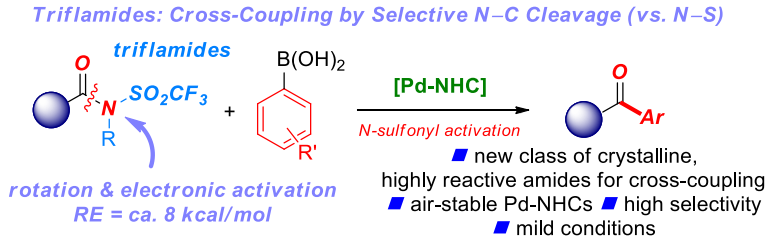
Triflamides: Highly Reactive, Electronically-Activated N-Sulfonyl Amides in Catalytic N–C(O) Amide Cross-Coupling

Shicheng Shi,[†] Roger Lalancette,[†] Roman Szostak,[‡] and Michal Szostak*,[†]

[†]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

[‡]Department of Chemistry, Wroclaw University, F. Joliot-Curie 14, Wroclaw 50-383, Poland

Supporting Information



ABSTRACT: The direct, highly chemoselective Suzuki-Miyaura cross-coupling of trifluoromethanesulfonamides (triflamides) by selective N–C(O) amide bond cleavage is reported. This operationally-simple, mild and user-friendly method accomplishes the direct synthesis of ketones from amides by a catalytic manifold as a powerful alternative to Weinreb amides. Mechanistic studies support rotational inversion and electronic activation, favoring selective insertion under mild conditions. Our data strongly suggest that triflamides should be routinely considered as precursors in amide bond cross-coupling.

The recent years have witnessed extraordinary progress in metal-catalyzed cross-couplings of amides by selective metal insertion into the inert N–C(O) bond (Figure 1A).[1–3] The capacity of the amide bond to control resonance ($n_N \rightarrow \pi^*_{C=O}$ donation, barrier to rotation, planar amides = 15-20 kcal/mol),[4,5] and therefore facility of metal insertion through N-substitution has engendered significant interest as a way to develop mild catalytic methods exploiting activation of N–C(O) bonds.[6–13] Given the ubiquity of amide bonds in drugs, polymers and functional materials, new selective methods for functionalization of amides offer great practical opportunities for organic synthesis in both academic and industrial settings.[14]

Most of the successful approaches in cross-coupling of amides to date utilize N-Ts (Ts = 4-toluenesulfonyl) as an activating group enabling metal insertion into the N–C(O) bond.[2,6–13] Harnessing N-Ts amides has been possible through resonance destabilization of the acyl amide bond (Ar = Ph, R = Ph, RE = 9.7 kcal/mol; τ = 18.8°; χ_N = 18.9°, RE = resonance energy).[5a] In this context, we were attracted by the trifluoromethanesulfonyl group as one of the most powerful electron-withdrawing groups in organic chemistry.[15] Drawing from our experience in amide bond destabilization,[5] we envisioned that N-Tf (Tf = triflyl) could be employed as a viable activating group for amides, wherein the electron-withdrawing effect would have a two-fold positive effect by (i) facilitating metal insertion,[16] and (ii) enhancing the leaving group potential,[15a] permitting cross-coupling under mild conditions.

Herein, we report the realization of this hypothesis and present the direct, highly chemoselective Suzuki-Miyaura cross-coupling of trifluoromethanesulfonamides (triflamides) by selective N–C(O) amide bond cleavage (Figure 1B). Most importantly, this study introduces triflamides as highly reactive, bench-stable, inexpensive N-sulfonyl amides for catalytic cross-couplings by N–C(O) bond activation with high selectivity. Our data strongly suggest that triflamides should be routinely considered as amide bond precursors in the burgeoning manifold of amide bond cross-coupling.[2,6–13]

Our investigations began with the examination of the Suzuki-Miyaura cross-coupling of a model N-Tf amide **1a** (N-phenyl-N-((trifluoromethyl)sulfonyl)benzamide) with 4-tolyl boronic acid using various Pd(II)-NHC (NHC = N-heterocyclic carbene) precatalysts (eq 1). There are two main challenges in catalytic activation of amides: (1) selective metal insertion into the N-acyl bond; (2) undesired cleavage of the N-sulfonyl group, deactivating the amide towards insertion.[2a,b] In addition, the stability of acyl-metal intermediate contributes to the efficiency of the cross-coupling. The use of bench-, air- and moisture-stable strongly σ-donating Pd(II)-NHC precatalysts provides an excellent avenue for the synthesis of acyl-metal intermediates from amides.[17] After extensive optimization, we were delighted to identify that the cross-coupling of N-Tf amide **1a** proceeds under exceedingly mild conditions at 40 °C (eq. 1, [Pd(IPr)(L)Cl] (3 mol%), K_2CO_3 (3 equiv), water (5 equiv), THF, 15 h). Importantly, the high reactivity was

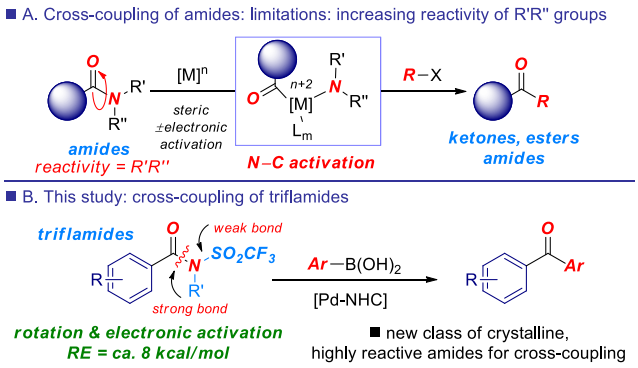
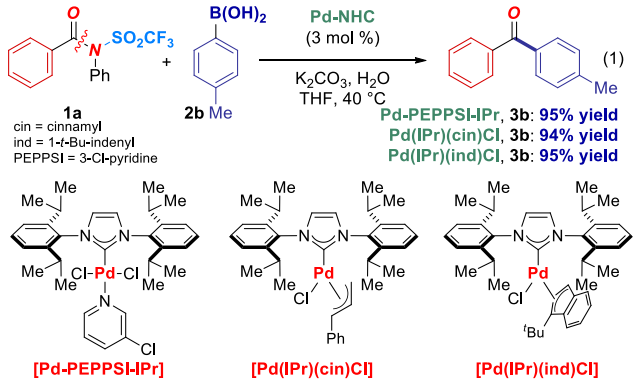


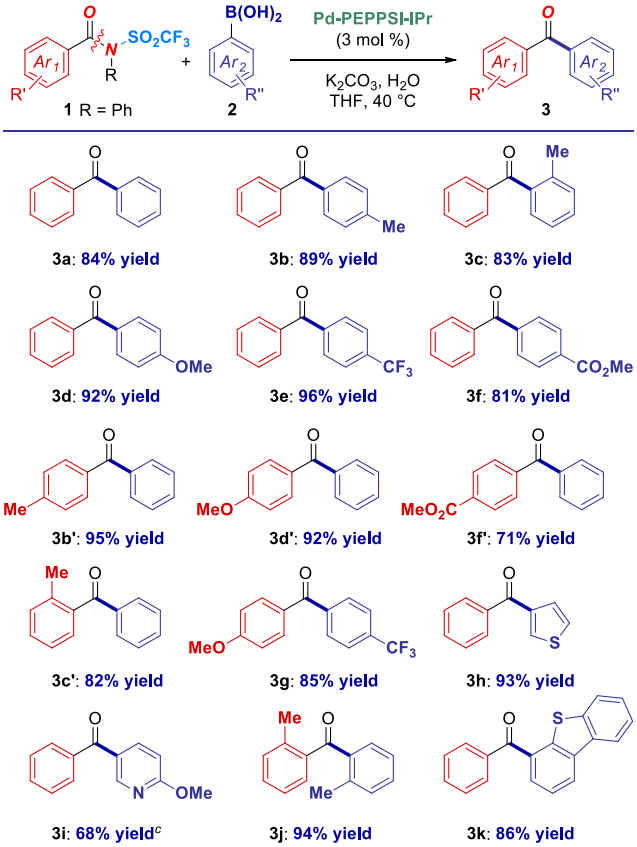
Figure 1. (a) Activation of amides and derivatives. (b) This work: triflamides: new class of highly reactive amides for cross-coupling.

observed using Pd-NHC precatalysts bearing various throw-away ligands (Pd-PEPPSI-IPr, 95%; Pd(IPr)(cin)Cl, 94%, Pd(IPr)(1-*t*-Bu-indenyl)Cl, 95%, eq. 1),[18] highlighting the aptitude of the N-Tf activating group as the acyl-metal precursor.[16] The observed reactivity of N-Tf amides compares very favorably with the current-state-of-the-art, namely, the cross-coupling of N-Ts amides, which proceeds at 30% conversion under the same conditions.[6g] Two additional points should be noted. (1) The cross-coupling of N-Tf amide **1a** proceeds in 33%, 38% and 79% yields at 23 °C using Pd-PEPPSI-IPr, Pd(IPr)(cin)Cl, and Pd(IPr)(1-*t*-Bu-indenyl)Cl. (2) Water has only a minor effect on the cross-coupling efficiency (Pd-PEPPSI-IPr, 40 °C, 88% yield),[19] consistent with facile N–C insertion. Furthermore, it should be noted that 56% yield of **3b** is obtained using 1.2 equiv of boronic acid vs. 2.0 equiv. 21% and 8% yield of biphenyl is formed under these standard conditions. The reaction in the absence of boronic acid leads to the cleavage of the N–Tf group; reductive coupling product or carboxylic acid are not observed. The high reactivity of triflamides may also result from sulfonyl chelation to Pd, assisting N–C cleavage. While all three catalysts (eq. 1) serve as excellent throw away ligands, Pd-PEPPSI was selected for further studies due to ease of synthesis, broad accessibility, low price, and versatility of this class of Pd-NHC precatalysts.[17]



Having identified optimal conditions for the cross-coupling of N-Tf amides, the scope of this protocol was next investigated (Scheme 1). As shown, a variety of N-Tf amides and aryl boronic acids undergo successful cross-coupling under exceedingly mild conditions. It is of note that neutral- (**3a-b**), sterically-hindered (**3c**), electron-donating (**3d**) and electron-withdrawing (**3e**) groups are well-tolerated on the boronic acid component without any modification of the reaction conditions. Pleasingly, the scope of the amide component is equally broad and accommodates electron-neutral (**3b'**), electron-donating (**3d'**), electron-withdrawing (**3f'**) and sterically-hindered (**3c'**) amides, delivering the cross-coupling products in high to excellent yields. Furthermore, this protocol can be used to readily assemble heterocyclic ketones (**3h**, **3i**, **3k**), albeit in some cases higher temperature is required (**3i**).

Scheme 1. Pd-NHC-Catalyzed Chemoselective Suzuki-Miyaura Cross-Coupling of Triflamides[a,b]



[a]Conditions: triflamide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol %), K_2CO_3 (3.0 equiv), THF (0.25 M), H_2O, 40 °C, 15 h. [b]Isolated yields. [c]110 °C. See Supporting Information (SI) for details.

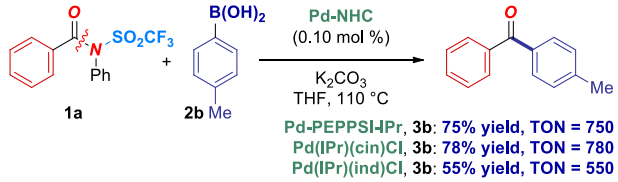
Nevertheless, we note that the formation of **3i** fails using N-Ts amide, highlighting the benefits of triflamide activation. As a testament to the high efficiency of N-Tf as the activating group, we demonstrated high facility in the cross-coupling to form a notoriously difficult doubly deactivated ketone **3g**, wherein both the amide electrophile and boronic acid are electronically-disfavored towards the coupling[17] as well as in the synthesis of bis-sterically-hindered di-*o*-tolylmethanone **3j**. The use of N-Ts amide leads to low conversion in both cases. At the present stage, other electron-withdrawing groups than CO_2Me on the amide have not been tested. Aliphatic amides are not compatible with the reaction conditions. N-Tf-substituted secondary amides are recovered from the reaction conditions. N-Benzyl has been selected as a representative N-alkyl group (vide infra). Ongoing studies are focused on further optimization of the reaction conditions. Collectively, the examined examples show that N-Tf amides permit a broad scope in the direct synthesis of ketones from amides, presenting a powerful alternative to the venerable Weinreb amides[20]

with superior functional group tolerance towards electrophilic functional groups.

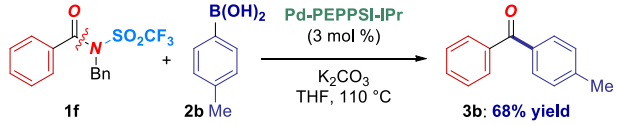
Given the high catalytic activity of N-Tf amides, we became interested in determining turnover number in the cross-coupling (Scheme 2).[17] As shown, the cross-coupling of **1a** proceeds with TON of 550-780 at 0.10 mol% loading at 110 °C using Pd-PEPPSI-IPr, Pd(IPr)(cin)Cl, and Pd(IPr)(1-*t*-Bu-indenyl)Cl, respectively. Furthermore, TON of 1150 was observed at 0.05 mol% loading using Pd-PEPPSI-IPr, attesting to the high catalytic efficiency of triflamides as acyl-metal precursors in amide N–C(O) cross-coupling.

Several additional results are worth mentioning. (1) Pleasingly, the use of N-Tf activating group could furthermore be applied utilizing N-aliphatic amides (Scheme 3). (2) Preliminary results demonstrate that the use of Pd-phosphane catalytic systems is also suitable for the cross-coupling of N-Tf amides (Scheme 4), providing an alternative to Pd-NHC. (3) Perhaps most intriguingly, N-Tf amides serve as efficient precursors in both Pd- and Ni-catalyzed Negishi cross-coupling (Scheme 5). To our knowledge, this is the first example of an acyl-aryl Negishi coupling of simple N-sulfonyl amides. The high reactivity of N-Tf amides bodes well for the development of a range of synthetic methods by selective N–C(O) cleavage that are unavailable to other amide precursors.

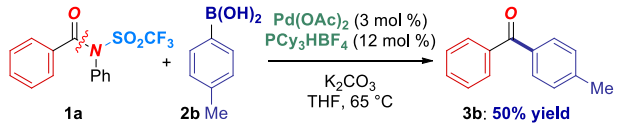
Scheme 2. Determination of TON in the Cross-Coupling of Triflamides



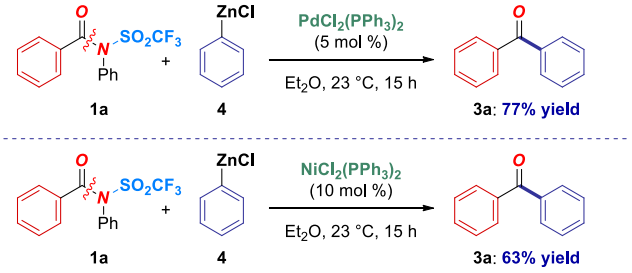
Scheme 3. Application of *N*-Alkyl Triflamides



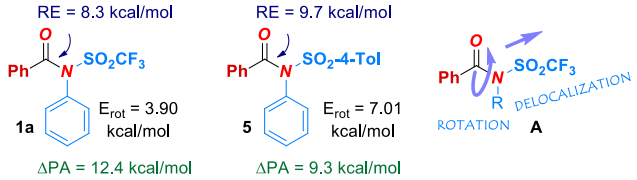
Scheme 4. Application of Pd-Phosphane Catalyst System



Scheme 5. Pd- and Ni-Catalyzed Negishi Cross-Coupling of Triflamides



Scheme 6. Effect of Activating N-Sulfonyl Group: Amides Used in Computational Studies[a]



[a]Activating effect of *N*-triflyl group (**1a**) and graphical model of amide bond destabilization in triflamides (**A**). Note for comparison Ph-C(O)NMePh, RE = 13.5 kcal/mol.

Next, extensive structural and computational studies were conducted to gain insight into the origin of high reactivity of N-Tf amides and lay the framework for the development of future amide precursors based on the N-sulfonyl amide activation concept (Figures 2-3 and Scheme 6). The X-ray structure

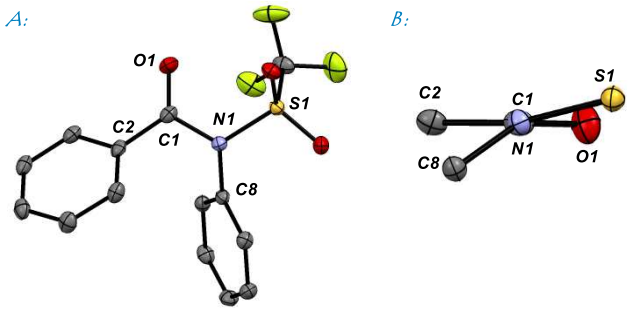


Figure 2. (a) Crystal structure of **1a**. (b) Newman projection along the N–C(O) bond are shown. Bond lengths (Å) and angles (deg): N1–C1, 1.425(2); C1–O1, 1.207(2); C1–C2, 1.490(2); N1–S1, 1.665(1); N1–C8, 1.456(2); C2–C1–N1–S1, –165.49(9); O1–C1–N1–C8, –143.6(1); O1–C1–N1–S1, 15.1(2); C2–C1–N1–C8, 35.9(2). It should be noted that N1–C1 bond is stronger than N1–S1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC-1882900).

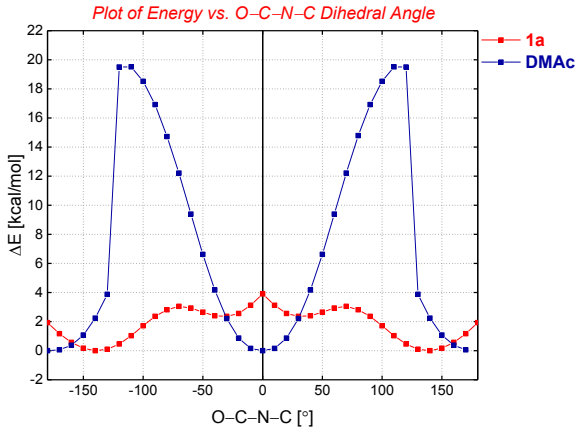


Figure 3. Rotational profile (**1a**, ΔE, kcal/mol, vs. O–C–N–C [°]). DMAC (N,N-dimethylacetamide) is shown for comparison.

of model triflamide, **1a** was determined (Figure 2). The amide bond is twisted (τ = 25.5°, χ_N = 21.4°, χ_C = 0.5°, additive Winkler-Dunitz parameter of 47°, corresponding to one third of the maximum theoretical amide distortion). The N–C(O), C=O and N–S bonds are 1.425 Å , 1.207 Å, and 1.665 Å long. Compared with the corresponding *N*-Ts amide (τ = 18.8°, χ_N = 19.8°, χ_C = 1.0°; N–C(O) = 1.410 Å; C=O = 1.215 Å, N–S = 1.697 Å), these values indicate a decrease of $n_N \rightarrow \pi^*_{C=O}$ conjugation, as a result of Nlp delocalization into the N-sulfonyl

group. The acyl C=O bond in **1a** is located in an antiperiplanar arrangement to the N–Ph bond, bisecting the CF_3–S–O angle.

Computations were employed to determine the energetics of the acyl amide bond undergoing N–C cleavage (Figure 3, Scheme 6 and SI, Supporting Information).

(1) Resonance energy (RE) in **1a** was determined by the COSNAR method.[1a,5] The conjugation in **1a** (RE = 8.3 kcal/mol) is significantly lower than in (i) N–CO planar amides, and (ii) analogous N-Ts amides (RE = 9.7 kcal/mol).

(2) Rotational profile of **1a** was determined by systematic rotation along the O–C–N–C dihedral angle. The energy minimum is located at ca. 140° O–C–N–C angle (τ = 31.21°; χ_N = 19.08°) in a syn O–C–N–S conformation (ca. 20.9° O–C–N–S dihedral angle). The energy maximum is at ca. 0° O–C–N–C dihedral angle (τ = 14.07°; χ_N = 22.92°) in an antiperiplanar O–C–N–S destabilizing conformation (157.1° dihedral angle, 3.90 kcal/mol). These values can be compared with the barrier of 7.01 kcal/mol in N-Ts amides. The less favorable conformation at 180° O–C–N–C dihedral angle is defined by a τ = 2.57°; χ_N = 6.80° geometry (6.8° O–C–N–S angle).

(3) The difference in N-/O-protonation affinities (ΔPA) determines that protonation at the acyl oxygen is strongly favored in N-Tf amide **1a** (ΔPA = 12.4 kcal/mol), which can be compared with N-Ts amides (ΔPA = 9.3 kcal/mol), and is consistent with the strong electron-withdrawing effect of the N-Tf group. Protonation of the amide oxygen is favored over sulfonamide oxygens (ΔPA = 14.8, 17.5 kcal/mol). Thus, activation of the N-acyl group in **1a** by N-protonation is unlikely.

Clearly, the distortion and activation parameters of the amide bond in triflamides emphasize rotational inversion and electronic activation as defining factors that favor selective metal insertion into the N–C(O) bond under mild conditions.

In closing, we have reported the first Suzuki-Miyaura cross-coupling of trifluoromethanesulfonamides (triflamides) by highly selective N–C(O) amide bond cleavage. Most crucially, this manuscript introduces N-Tf amides as novel amide bond precursors that favor metal insertion under exceedingly mild conditions. The method enables the catalytic synthesis of ketones as a serious alternative to Weinreb amides and related methods that have long been a mainstay of chemical synthesis. We have also demonstrated the first example of acyl-aryl Negishi cross-coupling using simple N-acyclic amides. Structural and computational studies have provided evidence for the ground-state destabilization pathway in the selective activation of the amide N–C(O) bond. At the center of the high reactivity of N-Tf amides is the powerful electron-withdrawing effect of the triflyl group. Our data strongly suggest that triflamides should be routinely considered as amide bond precursors in the growing arsenal of amide bond cross-coupling.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org. Experimental procedures and characterization data (PDF). X-ray crystallographic data for **1a** (CIF).

AUTHOR INFORMATION

Corresponding Author

michal.szostak@rutgers.edu

ACKNOWLEDGMENT

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support.

REFERENCES

(1) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, 2003. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (c) Ruider, S.; Maulide, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 13856.

(2) For reviews on N–C functionalization, see: (a) Meng, G.; Shi, S.; Szostak, M. *Synlett* **2016**, *27*, 2530. (b) Liu, C.; Szostak, M. *Chem. Eur. J.* **2017**, *23*, 7157. (c) Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, *46*, 5864. (d) Dander, J. E.; Garg, N. K. *ACS Catal.* **2017**, *7*, 1413. (e) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. *Chem. Soc. Rev.* **2018**, *47*, 7899. (f) Meng, G.; Szostak, M. *Eur. J. Org. Chem.* **2018**, *20-21*, 2352.

(3) (a) *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Molander, G. A.; Wolfe, J. P.; Larhed, M., Eds.; Thieme: Stuttgart, 2013. (b) *Metal-Catalyzed Cross-Coupling Reactions and More*, de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley: New York, 2014. (c) *New Trends in Cross-Coupling*; Colacot, T. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015.

(4) Pauling, L. *The Nature of the Chemical Bond*; Oxford University Press: London, 1940.

(5) For pertinent studies on amide destabilization in N–C cross-coupling, see: (a) Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, M. *J. Org. Chem.* **2016**, *81*, 8091. (b) Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *Chem. Eur. J.* **2016**, *22*, 14494. (c) Szostak, R.; Meng, G.; Szostak, M. *J. Org. Chem.* **2017**, *82*, 6373. (d) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *J. Am. Chem. Soc.* **2018**, *140*, 727.

(6) For representative acyl coupling, see: (a) 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. (b) Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364. (c) Meng, G.; Shi, S.; Szostak, M. *ACS Catal.* **2016**, *6*, 7335. (d) Meng, G.; Lei, P.; Szostak, M. *Org. Lett.* **2017**, *19*, 2158. (e) Amani, J.; Alam, R.; Badir, S.; Molander, G. A. *Org. Lett.* **2017**, 19, 2426. For excellent reductive coupling, see: (f) Ni, S.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* **2017**, *19*, 2536. For further examples, see: (g) Lei, P.; Meng, G.; Ling, Y.; An, J.; Szostak, M. *J. Org. Chem.* **2017**, *82*, 6638 and references cited therein.

(7) For representative decarbonylative coupling, see: (a) Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518. (b) Shi, S.; Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959. (c) Meng, G.; Szostak, M. *Org. Lett.* **2016**, *18*, 796. (d) Dey, A.; Sasmai, S.; Seth, K.; Lahiri, G. K.; Maiti, D. *ACS Catal.* **2017**, *7*, 433. (e) Yue, H.; Guo, L.; Liao, H. H.; Cai, Y.; Zhu, C.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 4282. (f) Yue, H.; Guo, L.; Lee, S. C.; Liu, X.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 3972. (g) Srimontree, W.; Chatupheeraphat, A.; Liao, H. H.; Rueping, M. *Org. Lett.* **2017**, *19*, 3091 and references cited therein.

(8) For reviews on decarbonylative cross-coupling, see: (a) Liu, C.; Szostak. M. *Org. Biomol. Chem.* **2018**, *16*, 7998. (b) Guo, L.; Rueping, M. *Acc. Chem. Res.* **2018**, *51*, 1185.

(9) For representative tandem coupling, see: Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. *J. Am. Chem. Soc.* **2017**, *139*, 10228 and references cited therein.

(10) For a biomimetic esterification by N–C activation, see: Wybon, C. C. D.; Mensch, C.; Hollanders, K.; Gadals, C.; Herrebout, W. A.; Ballet, S.; Maes, B. U. W. *ACS Catal.* **2018**, *8*, 203.

(11) For a chromium-catalyzed N–C activation, see: Chen, C.; Liu, P.; Luo, M.; Zeng, X. *ACS Catal.* **2018**, *8*, 5864.

(12) For a cobalt-catalyzed esterification by N–C activation, see: Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. *Chem. Eur. J.* **2017**, *23*, 10043.

(13) For palladium-catalyzed decarbonylative coupling, see: (a) Liu, L.; Zhou, D.; Liu, M.; Zhou, Y.; Chen, T. *Org. Lett.* **2018**, *20*,

2741. (b) Liu, C.; Szostak, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 12718. (c) Shi, S.; Szostak, M. *Org. Lett.* **2017**, *19*, 3095.

(14) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Kaspar, A. A.; Reichert, J. M. *Drug Discov. Today* **2013**, *18*, 807. (c) Marchildon, K. *Macromol. React. Eng.* **2011**, *5*, 22.

(15) (a) Shainyan, B. A.; Tolstikova, L. L. *Chem. Rev.* **2013**, *113*, 699. (b) Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412. (c) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607.

(16) Ritter, K. *Synthesis* **1993**, 735.

(17) Shi, S.; Nolan, S. P.; Szostak, M. *Acc. Chem. Res.* **2018**, *51*, 2589.

(18) (a) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440. (b) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. *ACS Catal.* **2015**, *5*, 3680. (c) Froese, R. D. J.; Lombardi, C.; Pompeo, M.; Rucker, R. P.; Organ, M. G. *Acc. Chem. Res.* **2017**, *50*, 2244.

(19) Li, G.; Lei, P.; Szostak, M.; Casals, E.; Poater, A.; Cavallo, L.; Nolan, S. P. *ChemCatChem* **2018**, *10*, 3096.

(20) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.