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Accepted Article

Title: Redox-Neutral Decarbonylative Cross-Couplings Coming of Age

Authors: Qun Zhao and Michal Szostak

To be cited as: *ChemSusChem* 10.1002/cssc.201900408

Link to VoR: http://dx.doi.org/10.1002/cssc.201900408

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemsuschem.org

Redox-Neutral Decarbonylative Cross-Couplings Coming of Age

Qun Zhao and Michal Szostak*

Carboxylic acids represent quintessential substrates for organic synthesis.[1] Diverse electrophilic and nucleophilic reactions of carboxylic acids form the foundation of daily research by practicing organic chemists[2] and feature as the pillar of all undergraduate organic chemistry textbooks.[3] The steadily increasing demand for efficient and sustainable carbon-carbon bond forming protocols has given rise to the exponential growth of transition-metal-catalyzed cross-coupling reactions as firmly manifested by the 2010 Nobel Prize in Chemistry.[4] Following the inspiring breakthrough reported by Gooßen in 2006,[5] traditionally, the cross-coupling of carboxylic acids is addressed via decarboxylation.[6] Typically, this involves generation of arenecarboxylate and extrusion of carbon dioxide, which converts carboxylic acids into aryl nucleophiles.[7] This approach has proven extremely valuable as it allows to exploit carboxylic acids as ubiquitous, orthogonal and readily accessible cross-coupling partners in paradigms under decarboxylative regimen. However, despite the profound impact on chemical synthesis, decarboxylative cross-couplings have been a challenge due to high energy required for the decarboxylation step,[5] which often requires stoichiometric metal additives, substrates that favor decarboxylation and typically demand high temperature.[6] Recently, significant progress has been made in the development of cross-coupling reactions of carboxylic acids via redox-neutral decarbonylative pathway (Figure 1). In this approach, carboxylic acid is first converted to an activated easily-accessible acyl carboxylic acid derivative, followed by metal insertion, transmetallation/ decarbonylation and reductive elimination, thus mimicking the classical M(0)/(II) (M = metal) cross-coupling mechanism under redox-neutral conditions (Figure 2). Altogether, this provides a powerful alternative approach to the decarboxylative cross-coupling of carboxylic acids[6] as well as the traditional cross-coupling of aryl halides.[4]

Surely, decarbonylative cross-couplings are not new.[4] One of the first efficient examples of a decarbonylative cross-coupling was reported by de Vries and colleagues in 1998 and involved the use of symmetrical anhydrides in a $PdCl_2$/LiCl-co-catalyzed decarbonylative Heck cross-coupling.[8,9] Subsequently, this approach was refined by Gooßen and colleagues who utilized aromatic esters and vinylic esters thus minimizing generation of toxic halide waste.[10] The idea of forming aryl electrophiles from carboxylic acids by decarbonylation laid dormant until 2012 when Itami et al. found that relatively unactivated phenolic esters can be induced to undergo selective decarbonylation/C–C cross-coupling with acidic heterocycles utilizing $Ni(cod)_2$ and dcype as a key bidentate ligand.[11] In 2015, our group introduced decarbonylative cross-coupling of amides by selective N–C activation using Pd, and later Rh and Ni,[12] and this approach was elegantly expanded by Rueping and colleagues.[13]

[*] Dr. Q. Zhao, Prof. Dr. M. Szostak
Department of Chemistry, Rutgers University
73 Warren Street, Newark, NJ 07102 (United States)
E-mail: michal.szostak@rutgers.edu
Website: https://szostakgroup.com

The developed decarbonylative strategies are important from the sustainability standpoint because they open up new avenues for utilization of carboxylic acids in the cross-coupling strategies of paramount significance in chemical synthesis. Because carboxylic acids are produced at much lower cost than aryl halides, efficient cross-coupling of these alternative substrates offers new ways of reducing energy, cost and time required for chemical processes. Another potentially intriguing aspect involves circumventing the release of carbon dioxide, which at present is considered as the major greenhouse gas.

Recent breakthroughs in novel decarbonylative cross-couplings can be classified into three main categories. In 2018, Schoenebeck and co-workers reported a Pd(0)/Xantphos-catalyzed decarbonylative trifluoromethylation of acid fluorides.[14] Subsequently, Sanford and co-workers described a $Ni(0)/PPh_2Me$-catalyzed Suzuki-Miyaura cross-coupling of the same class of substrates.[15] Ritter and co-workers have independently accomplished extraordinary mild, Pd(0)/RuPhos-catalyzed difluoromethylation of acid chlorides.[16] Our group together with Hong and co-workers reported a Pd(0)/dppb-catalyzed direct borylation of carboxylic acids using in situ piv_2O activation.[17] These methods combine the advantages of using carboxylic acids together with facile decarbonylation, thus establishing new general tactics in organic synthesis that can be incorporated into complex substrates and synthetic sequences.

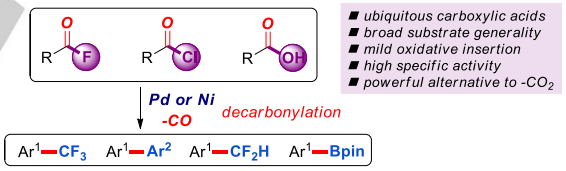


Figure 1. New vistas in decarbonylative cross-coupling of carboxylic acids.

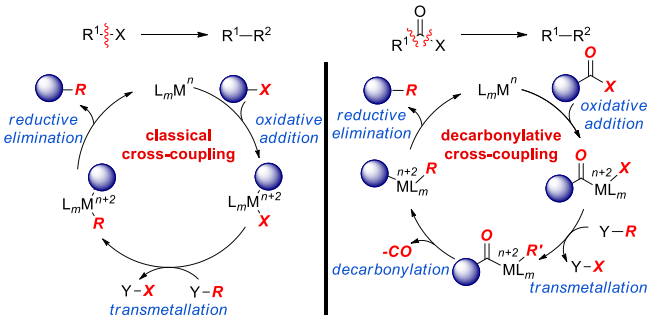
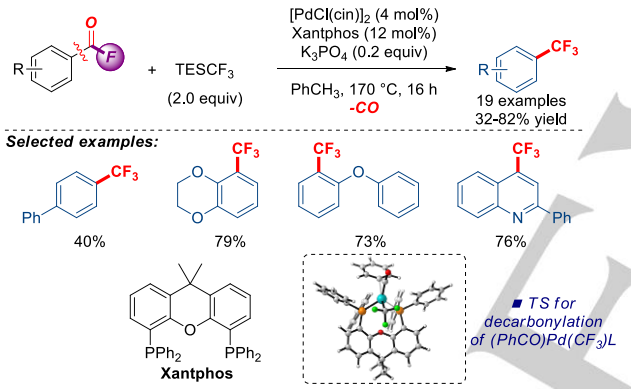


Figure 2. Catalytic cycles for classical and decarbonylative cross-coupling.

The benefits of these strategies include: (1) advantageous use of carboxylic acids as much more available, cheaper and less toxic substrates than the current state-of-the-art aryl halides or designer amides and esters; (2) access to unconventional downstream disconnections enabled by the inherent ubiquitous presence of carboxylic acids in natural products, functional materials, and most importantly, plethora of pharmaceuticals; (3)

capacity for orthogonal cross-coupling strategies in the presence of aryl halides; (4) novel approaches to biomass valorization.

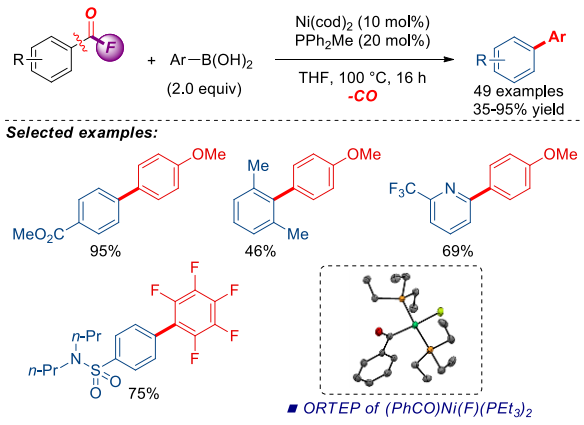
The strategy by Schoenebeck has provided the first example of a Pd(0)-catalyzed decarbonylative cross-coupling of acid fluorides (Scheme 1).[14] This process establishes a rare protocol for a Pd(0)/Pd(II) trifluoromethylation, introducing the biorelevant CF_3 motif with broad generality and very promising reaction scope. It is particularly noteworthy that (1) the method avoids the use of external fluoride additives, and (2) the process operates effectively with general Xantphos as a supporting ligand. As expected, the leaving F^- group serves as internal fluoride source, activating the trifluoromethylating agent. This in turn allows to limit the concentration of CF_3 anions, thus avoiding facile displacement of the phosphines from Pd.[18] On the basis of DFT studies, the authors proposed that the transmetallation step precedes decarbonylation ($\Delta G^{\ddagger}$ = 17.4 kcal mol^{-1} vs. $\Delta G^{\ddagger}$ = 27.3 kcal mol^{-1} from PhCO-[Pd]-CF_3 vs. PhCO-[Pd]-F, respectively). Furthermore, studies correlated the reaction selectivity (Ar–CF_3 vs. ArCO–CF_3) with temperature, with high temperatures favoring decarbonylation. As this protocol provides rapid entry to trifluoromethylated arenes, this method may find broad application in synthesis, agrochemistry and drug discovery.



Scheme 1. Selected examples of the Pd/Xantphos-catalyzed decarbonylative trifluoromethylation of acid fluorides. Inset shows TS for decarbonylation.

More generally, the reactivity of carboxylic acid halides should be benchmarked against the reactivity of other carboxylic acid derivatives. First, acid fluorides are more stable than the more commonly used in synthesis acid chlorides.[19] This is evidenced by the C–X bond lengths (MeC(O)–F: 1.37 Å, MeC(O)–Cl: 1.82 Å MeC(O)–Br: 2.00 Å), consistent with a decreasing $n_X \rightarrow \pi^*_{CO}$ conjugation in the series, while the C=O bond lengths are in the range of approx. 1.16 Å, which is shorter than in esters and signifies a more C=O double bond character. Second, recent studies make it quite clear that oxidative addition of C(O)–X bonds is relatively easy and cannot be considered a rate-determining step in these cross-couplings. The resonance energy (RE) of acid fluorides (PhC(O)–F = 14.0 kcal mol^{-1}), acid chlorides (PhC(O)–Cl = 5.1 kcal mol^{-1}) and acid bromides (PhC(O)–Br = 3.5 kcal mol^{-1}) is in the range of activated amides (PhC(O)–N(glutarimide) = –1.4 kcal mol^{-1}; PhC(O)–NPh/Me = 13.5 kcal mol^{-1}) and esters (barrier to rotation, PhC(O)–OPh, 9.3 kcal mol^{-1}; PhC(O)–OMe, 12.8 kcal mol^{-1}) indicating comparatively activated C(O)–X bonds.[20] In all cases, the elementary oxidative addition initiating the cross-coupling occurs readily at mild, room temperature conditions, highlighting the crucial role of rate-limiting decarbonylation or transmetallation. Third, acid halides and certainly carboxylic acids are readily available and over the years have become a classic group of substrates in the repertoire of organic chemists.[1–3] Since the redox neutral decarbonylative cross-coupling manifold offers evident advantages to chemists and exploits well-familiar substrates, which differ in their stability, ease of decarbonylation and transmetallation, thus allowing for control and fine-tuning of elementary reactions, the research is now perfectly poised for widespread adoption by the synthetic community pending the establishment of general cross-coupling methods.

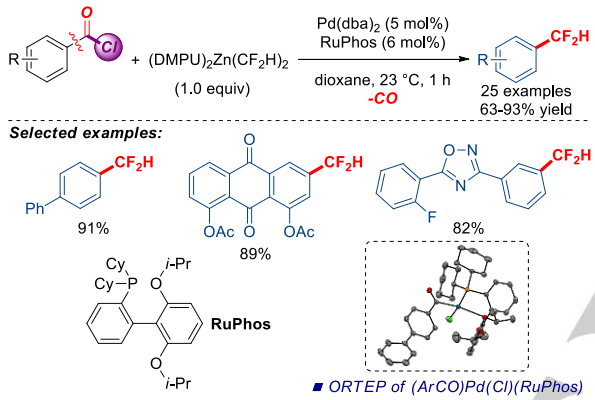
In this vein, following the pioneering work on trifluoromethylation,[14] Sanford el al. reported the Suzuki-Miyaura cross-coupling of acid fluorides (Scheme 2).[15] Impressive levels of selectivity for the synthesis of valuable biaryls[21] were achieved using an exogenous base-free protocol. Mechanistically, the authors showed that both oxidative addition of benzoyl fluoride and decarbonylation of the PhCO-[Pd(PCy_3)$_2$]-F intermediate occur readily at room temperature. Most crucially, they showed that the fluoride delivered by the acid electrophile is vital for the transmetallation step with aryl boronic acids, whereby the use of analogous acid chloride and bromide intermediates, PhCO-[Ni(PCy_3)$_2$]-X (X = Cl, Br), was unproductive. This is consistent with a "fluoride effect" to promote transmetallation,[21] thus switching to "transmetallation active" [Ar–M–X] intermediates in a selective manner enabled by an internal transfer of the F^- anion. The remarkable net result is that Suzuki cross-coupling operates under base-free regimen, which limits off-cycle side-reactions promoted by the base. This concept provides a highly attractive alternative for realizing the Suzuki cross-coupling of aryl halides and pseudohalides.



Scheme 2. Selected examples of the Ni/PPh_2Me-catalyzed decarbonylative Suzuki cross-coupling of acid fluorides. Inset shows (PhCO)Ni(F)(PEt_3)$_2$.

Recently, a pioneering example of Pd(0)-catalyzed decarbonylative cross-coupling of acid chlorides at room temperature was reported by Ritter and co-workers (Scheme 3).[16] They have shown that Pd(dba)$_2$ in combination with a bulky monodentate phosphine RuPhos and (DMPU)$_2$Zn(CF_2H)$_2$

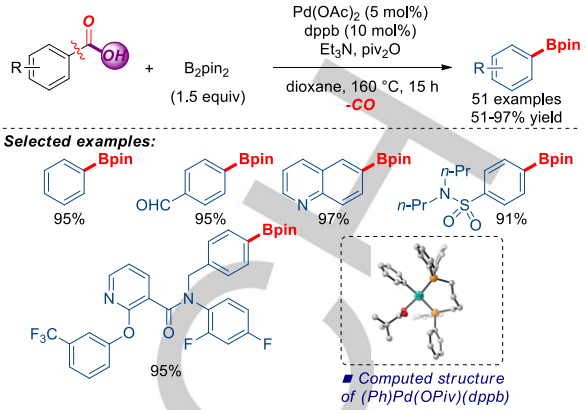
as a nucleophilic difluoromethylating agent promotes the decarbonylative cross-coupling within 5 min at room temperature. This remarkably facile process was explained by the mechanism involving (i) oxidative addition; (ii) rate-limiting transmetallation; (iii) decarbonylation promoted by the coordinatively unsaturated 3-coordinate Ar–Pd(RuPhos)–CF_2H complex; and (iv) reductive elimination. Furthermore, the authors clearly established that the rate and selectivity of the reductive elimination step is closely connected to electronic properties of the ligands on Pd, whereby (i) Ar–Pd(PR_3)–Cl leads to slower reductive elimination than Ar–Pd(PR_3)–CF_2H; (ii) electron-rich arenes lead to a competing ArC(O)/CF_2H reductive elimination. Thus, this elegant protocol provides not only a highly practical entry to the underrepresented CF_2H motif, but also furnishes many key insights into the future development of decarbonylative cross-couplings of the traditionally unstable acid chlorides.



Scheme 3. Selected examples of the Pd/RuPhos-catalyzed decarbonylative difluoromethylation of acid chlorides. Inset shows (ArCO)Pd(Cl)(RuPhos).

In addition, our group together with Hong and co-workers successfully developed a Pd(0)-catalyzed direct decarbonylative borylation of carboxylic acids (Scheme 4).[17] In contrast to other reports, this redox-neutral approach directly engages carboxylic acids by combining all reaction components in one-pot without the need for separate activation steps. The user-friendly catalyst system provides an efficient gateway to highly functionalized aryl–boron bonds, including a broad range of sensitive functional groups, direct functionalization of APIs and bioactive natural products. Detailed DFT studies indicated that the substituent at the carboxylic acid anhydride controls the selectivity of the C–O bond activation by sterics with the ArC(O)– vs. *t*-BuC(O)– activation favored by 4.7 kcal mol^{-1} and transmetallation as the rate-limiting step. Since the activation of acid anhydrides (RE of 5.1 kcal mol^{-1}) is facile, the anhydride is stable under the cross-coupling conditions and the reaction follows well-defined Pd(0)/(II) cycle, this approach could potentially enable a wide variety of cross-coupling protocols using directly ubiquitous carboxylic acid electrophiles.

In the context of decarbonylative cross-couplings of acid halides it is also important to mention two recent breakthroughs on functional group σ-bond metathesis of acid chlorides and aryl iodides reported independently by Morandi and Arndtsen.[22] These reports clearly foreshadow that (i) the oxidative addition



Scheme 4. Selected examples of the Pd/dppb-catalyzed decarbonylative borylation of carboxylic acids. Inset shows (Ph)Pd(OPiv)(dppb).

of acid chlorides is more facile than that of aryl iodides; (ii) Xantphos ligands are the privileged class of ligands for the selective oxidative addition of unstable acyl electrophiles.

In conclusion, major progress has recently been made in the challenging redox-neutral decarbonylative cross-coupling of carboxylic acids. For the first time, acid fluorides have been proved to be effective cross-coupling partners in the decarbonylative manifold allowing for the exquisite control of the decarbonylation selectivity, such that the challenging Pd(0)-catalyzed nucleophilic trifluoromethylation and exogenous base-free Suzuki cross-coupling have been achieved. Another significant advance is the use of acid chlorides in the room temperature difluoromethylation and the direct decarbonylative cross-coupling of carboxylic acids which open the door to the use of these classical substrates as aryl electrophiles in cross-coupling manifolds. Finally a comment should be made that despite the undeniable breakthroughs, several challenges still need to be addressed. Acid fluorides have emerged as the preferred acid derivatives for the cross-coupling; however, the synthesis of acyl fluorides is still not straightforward using cost-effective reagents. Second, thus far all but one protocol involve a separate preparation step. It would take us closer to the ideal cross-coupling paradigm if all reactions could be performed in a one-pot fashion. Third, the generality of the platform must be established so that different disconnections become available to practicing organic chemists for the efficient functionalization of carboxylic acids. Further developments in this important area[23] using general catalyst systems are certainly expected and will offer new sustainable tactics for organic synthesis.

Acknowledgements

We thank Rutgers University, the NSF (CAREER CHE-1650766) and the ACS PRF (DNI-55549) for generous financial support.

Keywords: decarbonylation • carboxylic acids • cross-coupling • homogeneous catalysis • arenes

[1] B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, **1991**.

[2] D. G. Brown, J. J. Boström, *J. Med. Chem.* **2016**, *59*, 4443.
[3] a) W. H. Brown, B. L. Iverson, E. V. Anslyn, C. S. Foote, *Organic Chemistry*, Cengage, **2018**; b) M. B. Smith, J. March, *Advanced Organic Chemistry*, Wiley, **2007**.
[4] a) A. de Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley, **2014**; b) G. A. Molander, J. P. Wolfe, M. Larhed, *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Thieme, **2013**; c) C. C. C. Johansson-Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; d) X. F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 9047.
[5] L. J. Gooßen, G. Dong, L. M. Levy, *Science* **2006**, *313*, 662.
[6] a) L. J. Gooßen, N. Rodriguez, K. Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100; b) N. Rodriguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030; c) W. Dzik, P. Lange, L. Gooßen, *Chem. Sci.* **2012**, *3*, 2671.
[7] A. Fromm, C. van Wüllen, D. Hackenberger, L. J. Gooßen, *J. Am. Chem. Soc.* **2014**, *136*, 10007.
[8] M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem. Int. Ed.* **1998**, *37*, 662.
[9] M. Oestreich, *The Mizoroki-Heck Reaction*, Wiley, **2009**.
[10] a) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2002**, *41*, 1237; b) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2004**, *43*, 1095.
[11] K. Amaike, K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 13573.
[12] a) G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2015**, *54*, 14518; b) S. Shi, G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2016**, *55*, 6959; c) G. Meng, M. Szostak, *Org. Lett.* **2016**, *18*, 796; For a review, see: d) C. Liu, M. Szostak, *Org. Biomol. Chem.* **2018**, *16*, 7998.
[13] L. Guo, M. Rueping, *Acc. Chem. Res.* **2018**, *51*, 1185.
[14] a) S. T. Keaveney, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 4073; For synthesis of acid fluorides, see: b) T. Scattolin, K. Deckers, F. Schoenebeck, *Org. Lett.* **2017**, *19*, 5740.
[15] C. A. Malapit, J. R. Bour, C. E. Brigham, M. S. Sanford, *Nature* **2018**, *563*, 100.
[16] F. Pan, G. B. Boursalian, T. Ritter, *Angew. Chem. Int. Ed.* **2018**, *57*, 16871.
[17] C. Liu, C. L. Ji, X. Hong, M. Szostak, *Angew. Chem. Int. Ed.* **2018**, *57*, 16721.
[18] V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644.
[19] M. F. Ansell, *The Chemistry of Acyl Halides*, Wiley, **1972**.
[20] S. Shi, S. P. Nolan, M. Szostak, *Acc. Chem. Res.* **2018**, *51*, 2589.
[21] L. Ackermann, *Modern Arylation Methods*, Wiley, **2009**.
[22] a) Y. H. Lee, B. Morandi, *Nat. Chem.* **2018**, *10*, 1016; b) M. De La Higuera Macias, B. A. Arndtsen, *J. Am. Chem. Soc.* **2018**, *140*, 10140.
[23] For additional studies on decarbonylative cross-coupling reactions of carboxylic acids and derivatives, see: a) Y. D. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964; b) J. F. Hu, Y. Zhao, J. J. Liu, Y. M. Zhang, Z. Z. Shi, *Angew. Chem. Int. Ed.* **2016**, *55*, 8718; c) X. H. Pu, J. F. Hu, Y. Zhao, Z. Z. Shi, *ACS Catal.* **2016**, *6*, 6692; d) L. Guo, M. Rueping, *Chem. Eur. J.* **2016**, *22*, 16787; e) Y. Ogiwara, Y. Maegawa, D. Sakino, N. Sakai, *Chem. Lett.* **2016**, *45*, 790; f) S. C. Lee, L. Guo, H. Yue, H. H. Liao, M. Rueping, *Synlett* **2017**, *28*, 2594; g) H. Ochiai, Y. Uetake, T. Niwa, T. Hosoya, *Angew. Chem. Int. Ed.* **2017**, *56*, 2482; h) T. Niwa, H. Ochiai, M. Isoda, T. Hosoya, *Chem. Lett.* **2017**, *46*, 1315; i) C. A. Malapit, N. Ichiishi, M. S. Sanford, *Org. Lett.* **2017**, *19*, 4142; j) Y. Ogiwara, Y. Sakurai, H. Hattori, N. Sakai, *Org. Lett.* **2018**, *20*, 4204; k) Y. Okuda, J. Xu, T. Ishiada, C. Wang, Y. Nishihara, *ACS Omega* **2018**, *2*, 13129; l) Z. Wang, X. Wang, Y. Nishihara, *Chem. Commun.* **2018**, *54*, 13969; For examples of decarboxylative cross-coupling reactions, see: m) C. Li, J. Wang, L. M. Barton, S. Yu, M. Q. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, 1045; n) L. Candish, M. Teders, F. Glorius, *J. Am. Chem. Soc.* **2007**, *139*, 7440; o) D. Hu, L. Wang, P. Li, *Org. Lett.* **2017**, *19*, 2770; p) A. Fawcet, J. Pradeilles, Y. H. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science* **2017**, *357*, 283.