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Communication

Decarboxylative Borylation and Cross-Coupling of (Hetero)aryl Acids Enabled by Copper Charge Transfer Catalysis

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ABSTRACT: We report a copper-catalyzed strategy for arylboronic ester synthesis that exploits photoinduced ligand-to-metal charge transfer (LMCT) to convert (hetero)aryl acids into aryl radicals amenable to ambient-temperature borylation. This near-UV process occurs under mild conditions, requires no prefunctionalization of the native acid, and operates broadly across diverse aryl, heteroaryl, and pharmaceutical substrates. We also report a one-pot procedure for decarboxylative cross-coupling that merges catalytic LMCT borylation and palladium-catalyzed Suzuki−Miyaura arylation, vinylation, or alkylation with organobromides to access a range of value-added products. The utility of these protocols is highlighted through the development of a heteroselective double-decarboxylative $C(sp^2)-C(sp^2)$ coupling sequence, pairing copper-catalyzed LMCT borylation and halogenation processes of two distinct acids (including pharmaceutical substrates) with subsequent Suzuki−Miyaura cross-coupling.

Cross-coupling reactions, particularly those between halide electrophiles and organometallic nucleophiles under transition metal catalysis, are widely used to produce complex molecules of value within academic and industrial research.[1] Among the possible organometallic cross-coupling partners, boronic acids and related ester derivatives are particularly desirable, partly due to their nontoxicity and bench stability.[2] Beyond advantages in ease of handling, organoboron reagents offer robust reactivity across numerous reaction types, including allylation,[3] conjugate addition,[4] Chan−Evans−Lam heteroatom arylation,[5] and Suzuki−Miyaura C−C coupling (Figure 1).[6] In particular, Suzuki−Miyaura cross-coupling remains among the most widely employed chemical reactions across medicinal chemistry,[7] underscoring the relevance of organoboron nucleophiles in the discovery of new medicines and other molecules of societal value.[1,6] Given these applications, the expedient production of organoboron compounds and their subsequent deployment in cross-coupling reactions remain of paramount importance to the synthetic community.

Despite modern developments in the preparation of arylboronic esters,[8,9] these valuable reagents are most conventionally generated either via addition of arylmetal nucleophiles to borate electrophiles[10] or through palladium-catalyzed Miyaura reactions between aryl halides and diboron compounds (Figure 1).[11] While versatile, both methods require synthetically prepared arene precursors, thereby lengthening step counts and lowering atom economy when converting from arene biomass to organoboron products.[12] Alternatively, approaches that produce boronic esters from naturally occurring precursors, such as Ir-catalyzed C−H borylation of arenes,[13] are more sustainable and efficient. When considering potential feedstocks, aryl carboxylic acids emerge as highly desirable substrates for regiospecific borylation, given their abundance and structural diversity in nature, commercial availability, and late-stage accessibility via oxidation or hydrolysis (Figure 1).[14] However, current approaches to aromatic decarboxylative borylation suffer from challenges associated with inducing CO_2 extrusion.[14,15] The prohibitively slow thermal decarboxylation of aryl acids often requires high temperatures, harsh reagents, or the presence of a destabilizing *ortho*-substituent,[14−20] conditions that generally preclude subsequent borylation steps. Moreover, despite the broad utility of photoredox catalysis for organic synthesis,[21,22] single-electron transfer decarboxylation (via aroyloxyl radicals) often suffers from undesired hydrogen atom transfer, back-electron transfer, and arene addition pathways that compete with sluggish decarboxylation steps.[23,24] Although photoredox and decarbonylative processes have occasionally been deployed to prepare borylated aryl acid derivatives, these protocols can require forcing conditions, specific ligands, or acid prefunctionalization and are sparingly applied to medicinally relevant, electron-deficient heteroaryl substrates.[25−28] Additionally, such technologies are infrequently merged with organohalide cross-coupling in single-vessel sequences, an advance that would enable direct feedstock-to-complex molecule synthesis while circumventing purification and handling of organoboron intermediates.[29] Overall, these outstanding challenges could be addressed using new mechanistic approaches to aromatic decarboxylative borylation.

Ligand-to-metal charge transfer (LMCT), a procedure for generating radical intermediates through photonic excitation of

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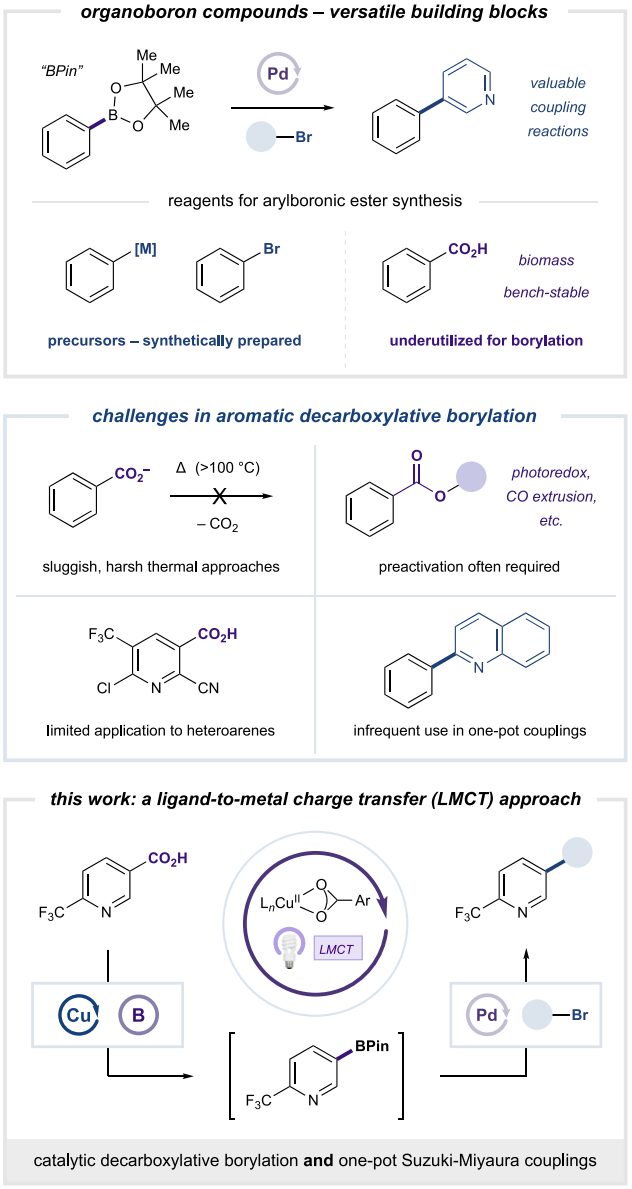

Figure 1. Decarboxylative borylation and C−C cross-coupling of (hetero)aryl acids via Cu-LMCT catalysis.

coordination complexes,[30] has emerged as a versatile platform for engaging alcohols,[31] halides,[32] and aliphatic carboxylates[33] as substrates in open-shell synthetic chemistry. Recently, LMCT activation was demonstrated to produce aryl radicals from aryl acids via near-UV excitation of Cu(II) carboxylates and subsequent CO_2 extrusion.[34] Notably, our lab also established this ambient-temperature process to be catalytic in copper when paired with turnover-inducing single-electron oxidants, a discovery that was generally applied to aromatic decarboxylative halogenation.[35] Given the extensive precedent for aryl radical borylation using diboron reagents,[9] we anticipated that Cu-LMCT decarboxylation could be a versatile catalytic strategy to access boronic ester adducts from a wide variety of (hetero)aryl acid substrates (Figure 1). Furthermore, the mild conditions of such a reaction should be compatible with reagents typically used for organoboron cross-coupling, thereby permitting single-vessel reaction sequences that transform aryl acids directly to value-added products. Herein, we report the successful design of a copper-catalyzed LMCT decarboxylative borylation platform and its merger with palladium-catalyzed Suzuki−Miyaura coupling for one-pot decarboxylative cross-couplings of diverse (hetero)aryl acids.

On the basis of our recently developed catalytic Cu-LMCT aryl acid decarboxylation,[35] we envisioned a plausible mechanism for decarboxylative borylation, shown in Scheme 1a. Initially, a Cu(I) precatalyst combines with an aryl carboxylate (generated *in situ* via aryl acid deprotonation) and a single-electron oxidant to provide a photoexcitable Cu(II) carboxylate complex. Under near-UV irradiation (365 nm), the complex enters into an excited state capable of intramolecular charge transfer (LMCT) from the carboxylate ligand to the Cu(II) center. This process furnishes a reduced Cu(I) catalyst and an aroyloxyl radical, which can extrude CO_2 to generate the key aryl radical intermediate.[34,35] In principle, this LMCT event could be reversible, allowing the aroyloxyl radical to be deleteriously sequestered by Cu(I) prior to decarboxylation; however, we envisioned that rapid geometric reorganization and ligand exchange of the newly formed Cu(I) complex would outcompete this undesired reverse pathway.[36] Following decarboxylation, the aryl radical can be functionalized according to well-established group transfer mechanisms using an activated metal boronate (generated *in situ* from diboron reagents and metal salt additives) to deliver the arylboronic ester product.[9,37,38] The Cu(I) complex produced by LMCT reduction can then ligate another aryl carboxylate and undergo reoxidation to continue the catalytic cycle.

In optimization studies, summarized in Scheme 1b,c, we investigated the decarboxylative borylation of 4-fluorobenzoic acid. Initial success was achieved using $Cu(MeCN)_4BF_4$ as the copper catalyst, *N*-fluorobenzenesulfonimide (NFSI) as an oxidant, bis(pinacolato)diboron (B_2Pin_2) as the diboron reagent, and the integrated photoreactor (IPR)[39] as a high-intensity light source for 365 nm irradiation. Using MeCN as solvent, this Cu-LMCT combination afforded the desired product **1** in 40% yield (entry 1). Recognizing the established need for anionic activation of the diboron reagent,[9,37] we identified tetrafluoroborate and fluoride salts as key beneficial additives (entries 2 and 3).[40] In particular, substoichiometric amounts of CsF afforded 82% yield of **1** in the presence of higher loadings of B_2Pin_2 and NFSI (entry 4); these results were replicated using 1 equiv of NaF as a nonhygroscopic fluoride source (entry 5). Ultimately, the use of NaF and $LiClO_4$ as tandem additives delivered an optimal yield of 85% (entry 6), providing conditions broadly applicable to both aryl and heteroaryl acids (see Supporting Information (SI) for additional optimization experiments). On the basis of prior evidence for the behavior of diboron reagents in radical borylation,[9,37,40] NaF and $LiClO_4$ most likely serve as MeCN-soluble ion sources required to generate the activated lithium fluoroborate shown in Scheme 1b; in contrast, the poorly soluble LiF salt is suboptimal for this transformation (entry 7). Control reactions (Scheme 1d) are consistent with the proposed LMCT pathway, as copper, oxidant, and light are essential for reactivity (entries 8−10). Near-UV IPR irradiation at maximum intensity is also favored for efficient decarboxylation, as lower-intensity UV Kessil lamps (entry 11) or red-shifted IPR LED sources (entries 12−14), while capable of furnishing product, result in reduced conversion.[41]

With optimized conditions in hand, we next sought to investigate the scope of this transformation with respect to the aryl acid component (Table 1). As an initial example, benzoic

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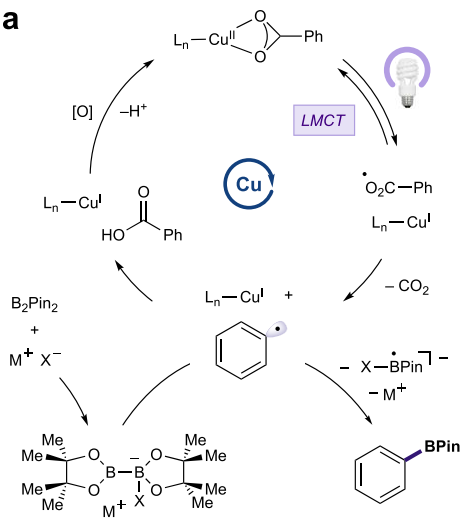
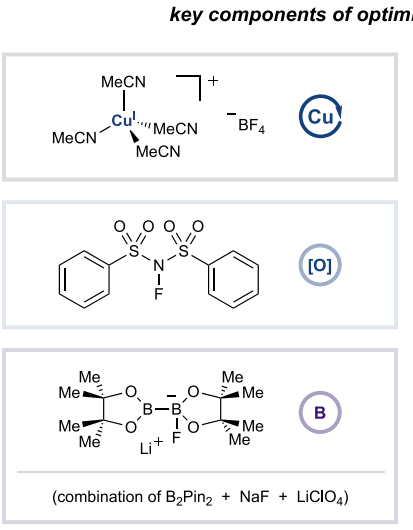
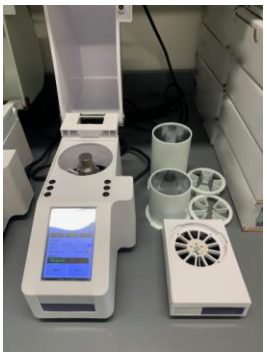
Scheme 1. Development of a Catalytic Cu-LMCT Decarboxylative Borylation Reaction: (a) Plausible Mechanism, (b) Key Components of Optimal Reaction Setup, (c) Summary of Optimization Studies, and (d) Control Reactions for Optimized Conditions

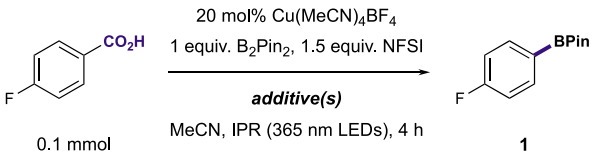






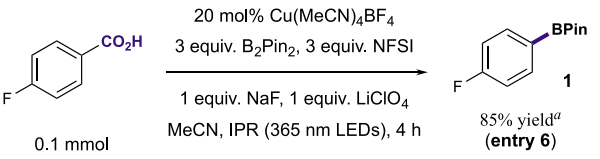
Light source:
Integrated Photoreactor (IPR) with 365 nm LED module

c ***optimization of Cu-catalyzed decarboxylative borylation***



entry	deviation/additive	yield[a]
1	none (no additive)	40%
2	10 equiv. $NaBF_4$ as additive	53%
3	50 mol% CsF as additive	57%
4	**entry 3** with 3 equiv. B_2Pin_2, 3 equiv. NFSI	82%
5	1 equiv. NaF as additive with 3 equiv. B_2Pin_2, 3 equiv. NFSI	84%
6	**entry 5 with 1 equiv. $LiClO_4$ (best for heteroaryl acids)**	**85%**
7	1 equiv. LiF as additive with 3 equiv. B_2Pin_2, 3 equiv. NFSI	53%

d ***control reactions for optimized LMCT conditions***



entry	deviation	yield[a]
8	no copper catalyst	<1%
9	no NFSI oxidant	<1%
10	ambient light only	<1%
11	390 nm Kessil lamps	60%
12	420 nm LEDs (IPR)	39%
13	450 nm LEDs (IPR)	22%
14	450 nm Kessil lamps	<1%

[a]Yields determined by ^{19}F NMR. 0.1 M MeCN used in all cases. See SI for experimental details. B_2Pin_2, bis(pinacolato)diboron; NFSI, *N*-fluorobenzenesulfonimide.

acid was readily borylated (**2**, 65% yield), suggesting that this method does not require electronically or sterically biased substrates to operate effectively. Gratifyingly, halogenated acids containing pharmacophores (**1** and **3**, 80% and 73% yield, respectively) or electrophilic coupling handles (**4**, 77% yield) were readily adopted in this protocol, as were electron-deficient aryl acids bearing nitrile, trifluoromethyl, or ester functionality (**5**–**8**, 55–78% yield). Moreover, acids bearing electron-donating alkyl groups were also broadly competent (**9**–**11**, 62–72% yield), highlighting both the electronic generality of this method and its tolerance for typically labile benzylic motifs. Additionally, *O*- and *S*-heteroatom substituents were effectively introduced around the arene periphery (**12**–**14**, 69–75% yield), and *ortho*-substitution was well-tolerated (**15**, 50% yield).

Encouraged by these results, we then investigated the heteroaryl acid scope, as general approaches to decarboxylative borylation for such medicinally relevant scaffolds remain elusive.[23,26] We were pleased to find that a range of pyridine-derived nicotinic acids were successfully borylated under the standard conditions (**16**–**20**, 45–73% yield), including substrates bearing various substitution patterns and sterically impeding *ortho*-chloro functionality. Other pyridine acid regioisomers, such as isonicotinic acids, also participated effectively in this reaction (**21**–**23**, 47–69% yield). Although the instability of 2-borylated nitrogen aromatics has thus far precluded use of the corresponding acids in this system,[42,43] a pharmaceutically relevant pyrimidine core (**24**, 51% yield) and a five-membered ring pyrazole system (**25**, 42% yield) were found to be competent substrates for LMCT-induced borylation. Furthermore, commercial aryl acid-bearing pharmaceutical agents such as Lumacaftor were readily amenable to borylation (**26**, 41% yield). Altogether, the ability of this Cu-LMCT decarboxylative borylation technology to accommodate an electronically diverse array of *ortho*-, *meta*-, or *para*-

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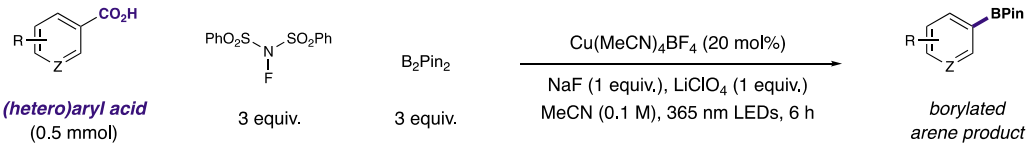
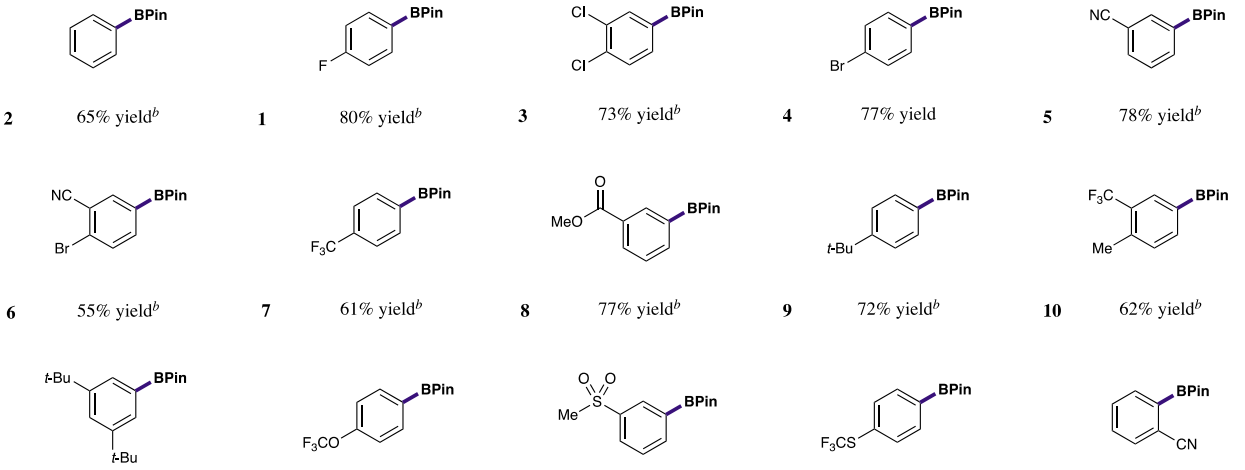
Table 1. (Hetero)aryl Acid Scope for Cu-LMCT Decarboxylative Borylation[a]



aryl carboxylic acids

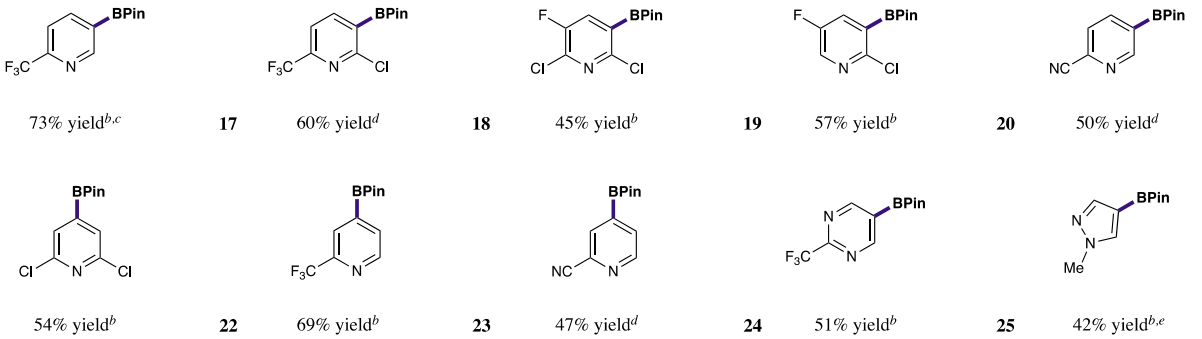


2 65% yield[b] **1** 80% yield[b] **3** 73% yield[b] **4** 77% yield **5** 78% yield[b]

6 55% yield[b] **7** 61% yield[b] **8** 77% yield[b] **9** 72% yield[b] **10** 62% yield[b]

11 65% yield[b] **12** 75% yield[b] **13** 69% yield[b] **14** 70% yield **15** 50% yield[b]

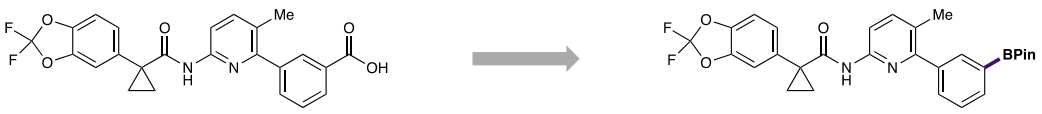
heteroaryl carboxylic acids



16 73% yield[b,c] **17** 60% yield[d] **18** 45% yield[b] **19** 57% yield[b] **20** 50% yield[d]

21 54% yield[b] **22** 69% yield[b] **23** 47% yield[d] **24** 51% yield[b] **25** 42% yield[b,e]

decarboxylative borylation of pharmaceutical agents



Lumacaftor (active ingredient in Orkambi)

26 41% yield[b]

[a]Isolated yields unless otherwise indicated. See SI for experimental details. [b]Yield of corresponding phenol following oxidative workup. [c]$Cu(OTf)_2$ (20 mol %) used as catalyst. [d]Yield determined by ^1H NMR. [e]5 equiv of B_2Pin_2 used; 1 equiv of LiF used instead of NaF/$LiClO_4$.

substituted (hetero)aryl substrates showcases the unique robustness and versatility of this reaction platform.[43]

In an effort to exploit the generality of this LMCT borylation reaction, we next pursued the development of a convenient protocol to directly deploy these arylboronic ester adducts in subsequent reactions, without further isolation. In particular, we envisioned that the mild conditions of our Cu-LMCT process would allow a subsequent cross-coupling step in the same vessel. Given the importance of the Suzuki–Miyaura coupling reaction,[6,7] we targeted the design of a one-pot decarboxylative arylation procedure encompassing sequential LMCT borylation and palladium-catalyzed coupling of the resultant boronic ester with bromide coupling partners.[44,45] Gratifyingly, this borylation/arylation sequence was executed by directly adding Suzuki–Miyaura reagents to the crude borylation mixture following irradiation (Table 2), using $Pd(PPh_3)_4$ as a commercially available palladium catalyst (see SI for optimization studies).

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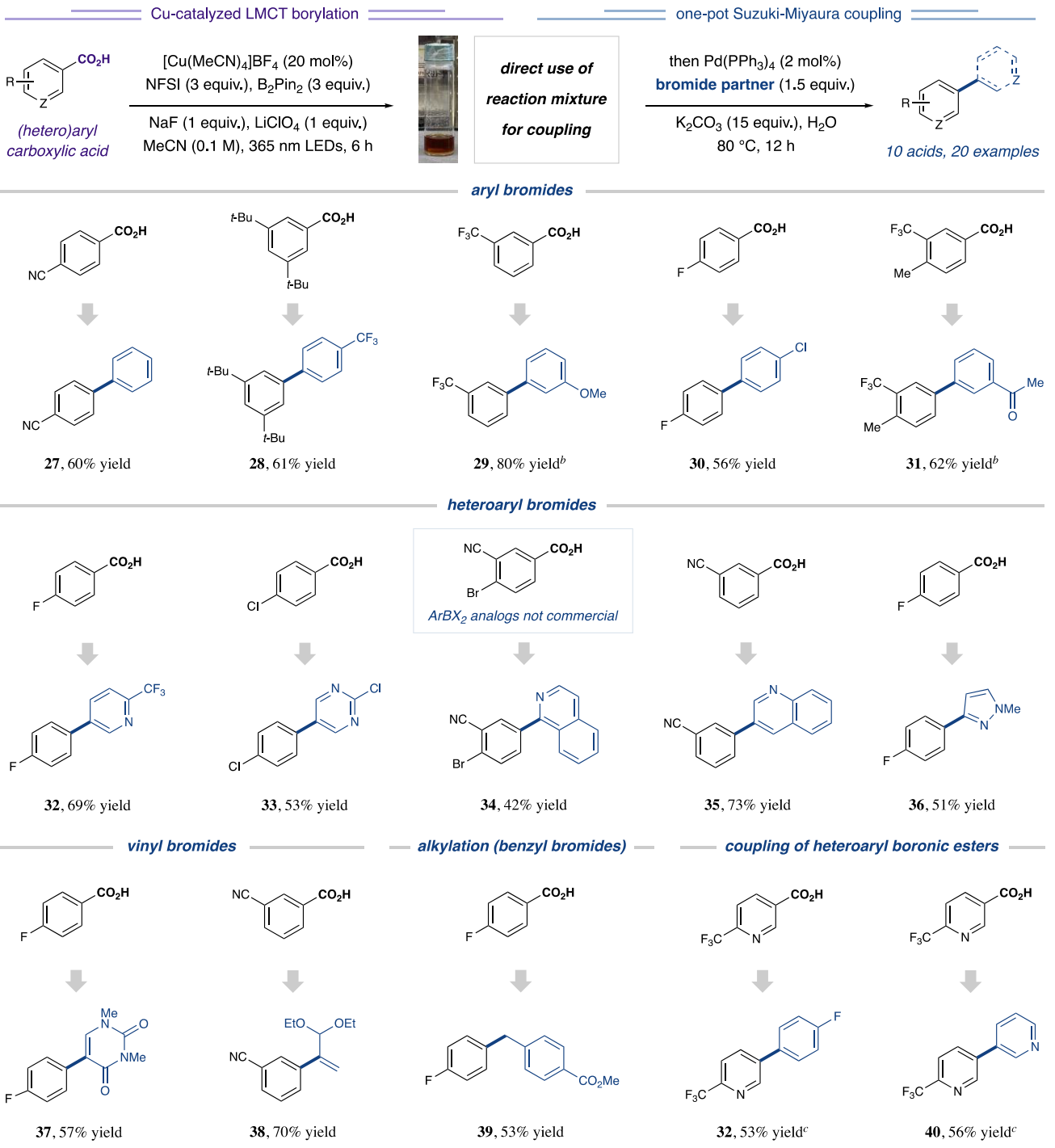
Table 2. Scope for Decarboxylative C−C Coupling via One-Pot Borylation/Suzuki−Miyaura Sequence[a]



[a]Isolated yields reported. 2:1 MeCN/H_2O (0.067 M) used as solvent for Suzuki−Miyaura step. See SI for experimental details and additional examples. [b]Cs_2CO_3 (15 equiv) used instead of K_2CO_3. [c]$Cu(OTf)_2$ (20 mol %) used instead of $[Cu(MeCN)_4]BF_4$.

Delightfully, this one-pot decarboxylative arylation was successfully conducted across a diverse range of benzoic acid substrates, including those for which the analogous organoboron reagents are not readily available.[46] As shown in Table 2, this sequence could incorporate a wide range of aryl bromides (**27**−**31**, 56−80% yield) and heteroaryl bromides (**32**−**35**, 42−73% yield), including a five-membered ring coupling partner (**36**, 51% yield), en route to a variety of (hetero)biaryl products. Perhaps most appealingly, these decarboxylative Suzuki−Miyaura reactions require no specific electronic or steric bias to facilitate CO_2 extrusion or cross-coupling.[14−20] Beyond arylation, the Suzuki−Miyaura step could be applied to decarboxylative vinylation, using vinyl bromides (**37** and **38**, 57% and 70% yield, respectively), and to decarboxylative alkylation with benzylic halides lacking elimination-prone β-hydrogens (**39**, 53% yield). Moreover, unactivated alkyl halides

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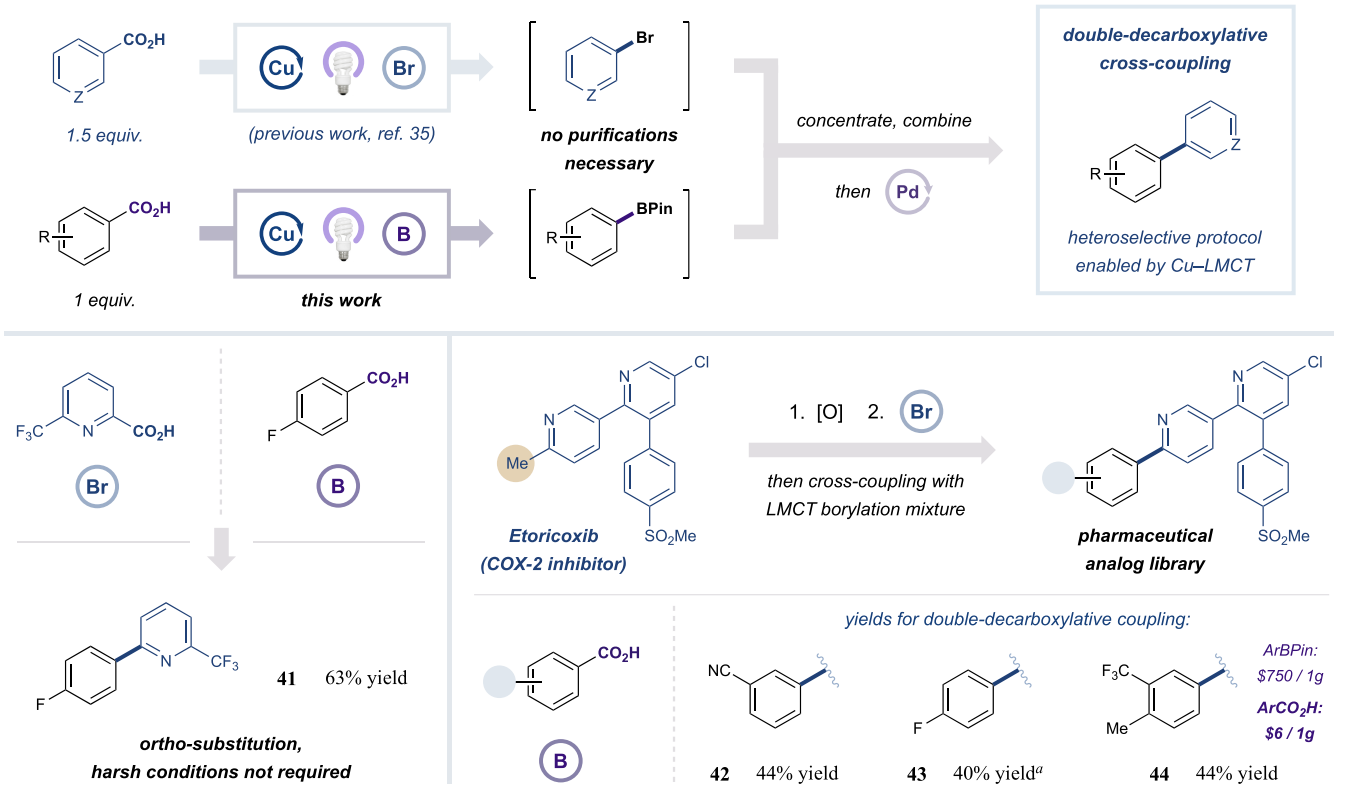
Scheme 2. Cu-LMCT Catalysis Sequence for Double-Decarboxylative Coupling of Two (Hetero)aryl Acids[b]



[a]Yield determined by ^{1}H NMR. [b]Isolated yields unless otherwise indicated. See SI for experimental details.

(i.e., MeI) enabled decarboxylative alkylation sequences when simple aqueous workups were performed following LMCT borylation (see SI for further details). In addition to benzoic acids, heteroaryl acids were susceptible to decarboxylative arylation with both aryl bromide (**32**, 53% yield) and heteroaryl bromide partners (**40**, 56% yield), circumventing the challenges often associated with handling heteroarene-based organoboron compounds.[42]

Lastly, we sought to merge our previously developed Cu-LMCT halogenation protocol with our new LMCT borylation/cross-coupling method. Specifically, we envisioned that LMCT approaches could furnish both the organoboron and aryl halide coupling partners from the corresponding (hetero)aryl acids, thereby enabling a heteroselective platform for the elusive double-decarboxylative cross-coupling of two distinct, non-*ortho*-substituted acids (Scheme 2).[47] Indeed, this cross-acid coupling sequence was executed by (i) performing parallel Cu-LMCT bromination and borylation procedures on distinct acids, (ii) concentrating the bromination reaction *in vacuo*, (iii) transferring the borylation mixture to the bromination vessel, and (iv) adding Suzuki–Miyaura reagents to the combined mixture. Encouragingly, this strategy enabled the coupling of a picolinic acid (subjected to LMCT bromination) with a benzoic acid (subjected to LMCT borylation) to furnish **41** in 63% yield. Moreover, the pharmaceutical etoricoxib, following tolyl-group oxidation, was coupled with a series of benzoic acids to directly afford an aryl-etoricoxib derivative library (**42**–**44**, 40–44% yield). Notably, this drug modification can employ low-cost acids that are more accessible than the corresponding organoboron analogues,[48] demonstrating unique advantages of this double-decarboxylative strategy. We expect these discoveries will permit new synthetic approaches for converting aryl acid feedstocks to value-added products, and further investigation of LMCT-enabled aromatic decarboxylative coupling is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c01630.

Additional experimental details and characterization data for isolated compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the Integrated Photoreactor.

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(45) For discussions regarding the feasibility of alternative one-pot cross-couplings which utilize the crude arylboronic esters as coupling partners, such as Chan−Evans−Lam couplings, see Tables S16−S18 in the Supporting Information.

(46) Commercial availability of organoboron substructures which represent analogues of the benzoic acid employed to synthesize **34** was determined using the *Reaxys* database (criteria of <$1000 per gram to designate as commercially available). *Reaxys*; Elsevier, n.d. https://www.reaxys.com/#/search/quick (accessed 2022-02-01).

(47) For examples of double-decarboxylative biaryl synthesis using exclusively two *ortho*-substituted benzoic acids as coupling partners, see: (a) Xie, K.; Wang, S.; Yang, Z.; Liu, J.; Wang, A.; Li, X.; Tan, Z.; Guo, C.-C.; Deng, W. Synthesis of Biaryls by Pd-Catalyzed Decarboxylative Homo- and Heterocoupling of Substituted Benzoic Acids. *Eur. J. Org. Chem.* **2011**, *2011*, 5787−5790. (b) Hu, P.; Shang, Y.; Su, W. A General Pd-Catalyzed Decarboxylative Cross-Coupling Reaction between Aryl Carboxylic Acids: Synthesis of Biaryl Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 5945−5949.

(48) Commercial prices for the benzoic acid employed to synthesize **44** and the corresponding pinacol boronic ester analogue were determined using the *Reaxys* database (values reported represent the lowest cost per 1 gram of material advertised across all listed vendors). *Reaxys*; Elsevier, n.d. https://www.reaxys.com/#/search/quick (accessed 2022-02-01).

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