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Decarboxylative, Radical C–C Bond Formation with Alkyl or Aryl Carboxylic Acids: Recent Advances

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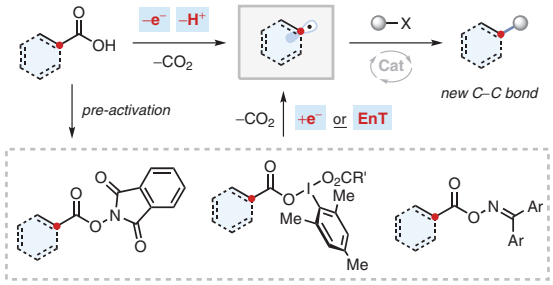

Dedicated to the memory of Professor John Fossey

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Abstract The ubiquity of carboxylic acids as naturally derived or man-made chemical feedstocks has spurred the development of powerful, decarboxylative C–C bond-forming transformations for organic synthesis. Carboxylic acids benefit not only from extensive commercial availability, but are stable surrogates for organohalides or organometallic reagents in transition-metal-catalysed cross-coupling. Open shell reactivity of carboxylic acids (or derivatives thereof) to furnish carbon-centred radicals is proving transformative for synthetic chemistry, enabling novel and strategy-level C(sp^3)–C bond disconnections with exquisite chemoselectivity. This short review will summarise several of the latest advances in this ever-expanding area.

Key words decarboxylative, C–C coupling, radicals, carboxylic acids, photoredox catalysis, electrochemistry

1 Introduction

Carboxylic acids are among the most abundant and diverse chemical building blocks available for organic synthesis, featuring prominently in naturally occurring feedstocks such as amino acids, fatty acids, and sugar acids. In addition to their classical, two-electron reactivity as nucleophiles or electrophiles,[1–4] or as directing groups for C–H activation,[5] they can serve as versatile reagents for decarboxylative[6] or decarbonylative[6s,7] cross-coupling to forge new C–C bonds. In this regard, carboxylic acids benefit not only from widespread commercial availability, but also lesser toxicity and/or increased bench-stability relative to more reactive coupling partners, such as halides or organometallics. Whilst aryl or heteroaryl carboxylic acids can enter into catalytic cycles predicated on *two-electron* decarboxylative or decarbonylative metalation (with transition metals like Cu, Ag, Pd, or Au), these reactions frequently require elevated temperatures and tend to be limited in scope (Scheme 1A).[6,7] Conversely, *alkyl* carboxylic acids 5 can serve as progenitors to alkyl radicals 7 *via* single-electron pathways involving extrusion of CO_2. Early forays into radical decarboxylative C–C bond formation were pioneered by Kolbe[8] and Barton,[9] but these protocols often lacked generality, required high-energy ultraviolet (UV) irradiation, or suffered from various practical drawbacks (Scheme 1B).

The majority of modern, chemoselective, decarboxylative C–C bond formations rely on one of three radical generation strategies, all of which are generally limited to alkyl carboxylic acids for the formation of alkyl radical intermediates (Scheme 2). The first strategy relies on SET oxidation of carboxylate ions **10** ($E_{1/2}$ = +1.25 to +1.31 V *vs* SCE)[10] and subsequent decarboxylation of the carboxyl radicals **11** (Scheme 2A). The SET step can be mediated by chemical oxidants (e.g., $K_2S_2O_8$), high valent metal catalysts [e.g., Ag(II)], excited photocatalysts, or an anode in an electrochemical cell.[6] The second strategy involves hydrogen atom abstraction from the strong O–H bond of the carboxylic acid **9** (BDE = 112 ± 3 kcal mol^{-1} for AcO–H) (Scheme 2B).[11] Given the difficulty of direct hydrogen atom transfer (HAT) from the O–H bond, this strategy is rare.[12] However, neutral acridine-based photocatalysts that can hydrogen bond to free car-

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Joshua Tibbetts graduated from the University of Cambridge in 2015 with an MSci in Natural Sciences. He carried out a final year project with Professor Steven Ley on the flow synthesis of peptides using *N*-carboxyanhydrides. He then joined Professor Steve Bull's lab at the University of Bath to conduct a PhD on catalytic transformations of monoterpenoid feedstocks, with a focus on the synthesis of valorised products in flow. In January 2020, he started a postdoctoral position in the Cresswell lab to work in the area of photoredox catalysis for primary amine C–H functionalisation.

Hannah Askey graduated from the University of Leeds in 2020 with an MChem degree in Medicinal Chemistry. They carried out their final year project with Professor Adam Nelson, where they expanded the substrate scope of a photoredox Minisci-type reaction for use in the elaboration of drug fragments. In their third year, Hannah undertook an industrial placement at AstraZeneca in Macclesfield, during which they were responsible for the process development of a Suzuki reaction that was later run on the plant. In Oct 2020, they started a PhD in the Cresswell group at the University of Bath, focusing on the photocatalytic C–H functionalisation of primary amines.

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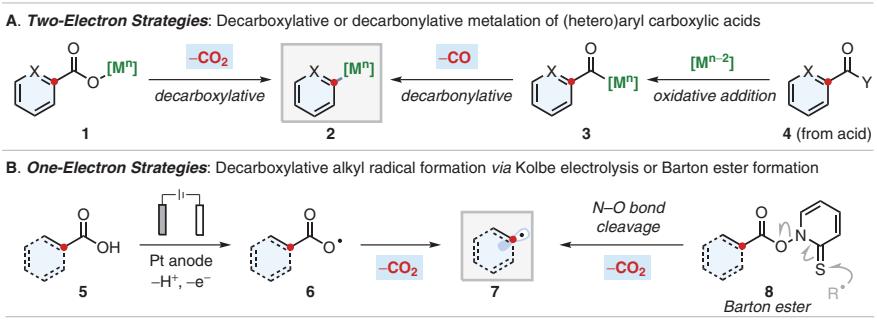
James Grayson graduated from the University of Nottingham in 2016 with an MChem degree in Chemistry. He then carried out his PhD at the University of Sheffield with Dr Ben Partridge, developing copper-catalysed transformations of alkylboronic esters. In July 2020, he started as a postdoctoral researcher in the Cresswell group at the University of Bath, working on photoredox catalysis for primary amine C–H functionalisation. In July 2022, he started as a Research Scientist in Radiochemistry at Selcia.

Sophie Hobson graduated from the Lancaster University in 2021 with an MChem degree in Chemistry. She completed a synthetic supramolecular chemistry summer internship with Dr Nicholas Evans in 2019 and a fourth-year research project focusing on the stereoselective synthesis of spirocycles for drug discovery with Dr Vilius Franckevičius. From Oct 2021, she carried out an MPhil project in the Cresswell group at the University of Bath, developing new strategies for *N*-heterocycle synthesis.

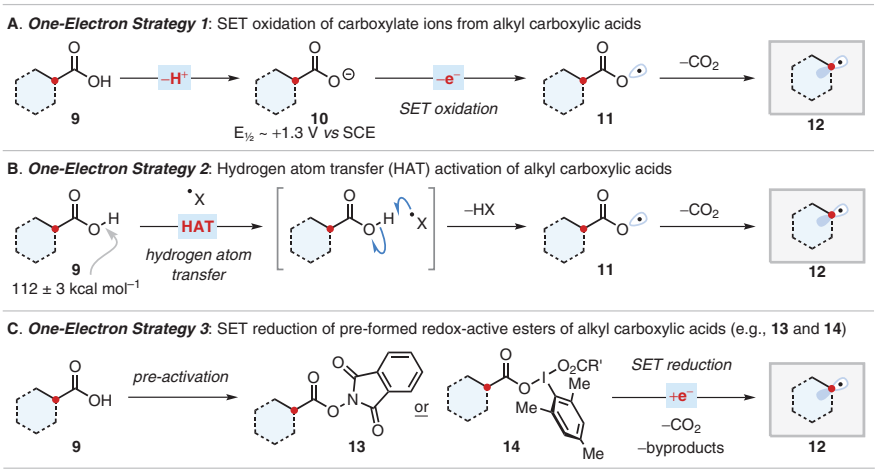
George Johnson graduated from the University of Durham in 2021 with an MChem degree in Chemistry. He carried out his final year project with Professor David Hodgson, working on the electrophilic fluorination of pyrroles. In Oct 2021, he started a PhD in the Marken and Cresswell groups at the University of Bath, focusing on new, single electron-mediated reactions for C–H heteroarylation of amines.

Jacob Turner-Dore graduated from the University of Bath in 2020 with an Integrated Master's in Chemistry with Drug Discovery. During his placement year at Charles River Laboratories, he worked on development of an inhaled drug to treat respiratory diseases. In Oct 2020, he started a PhD in the Cresswell group at the University of Bath, where he is developing photocatalytic routes towards (semi)saturated *N*-heterocycles, with key focuses on automation and mechanistic understanding.

boxylic acids **9** allow for radical generation by proton-coupled electron transfer (PCET), in the absence of added base.[13] The third strategy involves SET reductive generation of carbon-centred radicals **12** from carboxylic acids pre-activated as 'redox-active esters'; for example, *N*-(acyloxy)phthalimide (NHPI) esters **13**[6a–d,6g–i,6l–m,6o] and, more recently, hypervalent iodine(III) adducts **14**[14] (Scheme 2C). The NHPI esters **13** are bench-stable, but can in many cases be synthesised and reacted in a one-pot fashion, without the need for isolation.



Scheme 1 Classical one and two electron strategies for decarboxylative or decarbonylative radical formation from aryl/alkyl carboxylic acids

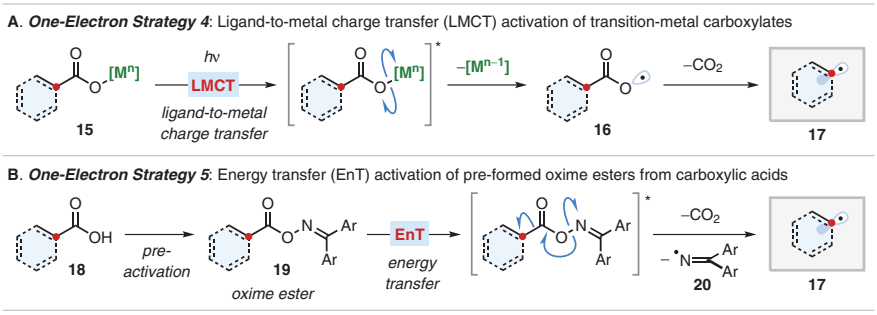


Scheme 2 Radical generation strategies using alkyl carboxylic acids for the formation of radical intermediates

Redox-active ester species based on activation using pyridine *N*-oxides have also been used to great effect.[15] The SET reduction step can be facilitated by chemical reductants (*via* outer sphere electron transfer or *via* EDA complexes[16]), low valent metal catalysts [e.g., Ni(I)], excited photocatalysts, or a cathode in an electrochemical cell.

Subsequent C–C bond formations of alkyl radical intermediates **12** can either be redox-neutral, net oxidative, or net reductive, depending on the philicity or oxidation level of the coupling partners employed. For example, the Ni-catalysed arylation of carboxylic acids with aryl halide electrophiles under photoredox conditions is redox-neutral,[17] as is the Ni/Fe-catalysed arylation of redox-active esters with nucleophilic aryl organometallics.[18] Conversely, cross-electrophile couplings require stoichiometric reducing agents (e.g., Zn, Mn, cathode)[16a,19] and cross-nucleophile couplings necessitate stoichiometric oxidants (e.g., $K_2S_2O_8$, O_2, anode).[6j,20] In terms of mechanism for the C–C bond-forming step, nucleophilic[21] alkyl radical intermediates **12** can rely either upon innate radical reactivity (e.g., addition to π-unsaturates[22,23] or suitably electrophilic aromatic rings[24]) or mergers with organometallic catalysis (i.e., C–C bond formation *via* reductive elimination from the coordination sphere of a transition metal). In the latter case, mergers of transition metal catalysis with photoredox catalysis ('metallaphotoredox' catalysis)[25] or electrochemistry[19a,26] have proven to be particularly fruitful areas of research.

Two new and emerging strategies have been introduced over the past several years, which offer some complementarity in that they are also applicable to *aryl radical* formation from *aromatic* carboxylic acids (Scheme 3). The first of these, we could call it Strategy 4, is based on the homolysis of O–M bonds of transition metal carboxylates **15** following a photon-induced ligand-to-metal charge transfer (LMCT) (Scheme 3A).[27] The fifth and final strategy is a redox-neutral decomposition of pre-formed oxime esters **19** *via* energy transfer (EnT)[28] activation (Scheme 3B).[29] Although less developed than many of the above strategies, the latter approach does provide one of the few effective means of generating aryl radicals from benzoic acids,[29c] and the iminyl radical **20** co-generated with radical **17** can be used productively to form C–N bonds alongside new C–C bonds.[29a,b]



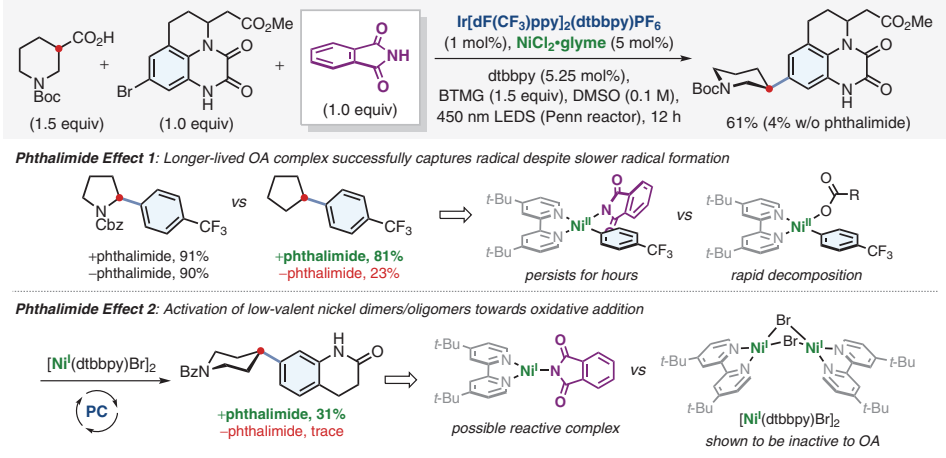
Scheme 3 Radical generation strategies using alkyl or (hetero)aryl carboxylic acids for the formation of radical intermediates

This article will not duplicate the coverage of previous reviews, but rather focus on providing a concise update on some recent major advances in the field of decarboxylative C–C formation.

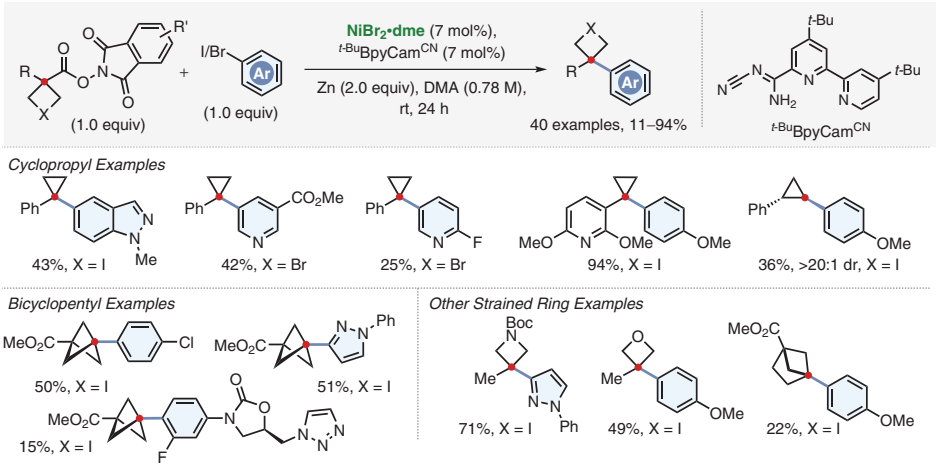
2 Improved Decarboxylative Arylations

The development of metallaphotoredox-catalysed, decarboxylative arylations of alkyl carboxylic acids with (hetero)aryl halides in 2014 was a watershed moment in organic synthesis, enabling alkyl–aryl cross-couplings with abundant α-amino acids.[17] However, these reactions are typically inefficient with: (1) nitrogen-rich substrates, (2) aryl bromides prone to protodehalogenation, (3) difficult oxidative additions (e.g., electron-rich Ar–Br), or (4) 1°/2° carboxylic acids that lack adjacent radical-stabilising groups (e.g., NBoc, O). To address these limitations, the MacMillan group have deployed a high-throughput screening approach to identify phthalimide as an additive that greatly increases reaction efficiency with many problematic acid and aryl halide partners (Scheme 4).[30] This modification was tested against 384 carboxylic acids as well as 384 (hetero)aryl bromides. The role of the phthalimide is complex, but it is believed to impart two distinct effects: (1) it leads to longer-lived oxidative addition complexes of Ni, enabling successful capture of these complexes with alkyl radicals that are otherwise slow to form and (2) it serves to deoligomerise off-cycle Ni species that are inactive towards oxidative addition. With this advance, unactivated carboxylic acids, many *N*-rich heteroarenes, and substrates bearing polar FGs (1,2-diols, aminopyridines) can now be coupled successfully. The use of phthalimide as an additive may also have wider implications for nickel-catalysed cross-couplings, beyond photoredox methods.

In an advance to the area of cross-electrophile coupling (XEC), García-Reynaga, Weix, and co-workers have reported a Ni-catalysed, reductive coupling of a variety of strained ring NHPI esters with (hetero)aryl halides.[31] This allows for cyclopropanation or bicyclopentylation of arenes, as well as installation of other strained rings (e.g., oxetanes, bicyclohexanes, azetidines). It is compatible with high-throughput experimentation (using Zn@ChemBeads) and the NPHI esters can be electronically tuned for improved yields. The ligand $^{t\text{-Bu}}$BpyCam^{CN} is commercially available, or can be made in 3 steps from dtbbpy. Using a zinc-packed bed, the



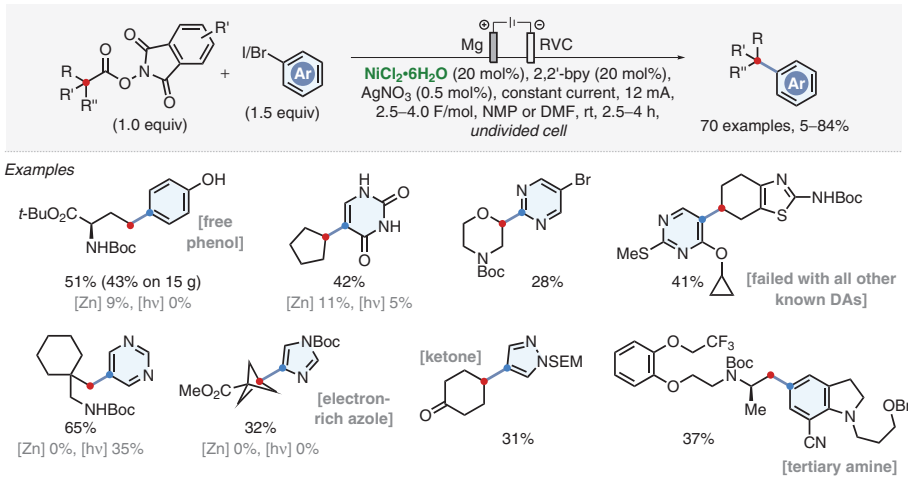
Scheme 4 Phthalimide used as a key additive to increase the efficiency of a decarboxylative metallaphotoredox reaction between carboxylic acids and aryl bromides



Scheme 5 Nickel-catalysed, reductive coupling of a variety of strained ring NHPI esters with (hetero)aryl halides

reaction could also be scaled up in continuous flow with a 45 min residence time (Scheme 5). Similar decarboxylative XEC reactions with strained carbo- or heterocycles have also recently been described, including for cyclopropylamine[32] and azetidine[33] NHPI esters, greatly expanding the 3D chemical space that is accessible using XEC reactions.

One general limitation of decarboxylative, reductive C(sp^3)–C(sp^2) cross-coupling is that electron-rich (hetero)aryl halides tend to be either challenging or wholly unreactive, regardless of any sensitive functionality. Moreover, the redox active esters can be prone to unproductive N–O bond heterolysis if catalytic turnover is inefficient, or the resultant alkyl radicals can undergo H-atom abstraction or dimerisation pathways. To overcome these limitations, the Baran group have developed a highly robust electrocatalytic protocol for decarboxylative arylation of redox-active esters (isolated or *in situ* generated) with (hetero)aryl halides (Scheme 6).[34] The crucial advance was inclusion of a substoichiometric silver nitrate ($AgNO_3$) additive, which leads to *in situ* deposited Ag nanoparticles (AgNPs) on the electrode surface.[35] These AgNPs play three key roles: (1) improving catalyst lifetime, (2) minimising background decomposition of the redox active ester, and most importantly, (3) lowering the required overpotential, which leads to greatly expanded functional group tolerance. The optimised protocol enables reactions to be carried out open to the air, using technical-grade solvents, and with a simple commercial potentiostat. Both parallel synthesis (mg scale) and recirculating flow (dg scale) was presented. Notably, benchmarking by the authors against several state-of-the-art methods, including metallaphotoredox-catalysed, phthalimide-mediated decarboxylative arylation (Scheme 4),[30] indicated that the Ag-Ni electrocatalytic protocol appears to have some complementarity in scope.

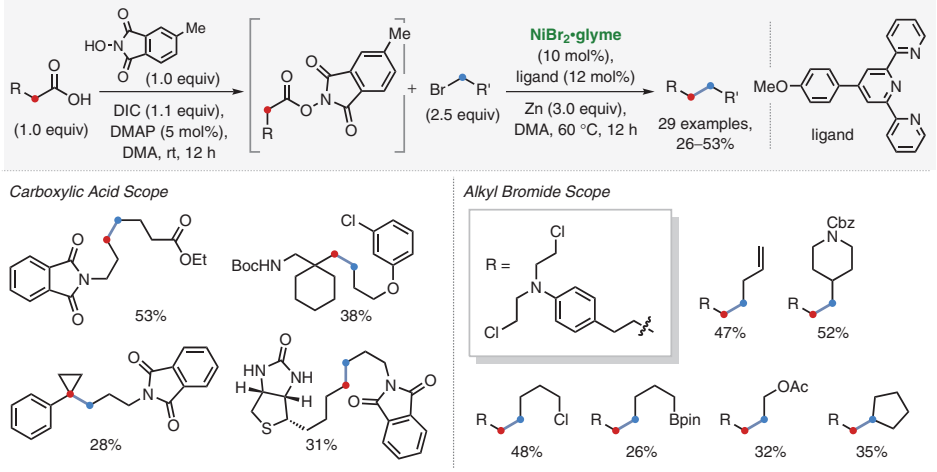


Scheme 6 Electrocatalytic decarboxylative (hetero)arylation of redox-active esters using 1°, 2°, and 3° alkyl carboxylic acids

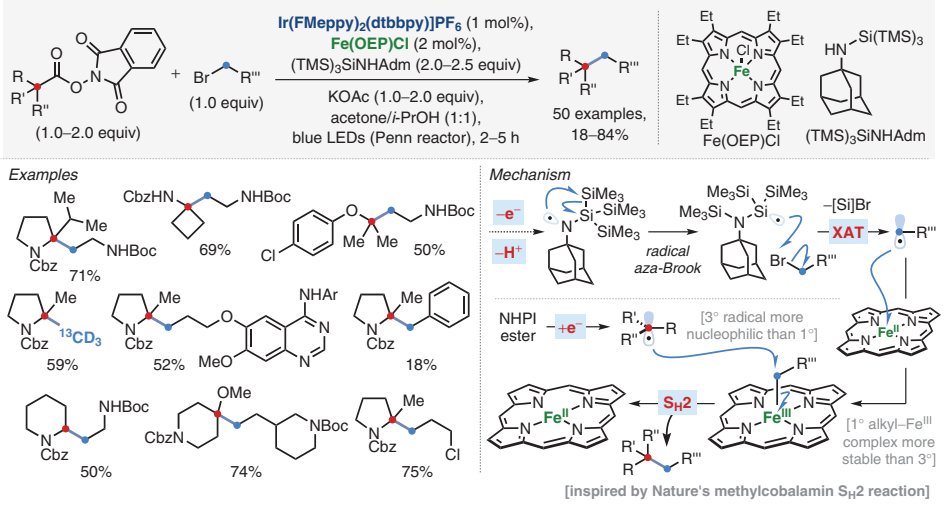
3 sp^3–sp^3 Cross-Coupling of Carboxylic Acids with Aliphatic Bromides

Decarboxylative C(sp^3)–C(sp^3) cross-coupling of alkyl carboxylic acids with unactivated alkyl bromides was reported by the MacMillan group in 2016, using a combination of photoredox and nickel catalysis.[36] In a recent and complementary advance, Weix and Kang have disclosed a Ni-catalysed, light-free reductive coupling of *in situ* generated alkyl NHPI esters with unactivated alkyl bromides that is effective for a variety of 1°/1° C(sp^3)–C(sp^3) linkages, albeit with relatively modest yields (Scheme 7).[37]

Building on their previously reported decarboxylative cross-coupling of 1° and 2° alkyl carboxylic acids with alkyl bromides,[34] the MacMillan group have now developed a photoredox-catalysed, reductive cross-coupling of 3° carboxylic acids (as redox-active NHPI esters) with 1° alkyl bromides.[38] By leveraging silyl radical mediated X-atom transfer (XAT) to activate the alkyl bromides using a $(TMS)_3SiNHAdm$ reductant, in combination with an iron(III) porphyrin complex, a wide range of tertiary and quaternary sp^3 carbon centres could be constructed (Scheme 8). The selectivity of the reaction for cross-coupling, as opposed to homocoupling of either electrophile, has its origins in a 'radical sorting' mechanism featuring a bio-inspired S_H2 attack of the 3° alkyl radical on a 1° alkyl–Fe(III) species to forge the new C–C bond. The higher stability of the 1° alkyl Fe(III) species [as opposed to the more sterically encumbered 3° alkyl–Fe(III) complex], as well as the higher nucleophilicity of 3° relative to 1° alkyl radicals, is responsible for the high levels of cross-selectivity.



Scheme 7 Nickel-catalysed, reductive coupling of *in situ* generated alkyl NHPI esters with unactivated alkyl bromides

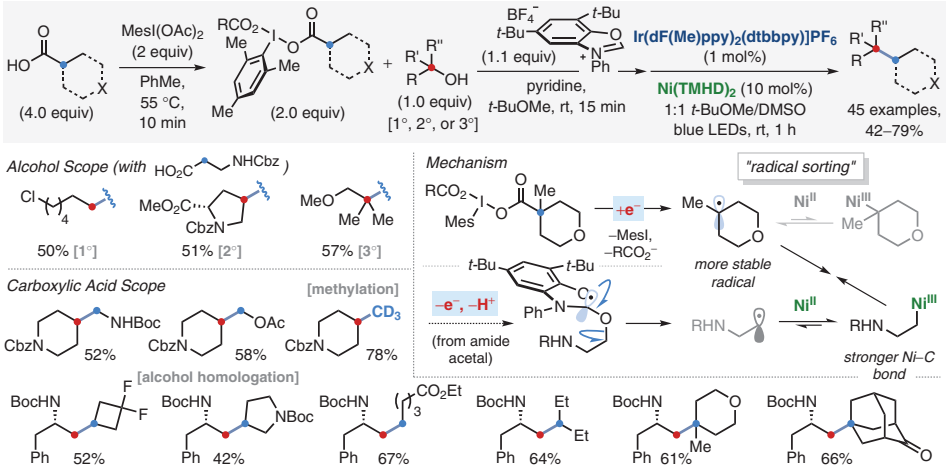


Scheme 8 Reductive cross-coupling of 3° alkyl redox-active NHPI esters with 1° alkyl bromides *via* a 'radical sorting' mechanism that features an S_H2 reaction

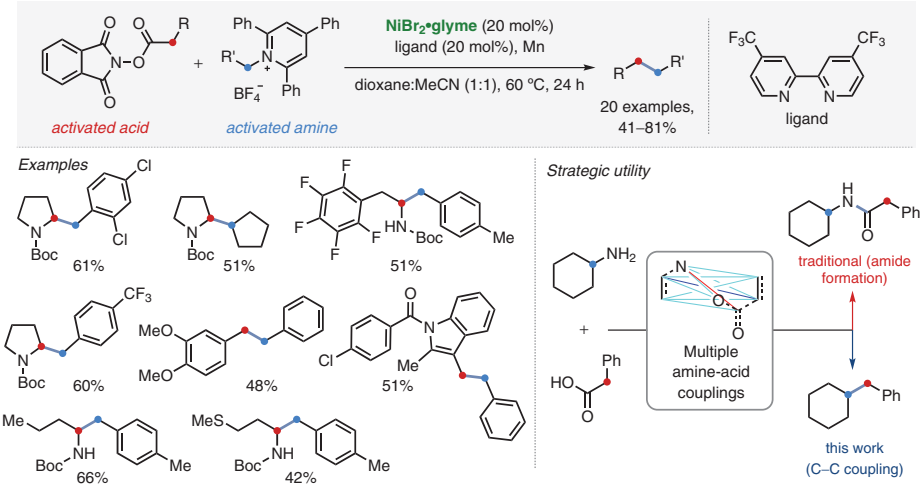
4 sp^3–sp^3 Cross-Coupling of Carboxylic Acids with Aliphatic Alcohols and Amines

The much lower availability of alkyl halides, relative to more abundant alkyl substrates bearing 'native' functionality such as alcohols or amines, has motivated the development of cross-coupling reactions able to utilise the latter substrates directly. In this regard, the MacMillan group have developed an C(sp^3)–C(sp^3) cross-coupling of alkyl carboxylic acids with aliphatic alcohols, by harnessing Ni-metallaphotoredox catalysis (Scheme 9).[39] Pre-activation of both coupling partners is necessary: the carboxylic acid component is converted into a redox-active ester (RAE) species by reaction with the hypervalent iodine(III) reagent MesI(OAc)$_2$, and the alcohol is activated as an amide acetal by reaction with an azolium salt reagent. Whilst these pre-activations do diminish the atom economy of the process, this is less of a concern for small-scale library synthesis. Moreover, both of these manipulations can be carried out *in situ*, which greatly increases the practical appeal of the method. The cross-selectivity of the coupling reaction is again dependent on a 'radical sorting' phenomenon (c.f. Scheme 8), with the more nucleophilic 2°/3° alkyl radical species selectively capturing the Ni(III) intermediate bearing a 1° alkyl group (i.e., stronger Ni–C bond). On this basis, it is possible to use *either* the carboxylic acid or the alcohol as the 2°/3° alkyl component, and the reaction will maintain cross-selectivity provided that the other coupling partner is 1° alkyl.

In a complementary report, Cernak and Zhang have described a deaminative, decarboxylative coupling of aliphatic primary amines with alkyl carboxylic acids. Pre-activation of the amines as Katritzky pyridinium salts, and the carboxylic acids as redox-active (NHPI) esters, was followed by a reductive Ni-catalysed cross-coupling to give C(sp^3)–C(sp^3) coupled products (Scheme 10).[40] Reaction optimisation was



Scheme 9 Nickel-metallaphotoredox-catalysed decarboxylative alkylation of alkyl carboxylic acids using aliphatic alcohols as coupling partners



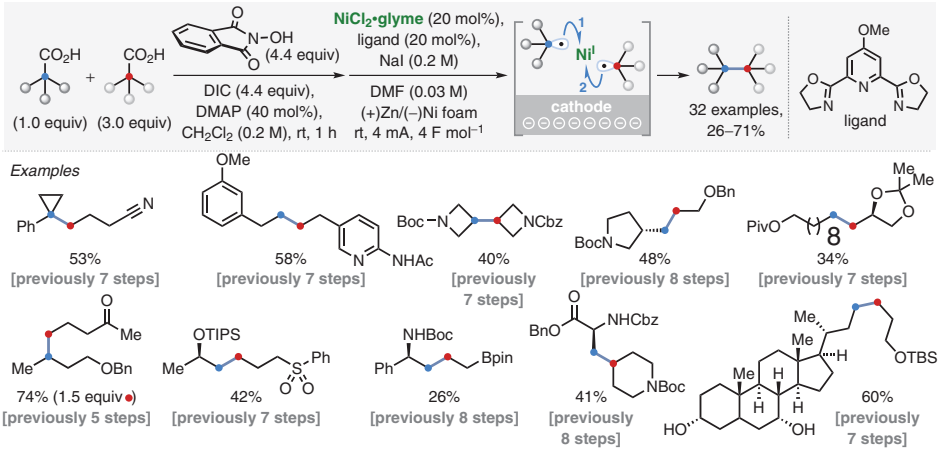
Scheme 10 Nickel-catalysed decarboxylative alkylation of alkyl carboxylic acids using amines pre-activated as Katritzky pyridinium salts as coupling partners

achieved by miniaturised high-throughput experimentation studies; 1392 datapoints were obtained, where >1000 gave no coupling product whatsoever. Variables including order of addition, use of binary solvent systems, and identity of the ligand all played crucial roles in this transformation. Both 1° and 2° alkyl carboxylic acids and amines could be used as substrates, but no 3° alkyl examples were reported. This coupling process is strategically notable from a library synthesis perspective, because it uses the same starting materials as a conventional amide bond formation, and yet allows for access to a completely distinct region of chemical space.

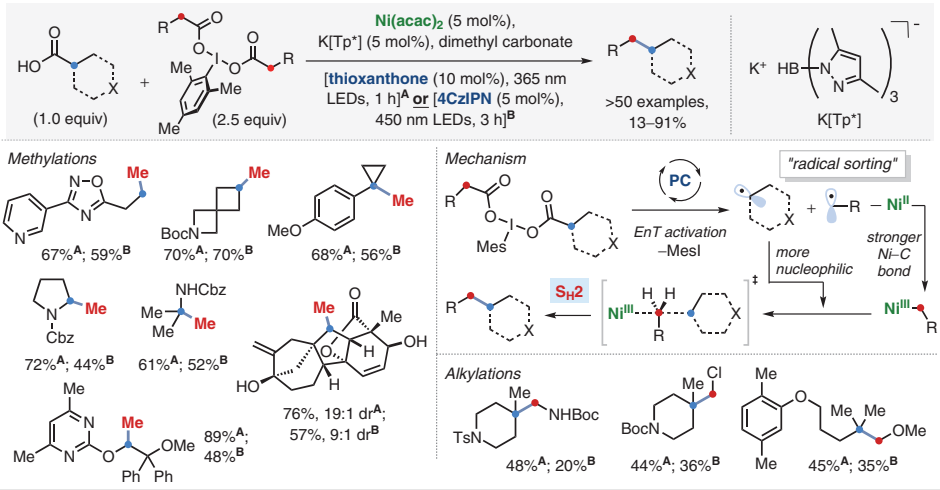
5 Doubly Decarboxylative sp^3–sp^3 Cross-Coupling of Carboxylic Acids

In addition to the aforementioned use of alcohols/amines as abundant coupling partners, it is now also possible to cross-couple two *different* alkyl carboxylic acids. Early examples of such 'doubly decarboxylative' cross-coupling can be found in Kolbe's seminal work on anodic coupling of carboxylic acids,[8] but this protocol was very limited in its scope, and has found no general application in synthesis. In a contemporary reimagining of this reaction, the Baran group have reported a polarity-inverted analogue of Kolbe's classic transformation, based instead on cathodic reduction. Thus, a doubly decarboxylative sp^3-sp^3 cross-coupling of two different alkyl carboxylic acids, each pre-activated as redox-active esters (RAEs), can be carried out at a Ni foam cathode (Scheme 11).[41] Selectivity is achieved by utilising a 3-fold excess of the more available acid (or 1.5 equiv for 2° acyclic acids or β,β-*gem*-disubstituted acids). Despite a near statistical homo/heterocoupling ratio, the protocol is nevertheless an attractive alternative to previous multistep syntheses. Surprisingly, the process only appears to work electrochemically, suggesting that a fine balance is needed between radical generation from the two RAEs and C–C bond formation processes catalysed by Ni. The precise role of the nickel catalyst is currently unclear, and it may be operating in an organometallic catalytic cycle [i.e., C–C bond formation from the coordination sphere of a Ni(III) dialkyl intermediate] or simply as a redox mediator for RAE reduction, with the C–C bonds formed by radical–radical combination processes. In a related contribution, the Roberts group have shown that photocatalytic reductive homocoupling of NHPI esters is possible to give homocoupled bibenzyl products, along with four examples of cross-coupled products in moderate yield.[42]

The MacMillan group have reported a complementary doubly decarboxylative C(sp^3)–C(sp^3) cross-coupling of alkyl carboxylic acids, based on visible-light photocatalysis and nickel catalysis (Scheme 12).[43] The less valuable acid partner requires pre-activation as a di(acyloxy)iodine(III) species Mesl(O_2CR)$_2$, and treatment of the limiting (more valuable) carboxylic acid with an excess of the former species generates a mixture of homo- and heteroleptic I(III) carboxylates. Irrespective of the precise speciation, the weak I–O bonds of these hypervalent iodine species are then homolysed by energy transfer (EnT) activation from the excited photocatalyst (^{3}PC*), to give alkyl radicals with concomitant loss of CO_2. These intermediates then enter a 'radical sorting' process[38,39] with a Ni(II) scorpionate complex, whereby methyl or 1° alkyl radicals are sequestered selectively by Ni(II) (on account of their stronger Ni–C bonds), and the persistent Ni(III)–alkyl complex is itself selectively intercepted by (more nucleophilic) 2°/3° alkyl radicals. The mechanism of C–C bond formation at the Ni(III) centre is proposed to occur *via* an unusual bimolecular homolytic substitution (S_H2) mechanism, as opposed to inner sphere reductive elimination. By using commercially available Mesl(OAc)$_2$ as the hypervalent iodine reagent, a decarboxylative methylation reaction of alkyl carboxylic acids can be achieved, and other valuable C–C bond formations



Scheme 11 Doubly decarboxylative, electroreductive sp^3-sp^3 cross-coupling between NHPI-activated alkyl carboxylic acids using a Ni-foam cathode



Scheme 12 Doubly decarboxylative sp^3-sp^3 cross-coupling between iodine(III)-activated alkyl carboxylic acids using photocatalysis and Ni catalysis

such as (amino)methylation and (chloro)methylation can also be executed. The authors also showcase the value of the method for late-stage methylation of a range of complex molecules, including pharmaceuticals, as well as installation of ^{13}C labels.

6 Decarboxylative C–C Bond Formation from (Hetero)aryl Carboxylic Acids

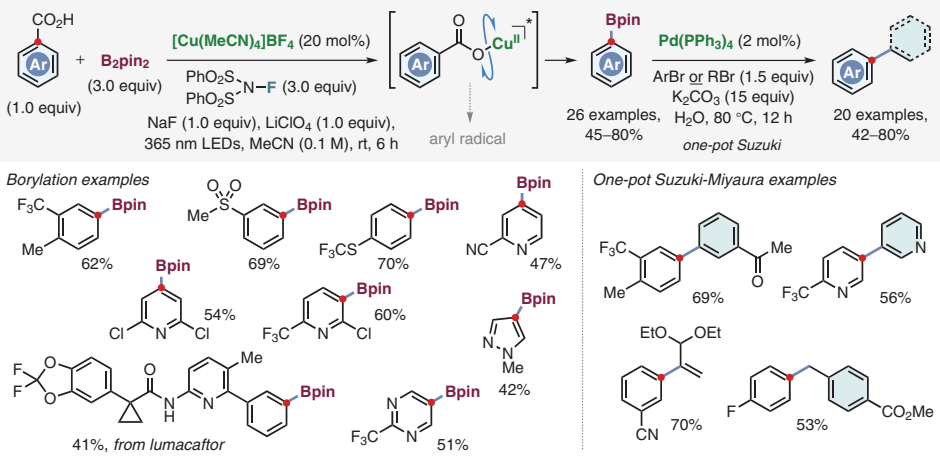
The use of (hetero)aryl carboxylic acids in radical, decarboxylative C–C bond formation has been hampered by the slow decarboxylation of aroyloxyl radicals, and this has necessitated harsh conditions and/or the presence of *ortho*-substituents to outcompete other undesired reactions (e.g., HAT, back-electron transfer, arene addition).[6m,v,44–46] Ligand-to-metal charge transfer (LMCT) is fast emerging as a general strategy for generation of radical intermediates from metal coordination complexes, and has previously been applied to alkyl radical formation from aliphatic carboxylates.[47] Aryl radicals can now also be generated *via* LMCT of aryl copper(II) carboxylates, either stoichiometrically[48] or catalytically[49] in copper, and this has been leveraged in decarboxylative aromatic halogenation reactions. The MacMillan group have recently extended this concept to the radical, decarboxylative borylation[50] of aryl carboxylic acids using a copper catalyst.[51] The copper(II) carboxylates that are formed *in situ* undergo photoinduced LMCT at 365 nm to afford aroyloxyl radicals that can decarboxylate to the desired aryl radicals. Subsequent capture with B_2pin_2 (complexed with NaF and $LiClO_4$) gives the corresponding boronic esters. To render the process catalytic in copper, NFSI was employed as a stoichiometric reoxidant. The crude boronic acids could be immediately engaged in Suzuki–Miyaura coupling to give arylated, alkenylated, or alkylated products, such that the telescoped process can be considered a one-pot, decarboxylative C–C bond formation directly from (hetero)aryl carboxylic acids (Scheme 13).

Given the ubiquity of the latter starting materials, this protocol will undoubtedly find widespread use in organic synthesis, including for the generation of compound libraries.

7 Conclusions

Decarboxylative, radical-based C–C bond formations have now advanced to the stage where synthetic chemists can consider these disconnections for almost any type of C–C bond in a target molecule. The discovery of new additives for Ni-catalysed decarboxylative arylations (i.e., phthalimide in metalla-photoredox catalysis or $AgNO_3$ in electrochemical reactions) has expanded the generality of these powerful reactions to include previously challenging substrates (e.g., unactivated carboxylic acids, nitrogen-rich heteroaromatics, polar functionality). Strained ring carbocycles (e.g., cyclopropanes, bicyclopentanes, bicyclohexanes) and heterocycles (e.g., oxetanes, azetidines) can now readily be appended to (hetero)aromatic cores by exploiting state-of-the-art decarboxylative cross-electrophile couplings (XECs).

Alkyl–alkyl cross-couplings, once considered the most difficult class of catalytic C–C bond-formations, can now be executed straightforwardly from carboxylic acids with a range of abundant coupling partners, including alkyl bromides, aliphatic alcohols and amines, or even other alkyl carboxylic acids. Quaternary carbon centres are fast becoming a solved problem for cross-coupling, with the deployment of β-ketonate ligands on Ni or the exploitation of unusual bimolecular homolytic substitution (S_H2) mechanisms for C–C bond formation from transition metal alkyl



Scheme 13 Decarboxylative borylation of aryl carboxylic acids *via* LMCT of Cu(II) carboxylates, followed by Suzuki–Miyaura coupling

intermediates. The concept of 'radical sorting' by transition metal complexes bearing porphyrin or scorpionate ligands has been advanced as a ground-breaking new strategy for radical–radical cross-coupling, without the requirement for one of the radicals to be persistent.

Finally, the use of ligand-to-metal charge transfer (LMCT) as an activation concept has created new opportunities to exploit abundant (hetero)aryl carboxylic acids as radical precursors for C–C bond formation, albeit indirectly at the present time (i.e., *via* borylated intermediates).

Despite the aforementioned breakthroughs, there is still ample opportunity for continued innovation in the area of decarboxylative cross-coupling. Pre-activation of carboxylic acids as redox-active esters or di(acyloxy)iodine(III) species inevitably generates significant waste streams on larger scales, as does the pre-activation of alcohols or amines as coupling partners. This is clearly of concern for kilogram- or tonne-scale applications (e.g., drug manufacture) but it can also complicate the automation of microscale reactions for library synthesis. The control of absolute or relative stereochemistry in decarboxylative couplings with C(sp^3) partners is an ongoing challenge, but impressive advances in enantioconvergent cross-coupling continue to be made.

Whatever the rate of further progress, decarboxylative cross-couplings are fast becoming an established and reliable transformation in the organic chemist's synthetic toolbox.

Conflict of Interest

The authors declare no conflict of interest.

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References

(1) For a review of carboxylic acids as building blocks in catalytic asymmetric reactions, see: Majumdar, N. *ACS Catal.* **2022**, *12*, 8291.
(2) For a review of large-scale amidations in process chemistry, see: Magano, J. *Org. Process Res. Dev.* **2022**, *26*, 1562.
(3) (a) For a review of partial reductions of carboxylic acids and their derivatives to aldehydes, see: Yang, Z. *Org. Chem. Front.* **2022**, *9*, 3908. (b) For a recent catalytic reduction of carboxylic acids to alcohols, see: Stoll, E. L.; Barber, T.; Hirst, D. J.; Denton, R. M. *Chem. Commun.* **2022**, *58*, 3509.
(4) For a review of the Curtius rearrangement, see: Ghosh, A. K.; Brindisi, M.; Sarkar, A. *ChemMedChem* **2018**, *13*, 2351.
(5) Dutta, S.; Bhattacharya, T.; Geffers, F. J.; Bürger, M.; Maiti, D.; Werz, D. B. *Chem. Sci.* **2022**, *13*, 2551.
(6) For reviews of decarboxylative cross-coupling, see: (a) Zhu, X.; Fu, H. *Chem. Commun.* **2021**, *57*, 9656. (b) Karmakar, S.; Silamkoti, A.; Meanwell, N. A.; Mathur, A.; Gupta, A. K. *Adv. Synth. Catal.* **2021**, *363*, 3693. (c) Parida, S. K.; Mandal, T.; Das, S.; Hota, S. K.; De Sarkar, S.; Murarka, S. *ACS Catal.* **2021**, *11*, 1640. (d) Chen, H.; Liu, Y. A.; Liao, X. *Synthesis* **2021**, *53*, 1.

(e) Moon, P. J.; Lundgren, R. J. *ACS Catal.* **2020**, *10*, 1742. (f) Penteado, F.; Lopes, E. F.; Alves, D.; Perin, G.; Jacob, R. G.; Lenardão, E. J. *Chem. Rev.* **2019**, *119*, 7113. (g) Rahman, M.; Mukherjee, A.; Kovalev, I. S.; Kopchuk, D. S.; Zyryanov, G. V.; Tsurkan, M. V.; Majee, A.; Ranu, B. C.; Charushin, V. N.; Chupakhin, O. N.; Santra, S. *Adv. Synth. Catal.* **2019**, *361*, 2161. (h) Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735. (i) Schwarz, J.; König, B. *Green Chem.* **2018**, *20*, 323. (j) Perry, G. J. P.; Larrosa, I. *Eur. J. Org. Chem.* **2017**, 3517. (k) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864. (l) Jin, Y.; Fu, H. *Asian J. Org. Chem.* **2017**, *6*, 368. (m) Patra, T.; Maiti, D. *Chem. Eur. J.* **2017**, *23*, 7382. (n) Guo, L.-N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380. (o) Xuan, J.; Zhang, Z.-G.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15632. (p) Miao, J.; Ge, H. *Synlett* **2014**, *25*, 911. (q) Wang, Z.-L. *Adv. Synth. Catal.* **2013**, *355*, 2745. (r) Park, K.; Lee, S. *RSC Adv.* **2013**, *3*, 14165. (s) Dzik, W. I.; Lange, P. P.; Gooßen, L. J. *Chem. Sci.* **2012**, *3*, 2671. (t) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653. (u) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670. (v) Rodríguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (w) Gooßen, L. J.; Collet, F.; Gooßen, K. *Isr. J. Chem.* **2010**, *50*, 617. (x) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100.

(7) For reviews of decarbonylative cross-coupling, see: (a) Lu, H.; Yu, T.-Y.; Xu, P.-F.; Wei, H. *Chem. Rev.* **2021**, *121*, 365. (b) Wang, Z.; Wang, X.; Nishihara, Y. *Chem. Asian J.* **2020**, *15*, 1234.

(8) Kolbe, H. *Ann. Chem. Pharm.* **1848**, *64*, 339.

(9) For reviews on Barton decarboxylation reactions, see: (a) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675. (b) Saraiva, M. F.; Couri, M. R. C.; Le Hyaric, M.; de Almeida, M. V. *Tetrahedron* **2009**, *65*, 3563. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.

(10) Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340.

(11) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies, 1st ed*; CRC Press: Boca Raton, FL, **2007**.

(12) (a) Mao, R.; Bera, S.; Turla, A. C.; Hu, X. *J. Am. Chem. Soc.* **2021**, *143*, 14667. (b) Na, C. G.; Ravelli, D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2020**, *142*, 44.

(13) Dang, H. T.; Haug, G. C.; Nguyen, V. T.; Vuong, N. T. H.; Arman, H. D.; Larionov, O. V. *ACS Catal.* **2020**, *10*, 11448.

(14) Liang, Y.; Zhang, X.; MacMillan, D. W. C. *Nature* **2018**, *559*, 83.

(15) (a) McClain, E. J.; Wortmana, A. K.; Stephenson, C. R. J. *Chem. Sci.* **2022**, *13*, 12158. (b) McClain, E. J.; Monos, T. M.; Mori, M.; Beatty, J. W.; Stephenson, C. R. J. *ACS Catal.* **2020**, *10*, 12636. (c) Chen, H.; Liao, X. *Tetrahedron* **2019**, *75*, 4186. (d) Chen, H.; Sun, S.; Liao, X. *Org. Lett.* **2019**, *21*, 3625. (e) Chen, H.; Hu, L.; Ji, W.; Yao, L.; Liao, X. *ACS Catal.* **2018**, *8*, 10479. (f) McAtee, R. C.; Beatty, J. W.; McAtee, C. C.; Stephenson, C. R. J. *Org. Lett.* **2018**, *20*, 3491. (g) Beatty, J. W.; Douglas, J. J.; Miller, R.; McAtee, R. C.; Cole, K. P.; Stephenson, C. R. J. *Chem* **2016**, *1*, 456. (h) Beatty, J. W.; Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *Nat. Commun.* **2015**, *6*, 7919.

(16) (a) Kammer, L. M.; Badir, S. O.; Hu, R.-M.; Molander, G. A. *Chem. Sci.* **2021**, *12*, 5450. (b) Zheng, C.; Wang, G.-Z.; Shang, R. *Adv. Synth. Catal.* **2019**, *361*, 4500.

(17) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

(18) (a) Chen, T.-G.; Zhang, H.; Mykhailiuk, P. K.; Merchant, R. R.; Smith, C. A.; Qin, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2019**, *58*, 2454. (b) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174. (c) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132. (d) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801.

(19) (a) Li, H.; Breen, C. P.; Seo, H.; Jamison, T. F.; Fang, Y.-Q.; Bio, M. M. *Org. Lett.* **2018**, *20*, 1338. (b) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016.

(20) Zhang, T.; Wang, N.-X.; Xing, Y. *J. Org. Chem.* **2018**, *83*, 7559.

(21) Parsaee, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. *Nat. Rev. Chem.* **2021**, *5*, 486.

(22) (a) Kitcatt, D. M.; Nicolle, S.; Lee, A.-L. *Chem. Soc. Rev.* **2022**, *51*, 1415. (b) Kanegusuku, A. L. G.; Roizen, J. L. *Angew. Chem. Int. Ed.* **2021**, *60*, 21116.

(23) For a representative example of addition to aldehydes see: Xiao, J.; Li, Z.; Montgomery, J. *J. Am. Chem. Soc.* **2021**, *143*, 21234.

(24) Proctor, R. S. J.; Phipps, R. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 13666.

(25) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485.

(26) (a) Gao, Y.; Hill, D. E.; Hao, W.; McNicholas, B. J.; Vantourout, J. C.; Hadt, R. G.; Reisman, S. E.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2021**, *143*, 9478. (b) Koyanagi, T.; Herath, A.; Chong, A.; Ratnikov, M.; Valiere, A.; Chang, J.; Molteni, V.; Loren, J. *Org. Lett.* **2019**, *21*, 816.

(27) Li, Q. Y.; Gockel, S. N.; Lutovsky, G. A.; DeGlopper, K. S.; Baldwin, N. J.; Bundesmann, M. W.; Tucker, J. W.; Bagley, S. W.; Yoon, T. P. *Nat. Chem.* **2022**, *14*, 94.

(28) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, *47*, 7190.

(29) (a) Tan, G.; Das, M.; Keum, H.; Bellotti, P.; Daniliuc, C.; Glorius, F. *Nat. Chem.* **2022**, *14*, 1174. (b) Patra, T.; Bellotti, P.; Strieth-Kalthoff, F.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 3172. (c) Patra, T.; Mukherjee, S.; Ma, J.; Strieth-Kalthoff, F.; Glorius, F. *Angew. Chem. Int. Ed.* **2019**, *58*, 10514.

(30) Kullmer, C. N. P.; Kautzky, J. A.; Krska, S. W.; Nowak, T.; Dreher, S. D.; MacMillan, D. W. C. *Science* **2022**, *376*, 532.

(31) Salgueiro, D. C.; Chi, B. K.; Guzei, I. A.; García-Reynaga, P.; Weix, D. J. *Angew. Chem. Int. Ed.* **2022**, *61*, e202205673.

(32) West, M. S.; Gabbey, A. L.; Huestis, M. P.; Rousseaux, S. A. L. *Org. Lett.* **2022**, *24*, 8441.

(33) Brewster, J. T. II.; Randall, S. D.; Kowalski, J.; Cruz, C.; Shoemaker, R.; Tarlton, E.; Hinklin, R. J. *Org. Lett.* **2022**, *24*, 9123.

(34) Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blasczak, V. D.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.; Vokits, B.; Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S. *J. Am. Chem. Soc.* **2022**, *144*, 17709.

(35) Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. L.; Baran, P. S. *Science* **2022**, *375*, 745.

(36) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322.

(37) Kang, K.; Weix, D. J. *Org. Lett.* **2022**, *24*, 2853.

(38) Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcázar, J.; MacMillan, D. W. C. *Science* **2021**, *374*, 1258.

(39) Sakai, H. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6185.

(40) Zhang, Z.; Cernak, T. *Angew. Chem. Int. Ed.* **2021**, *60*, 27293.
(41) Zhang, B.; Gao, Y.; Hioki, Y.; Oderinde, M. S.; Qiao, J. X.; Rodriguez, K. X.; Zhang, H.-J.; Kawamata, Y.; Baran, P. S. *Nature* **2022**, *606*, 313.
(42) Seong, C. M.; Ansel, A. Q.; Roberts, C. C. *J. Org. Chem.* **2023**, *88*, 3935.
(43) Tsymbal, A. V.; Bizzini, L. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 21278.
(44) Hoover, J. M. *Comments Inorg. Chem.* **2017**, *37*, 169.
(45) Varenikov, A.; Shapiro, E.; Gandelman, M. *Chem. Rev.* **2021**, *121*, 412.
(46) For a general review of single-electron aromatic decarboxylation, see: Hu, X.-Q.; Liu, Z.-K.; Hou, Y.-X.; Gao, Y. *iScience* **2020**, *23*, 101266.
(47) Abderrazak, Y.; Bhattacharyya, A.; Reiser, O. *Angew. Chem. Int. Ed.* **2021**, *60*, 21100.
(48) (a) Xu, P.; López-Rojas, P.; Ritter, T. *J. Am. Chem. Soc.* **2021**, *143*, 5349. (b) Su, W.; Xu, P.; Ritter, T. *Angew. Chem. Int. Ed.* **2021**, *60*, 24012.
(49) Chen, T. Q.; Pedersen, P. S.; Dow, N. W.; Fayad, R.; Hauke, C. E.; Rosko, M. C.; Danilov, E. O.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; Castellano, F. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 8296.
(50) For other examples of decarboxylative borylation of aromatic carboxylic acids, see: (a) Wei, Q.; Lee, Y.; Liang, W.; Chen, X.; Mu, B.-s.; Cui, X.-Y.; Wu, W.; Bai, S.; Liu, Z. *Nat. Commun.* **2022**, *13*, 7112. (b) Deng, X.; Guo, J.; Zhang, X.; Wang, X.; Su, W. *Angew. Chem. Int. Ed.* **2021**, *60*, 24510.
(51) Dow, N. W.; Pedersen, P. S.; Chen, T. Q.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2022**, *144*, 6163.