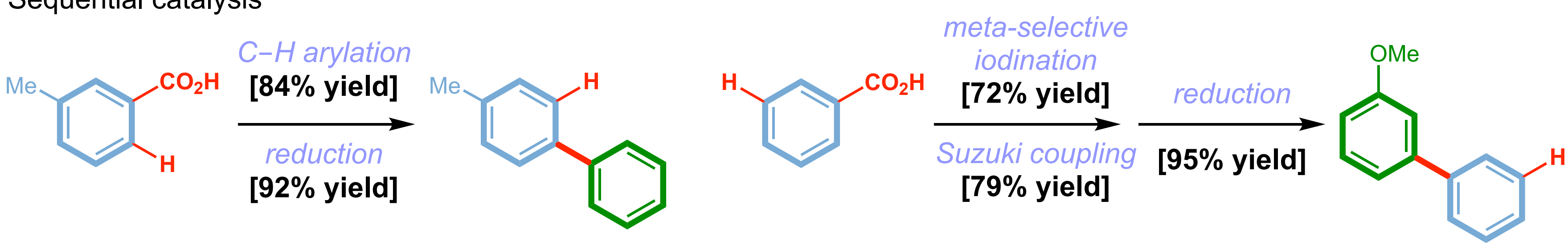


■ Broad scope and selectivity via selective insertion into ArCO−Opiv using well-defined Pd(0)/(II) cycle



FG tolerated: MeO, CF_3, OH, NMe_2, CN, CO_2Me, COMe, CHO, OTs, Cl, OAc OPh, NCOR, heterocycles

■ Sequential catalysis

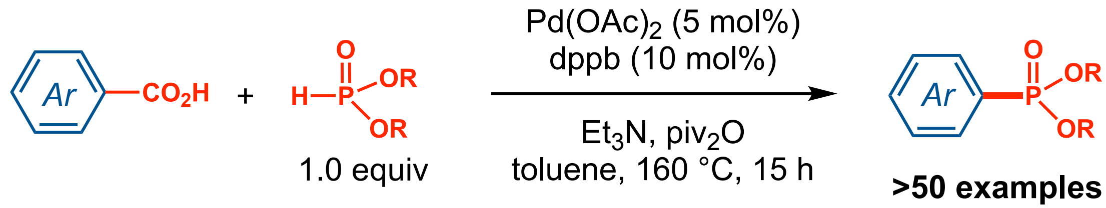


Reduction: Liu, C.; Qin, Z. X.; Ji, C. L.; Hong, X.; Szostak, M. *Chem. Sci.* **2019**, *10*, 5736.

General Strategy for Cross-Coupling of Carboxylic Acids

Development of general catalytic manifolds

■ Decarbonylative phosphorylation of carboxylic acids (Hirao cross-coupling)

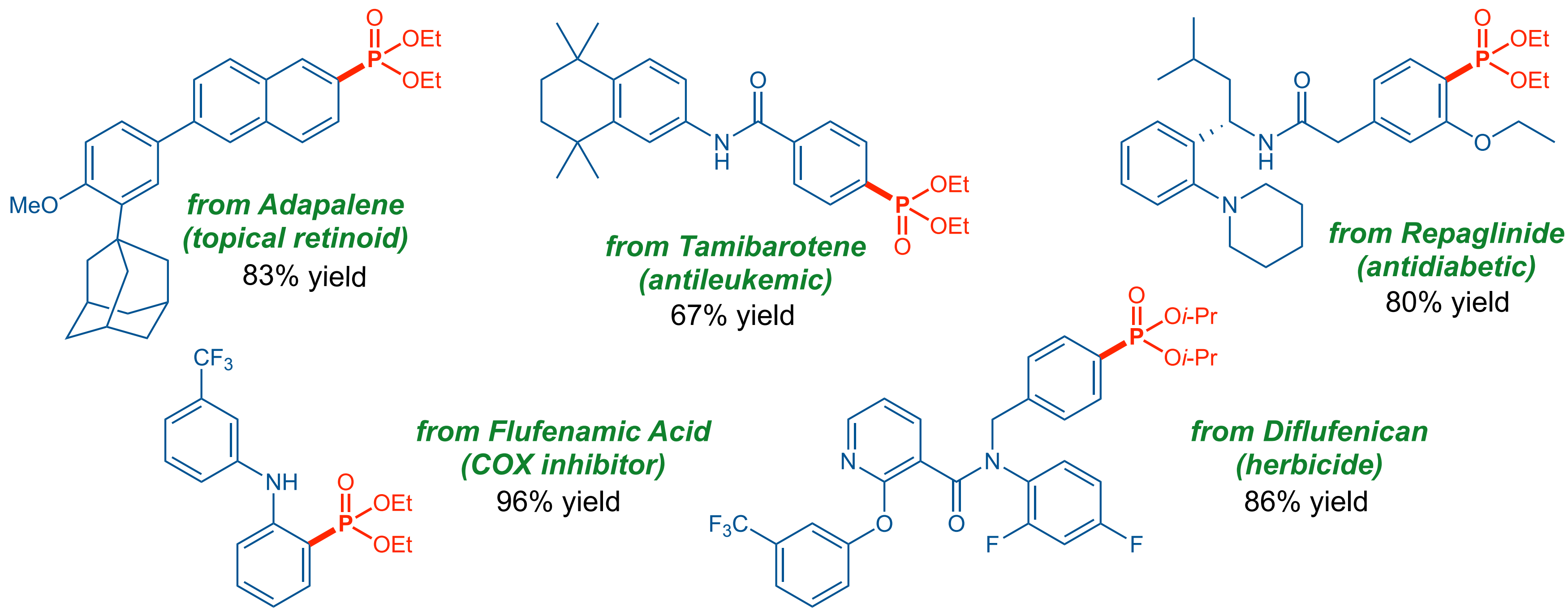


carboxylic acids

direct C−P bond formation

■ also works for $HPPh_2$

■ Broad scope and selectivity via selective insertion into ArCO−Opiv using well-defined Pd(0)/(II) cycle



from Adapalene (topical retinoid)
83% yield

from Tamibarotene (antileukemic)
67% yield

from Repaglinide (antidiabetic)
80% yield

from Flufenamic Acid (COX inhibitor)
96% yield

from Diflufenican (herbicide)
86% yield

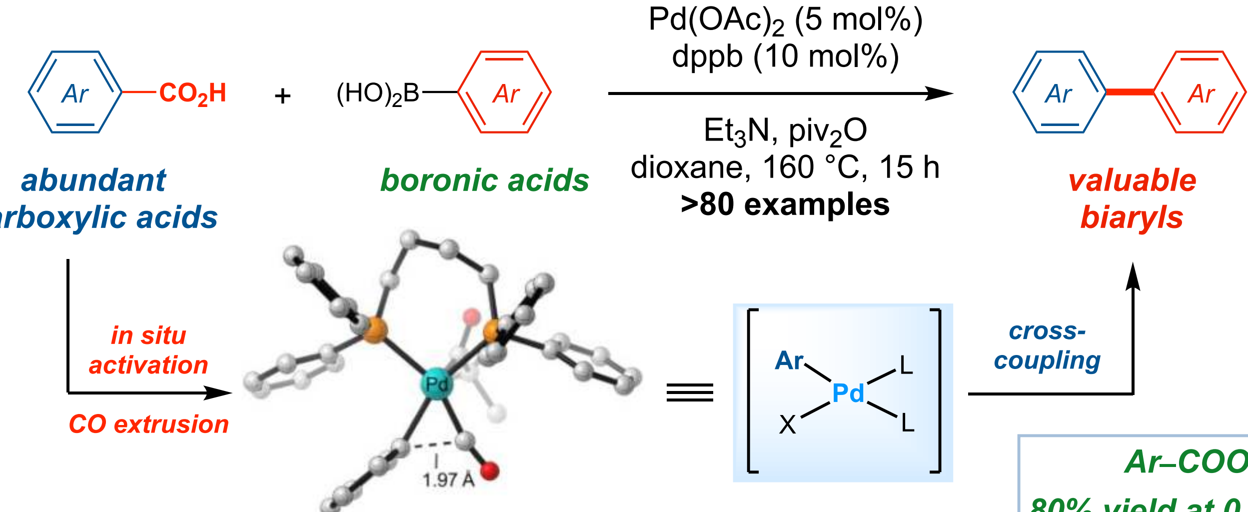
FG groups tolerated: MeO, CF_3, Cl, CN, CO_2Me, COMe, CHO, NMe_2, OH, OTs, NAc, OCOR, OCF_3, heterocycles

Phosphorylation: Liu, C.; Ji, C. L.; Zhou, T.; Hong, X.; Szostak, M. *Org. Lett.* **2019**, *21*, 9256.
For phosphorylation of amides, see: Liu, C.; Szostak, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 12718.

General Strategy for Cross-Coupling of Carboxylic Acids

Development of general catalytic manifolds

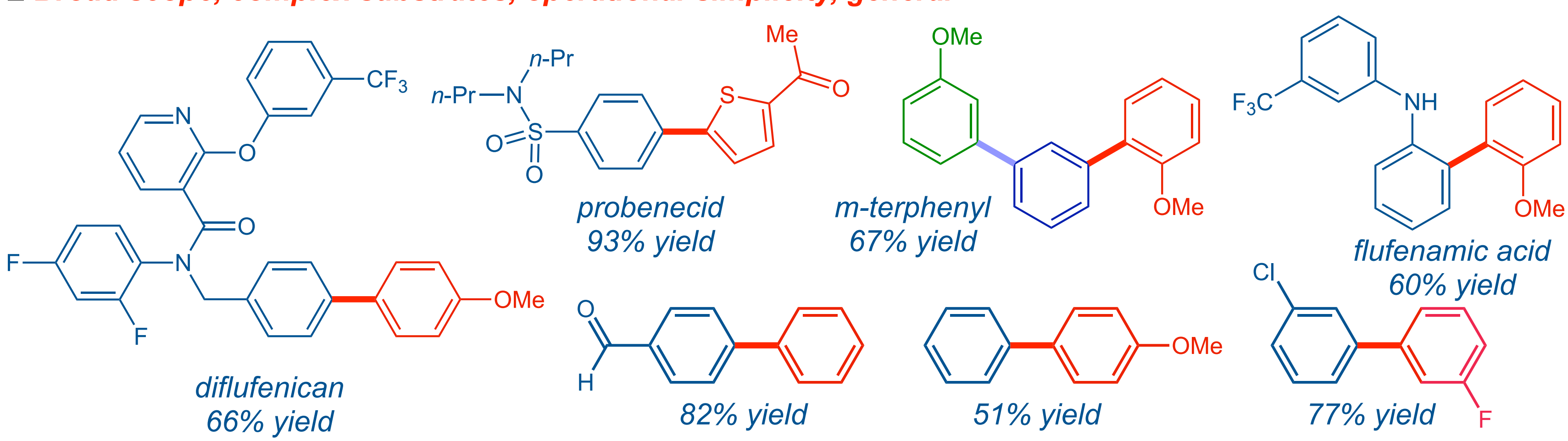
■ ***Decarbonylative (-CO) Suzuki Cross-Coupling of Ubiquitous Carboxylic Acids***



Ar–COOH ≈ Ar–Br

80% yield at 0.10 mol% of [Pd]

■ ***Broad scope, complex substrates, operational-simplicity, general***



Liu, C.; Li, C. L.; Qin, Z. X.; Hong, X.; Szostak, M. *iScience* **2019**, *19*, 749, DOI: *10.1016/j.isci.2019.08.021*.

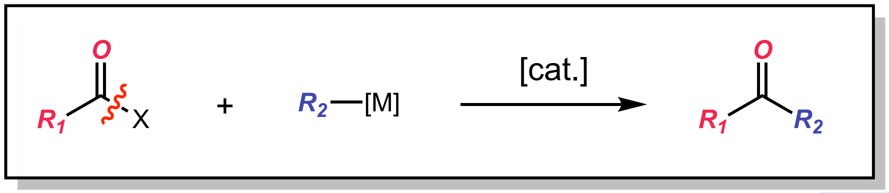
Ni-catalyzed decarbonylative Suzuki of acyl fluorides: Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. *Nature* **2018**, *563*, 100.

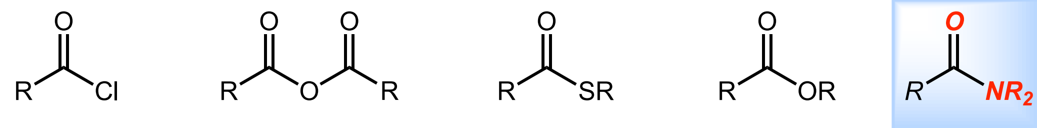
Decarboxylative ($-CO_2$) biaryl coupling of carboxylic acids: Goo*ß*en, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.

General Strategy for Amide N–C Bond Activation

Traditional electrophiles in acyl- and aryl cross-coupling

■ Acyl electrophiles

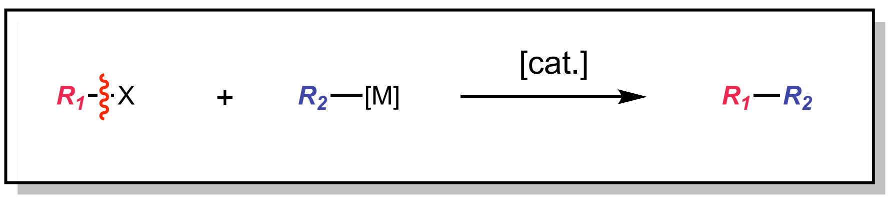




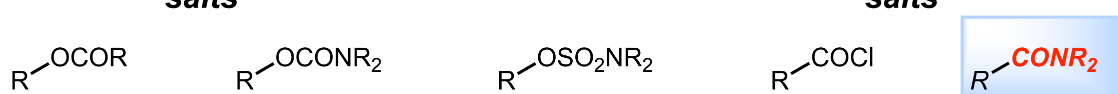
chlorides ***anhydrides*** ***thioesters*** ***esters*** ***amides***

unknown until 2015

■ Aryl electrophiles



halides ***diazonium salts*** ***triflates*** ***tosylates*** ***mesylates*** ***ammonium salts*** ***ethers***



esters ***carbamates*** ***sulfamates*** ***aroyl halides*** ***amides***

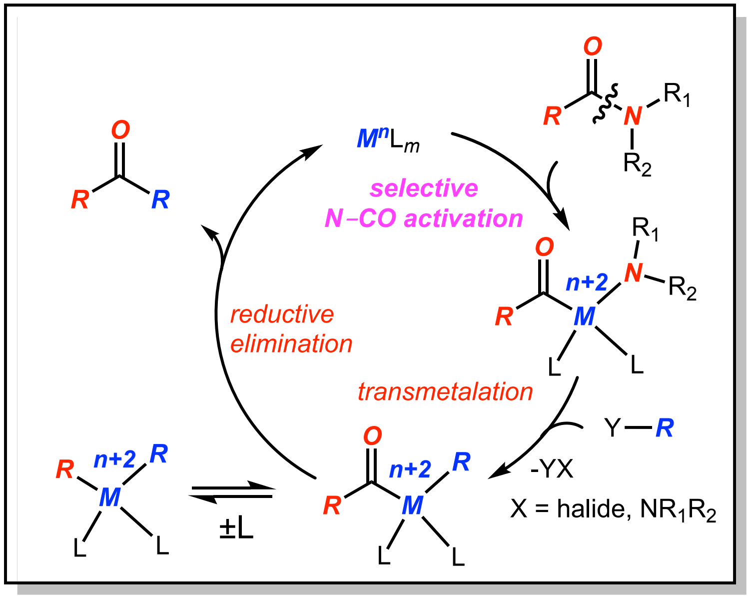
unknown until 2015

General Strategy for Amide N–C Bond Activation

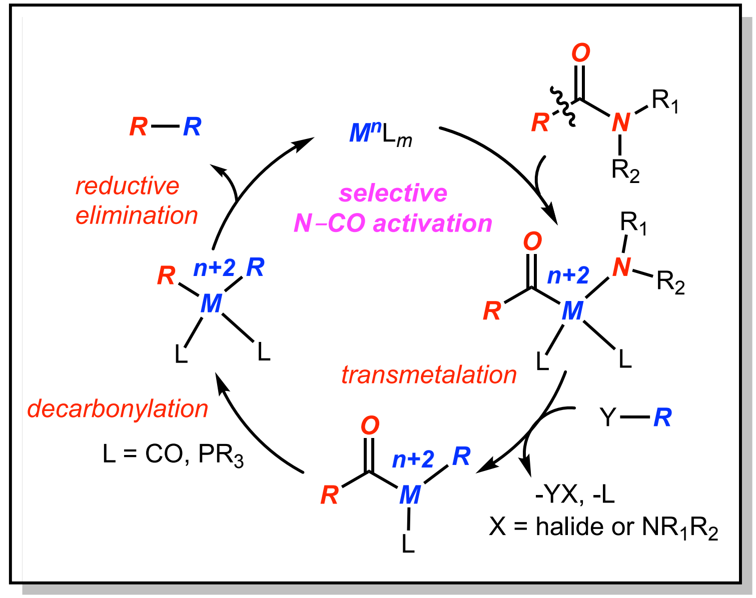
Acyl- vs. aryl cross-coupling

■ Mechanistic pathways generating acyl-metal and aryl-metal intermediates by amide N–C bond cleavage

Amide acyl N–C cross-coupling



Amide aryl N–C cross-coupling



■ Advantages of amides in cross-coupling manifolds by selective N–C bond cleavage

■ prevalence in biomolecules, polymers, functional materials

■ bench-stability, ease of synthesis, typically solids

■ 2-point reactivity control by N-substituents

Progress by Garg, Zou, Shi, Zeng, Maiti, Rueping, Molander, Han, Stanley, Hong and others

Reviews on N–C activation: Meng, G.; Shi, S.; Szostak, M. *Synlett* **2016**, 2530. Liu, C.; Szostak, M. *Chem. Eur. J.* **2017**, *23*, 7157.
General review: Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, *46*, 5864.
Ni catalysis in N–C activation: Dander, J. E.; Garg, N. K. *ACS Catal.* **2017**, *7*, 1413. N-Acyl-glutarimides: Meng, G.; Szostak, M. *EJOC* **2018**, *20-21*, 2352.
Pd-NHC catalysis: Shi, Nolan, Szostak, *Acc. Chem. Res.* **2018**, *51*, 2589. Decarbonylative coupling: Liu, C.; Szostak, M. *Org. Biomol. Chem.* **2018**, *16*, 7998.
Acyl coupling: Buchspies, Szostak, *Catalysts* **2019**, *9*, 53. Control by N-pyramidalization: Liu, C.; Achtenhagen, M.; Szostak, M. *Org. Lett.* **2016**, *18*, 2375.

Acknowledgements

- Shicheng Shi
- Guangrong Meng
- Chengwei Liu
- Peng Lei
- Marcel Achtenhagen
- Syed Huq
- Yongmei Liu
- Mina Hanna
- Manshi Patel
- Marco Ashamalla
- Ricky Diao
- Yuki Osumi
- Pradeep Nareddy
- Feng Hu
- Guangchen Li
- Qun Zhao
- Qinqin Xia
- Kostyantyn Bloshko
- Ivan Cruz

- Daniel Pyle
- Pengcheng Gao
- Tongliang Zhou
- Jin Zhang
- Jonathan Buchspies
- Md. Mahbubur Rahman
- Jonelson Dessin
- Niccole Rodriguez
- Neyssa Deriphonse
- Mohamed Moussa

Iron catalysis

- Elwira Bisz
- Aleksandra Olszowy
- NCN 2014/15/D /ST5/02731

Collaboration

- Mehulkumar Patel
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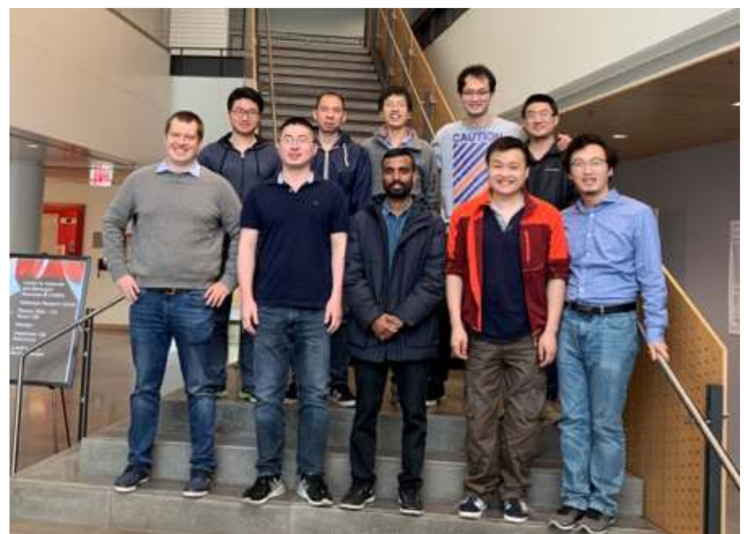
- Prof. Eric Garfunkel
- Prof. Huixin He
- Prof. Roger Lalancette
- Prof. Frank Jordan
- Prof. Roman Szostak
- Prof. Vittorio Pace
- Prof. Wolfgang Holzer
- Prof. Steven Nolan
- Prof. Albert Poater
- Prof. Xin Hong

Funding

- Chemistry Department, Office of the Dean, FASN
- Chancellor's Seed Grant Program
- Rutgers Centers for Global Advancement (GAIA)
- Oak Ridge Associated Universities (ORAU)
- Rutgers Research Council ■ ACS PRF (DNI-55549)
- National Science Foundation (CAREER CHE-1650766)
- The National Institutes of Health (R35GM133326)



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