JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

One-Pot Synthesis of Sulfonamides from Unactivated Acids and Amines via Aromatic Decarboxylative Halosulfonylation

P. Scott Pedersen, David C. Blakemore, Gary M. Chinigo, Thomas Knauber, and David W. C. MacMillan*

Cite This: J. Am. Chem. Soc. 2023, 145, 21189–21196
Read Online

ABSTRACT: The coupling of carboxylic acids and amines to form amide linkages is the most commonly performed reaction in the pharmaceutical industry. Herein, we report a new strategy that merges these traditional amide coupling partners to generate sulfonamides, important amide bioisosteres. This method leverages copper ligand-to-metal charge transfer (LMCT) to convert aromatic acids to sulfonyl chlorides, followed by one-pot amination to form the corresponding sulfonamide. This process requires no prefunctionalization of the native acid or amine and extends to a diverse set of aryl, heteroaryl, and *s*-rich aliphatic substrates. Further, we extend this strategy to the synthesis of (hetero)aryl sulfonyl fluorides, which have found utility as "click" handles in chemical probes and programmable bifunctional reagents. Finally, we demonstrate the utility of these protocols in pharmaceutical analogue synthesis.

Carboxylic acids and amines have high structural diversity, synthetic utility, and broad availability from both natural and commercial sources.[1,2] These two functionalities are the traditional partners of the amide coupling, the most commonly performed reaction by medicinal chemists.[3,4] Amides, however, can be metabolically labile toward hydrolysis and may not possess the ideal binding properties for a given target.[5] To address these shortcomings, several amide bioisosteres have been identified that retain similar geometric properties to amides while displaying modified metabolic stability or binding affinity.[6]

One notable amide isostere is the sulfonamide, which features similar geometry, an additional hydrogen bond acceptor (HBA), improved hydrolytic stability, and increased polar surface area (PSA).[7] These features can lead to dramatic improvements in physiochemical properties or binding affinity, with examples showing nearly 200-fold increases in binding with no other structural modification.[8] Beyond medicinal chemistry, sulfonamides have been used in place of amides to tune the gelation properties of physical gels.[9] Despite high interest, the preparation of sulfonamide analogues typically necessitates de novo synthesis of a sulfonyl chloride partner or a multistep sequence proceeding through high-energy diazonium intermediates.[8,10] Therefore, a method for the expedient synthesis of sulfonamides from the same partners used in conventional amide coupling would accelerate the preparation of amide analogues in drug discovery campaigns.

We envisioned the synthesis of sulfonamides from aryl carboxylic acids and amines could be achieved through an initial decarboxylative chlorosulfonylation, followed by a one-pot sulfonamide formation via the addition of an amine (Figure 1). This strategy confers several benefits. First, the reaction between amines and sulfonyl chlorides occurs rapidly and is robust in scope.[11] Second, sulfonyl chlorides themselves are valuable synthetic intermediates and can be used as a lynchpin functionality toward the synthesis of diverse sulfur containing functionalities, such as sulfonates,[12] sulfones,[13] sulfinates,[14] and thiophenols.[15] Moreover, we anticipated that a decarboxylative halosulfonylation strategy would extend to aryl sulfonyl fluorides, valuable "click" handles for sulfur(VI)–fluoride exchange[16,17] with broad utility as chemical probes,[18] programmable bifunctional reagents,[19] and versatile functional handles.[20] While several methodologies have been developed in recent years for accessing aryl sulfonyl halides from aryl boronic esters,[21] halides,[22] diazoniums,[23] and several sulfur-containing functionalities,[24] a direct approach beginning from aryl carboxylic acids has not been reported to date.[17]

Despite its appeal, the development of a versatile decarboxylative halosulfonylation protocol presents several challenges. While the decarboxylative halosulfonylation of related aliphatic systems has been reported,[25] aromatic decarboxylation is significantly more challenging.[1] Recently, both Ritter and our group have demonstrated that copper ligand-to-metal charge transfer (LMCT) is a mild and general approach for traditionally challenging aromatic decarboxylative functionalizations including halogenation,[26,27] borylation,[28] hydroxylation,[29] and sulfoximination.[30,31] Notably, our lab rendered this strategy catalytic in copper by including a single electron oxidant.[27,28] Given the broad precedent for engaging aryl radicals with SO_2 to forge C–S bonds,[32] we anticipated that a Cu-LMCT strategy could be successful for catalytic decarboxylative halosulfonylation. Additionally, we expected

Received: July 31, 2023
Published: September 20, 2023

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189–21196

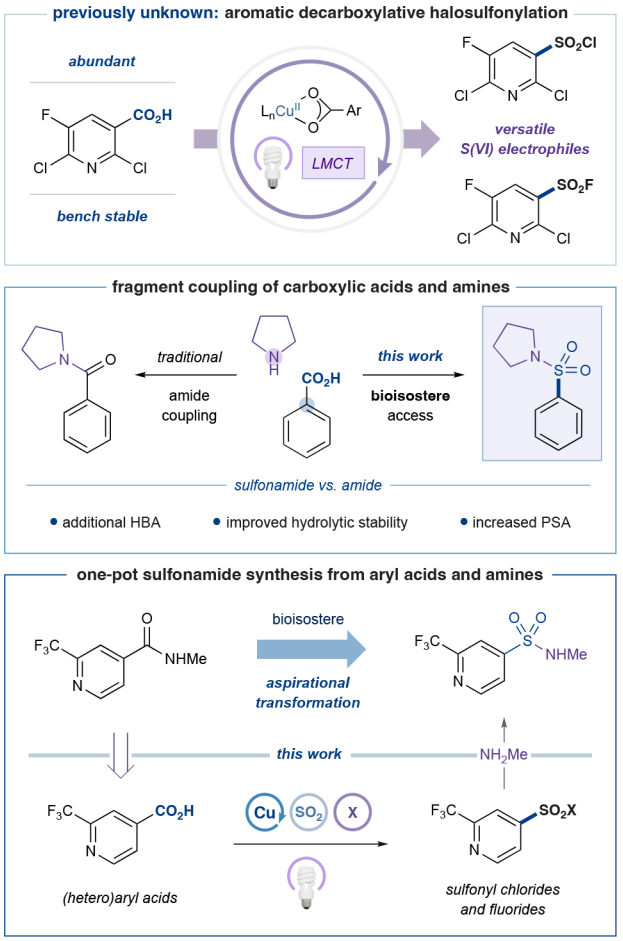


Figure 1. Decarboxylative halosulfonylation and subsequent amination of (hetero)aryl acids via Cu-LMCT catalysis.

that the mild nature of LMCT decarboxylation could allow a highly efficient one-pot conversion of sulfonyl chlorides to sulfonamides, circumventing the isolation of highly reactive electrophiles. Herein, we describe the successful development of a copper-catalyzed aromatic decarboxylative halosulfonylation, expediently accessing sulfonamides from aryl carboxylic acids and amines.

We propose the general design plan for decarboxylative halosulfonylation, as detailed in Figure 2. First, a Cu(II) catalyst combines with an in situ generated aryl carboxylate, providing a photoactive Cu(II) carboxylate. Upon irradiation, this complex can undergo LMCT, inducing Cu−O bond homolysis and furnishing an aroyloxy radical as well as a reduced Cu(I) species. We hypothesize these two species can recombine, regenerating the ground state Cu(II) carboxylate complex and suppressing competitive, deleterious bimolecular reaction pathways.[33] The aroyloxy radical can also undergo decarboxylation, furnishing the desired aryl radical. Radical capture by SO_2 would then forge the desired C(sp^2)−S bond and generate an aryl sulfonyl radical.[32] We propose that this sulfur-centered radical could react with various electrophilic halogenation reagents to afford the desired aryl sulfonyl halide products. Finally, a suitable single electron oxidant can oxidize Cu(I) to Cu(II), closing the catalytic cycle.

We began optimization studies by attempting the decarboxylative chlorosulfonylation of 4-fluorobenzoic acid. By employing $Cu(MeCN)_4BF_4$ as the most generally successful copper

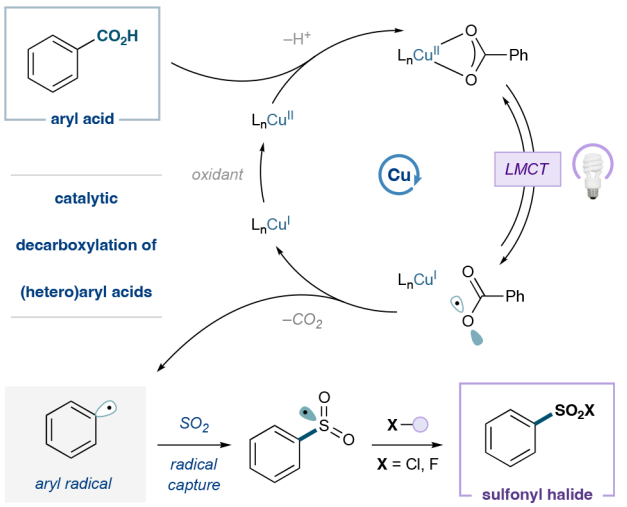
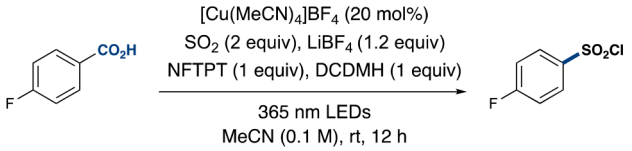


Figure 2. General design plan for the decarboxylative halosulfonylation of (hetero)aryl acids.

Table 1. Control Experiments and Optimization for LMCT Decarboxylative Chlorosulfonylation and One-Pot Sulfonamide Formation



entry[a]	deviations	yield[b]
1	none	69%
2	no $LiBF_4$	62%
3	ambient light only	0%
4	no Cu	0%
5	no NFTPT	0%
6	no DCDMH	0%
7	no SO_2	0%
8	with $Na_2S_2O_5$ (2 equiv) instead of SO_2	2%
9	with DABSO (1 equiv) instead of SO_2	0%
10	**entry 2** *then* morpholine (2 equiv) and DIPEA (2 equiv)	50%[c]
11	**entry 1** *then* morpholine (2 equiv) and DIPEA (2 equiv)	68%[c]

[a]0.1 mmol scale. [b]Yields determined by ^{19}F NMR analysis. [c]Yield of the corresponding morpholine sulfonamide. See SI for experimental details. NFTPT, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate. DCDMH, 1,3-dichloro-5,5-dimethylhydantoin.

catalyst, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (NFTPT) as the single electron oxidant, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as a chlorine atom source, and the integrated photoreactor (IPR) as a high intensity source of 365 nm light,[34] we observed a 2% yield of the desired sulfonyl chloride product with sodium metabisulfite as the SO_2 source (Table 1, entry 8). While other SO_2 surrogates from the literature were similarly unsuccessful,[35] super stoichiometric loadings of copper did lead to improved yield in some cases (see SI for experimental details). Recognizing the sensitivity of Cu-LMCT decarboxylation to the Lewis basic functionality present in each of these surrogates, we sought to employ SO_2 directly by evaluating stock solutions of SO_2. We were delighted to find that by using a solution of SO_2 in acetonitrile,[22c,35a,36] we observed formation of the desired product in 62% yield (Table 1, entry 2). Though we prepared

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196

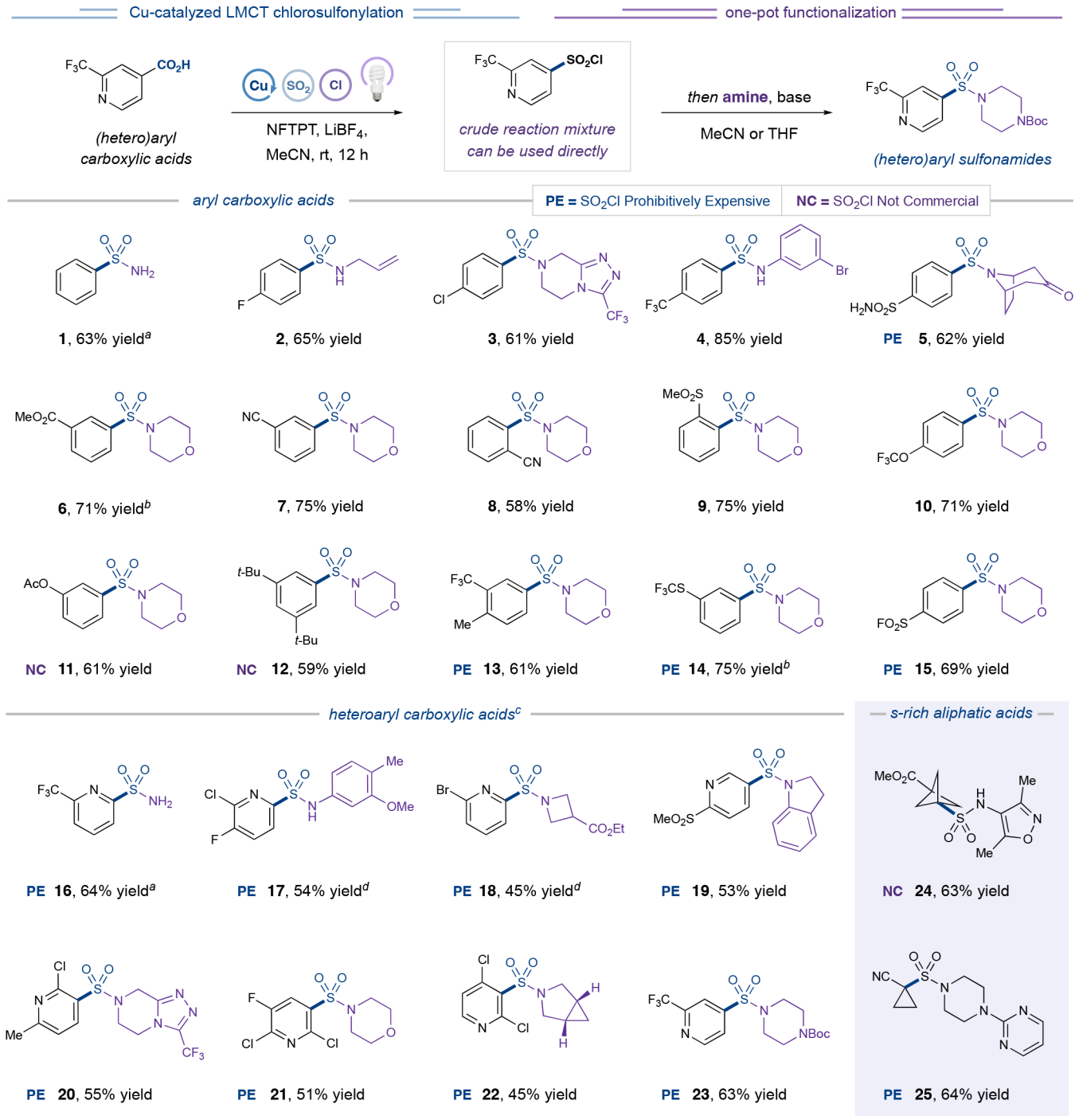


Figure 3. Decarboxylative chlorosulfonylation and one-pot sulfonamide formation. Reactions were performed on a 0.5 mmol scale with (hetero)aryl acid (1 equiv), $[Cu(MeCN)_4]BF_4$ (20 mol %), 1,3-dichloro-5,5-dimethylhydantoin (1 equiv), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1 equiv), $LiBF_4$ (1.2 equiv), SO_2 (2 equiv), MeCN (0.1 M), 365 nm LEDs, 12 h. Amination conducted in MeCN or THF (0.1 M) with amine or amine·HCl (2 equiv) and DIPEA or pyridine (2−4 equiv). See SI for experimental details. All yields isolated. [a]Amination performed with 25 equiv of NH_4OH. [b]With *N*-chlorosuccinimide (2.5 equiv) as the chlorination reagent. [c]With *N*-chlorophthalimide (2 equiv) as chlorination reagent. [d]With 10 mol % $[Cu(MeCN)_4]BF_4$.

our solution in house, similar stock solutions of SO_2 in acetonitrile are commercially available. This solution could be stored over extended periods of time in a sealed vessel at −20 °C. Despite frequent use, no decrease in reaction performance was observed when using a single 4.0 M stock solution for >6 months. Control reactions are consistent with the proposed LMCT pathway, as copper, oxidant, and light are all essential for reactivity (Table 1, entries 3−5).

We next attempted to convert the sulfonyl chlorides to sulfonamides in the same reaction vessel. We found that this functionalization could be achieved in near quantitative yield from the intermediate sulfonyl chloride by adding morpholine and DIPEA to the crude reaction mixture following irradiation and removal of unreacted SO_2.[37] Across both steps, we found that $LiBF_4$ was a beneficial additive for avoiding the formation of an undesired sulfonyl fluoride byproduct, ultimately

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196

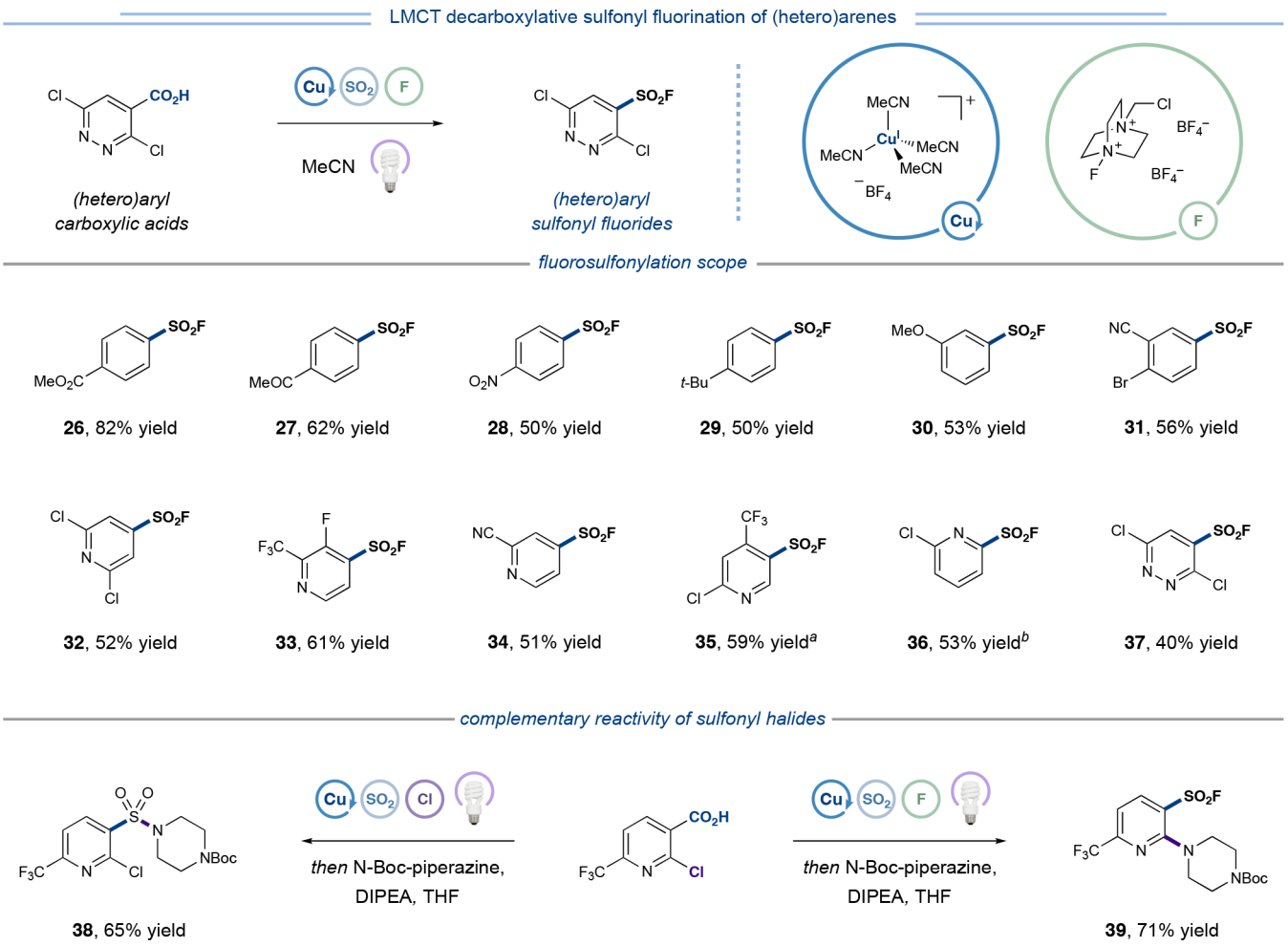


Figure 4. Decarboxylative fluorosulfonylation of (hetero)aryl carboxylic acids. Reactions were performed on a 0.5 mmol scale with (hetero)aryl acid (1 equiv), $[Cu(MeCN)_4]BF_4$ (50 mol %), Selectfluor (1.5 equiv), SO_2 (2 equiv), and MeCN (0.5 M), 365 nm LEDs, 12 h. All yields isolated. [a]Isolated as the S_NAr product with N-Boc piperazine. [b]Via halogen exchange from the corresponding sulfonyl chloride. See SI for experimental details.

delivering the desired morpholine sulfonamide in 68% yield (Table 1, entry 11).

Excitingly, this strategy was extended to efficient decarboxylative fluorosulfonylation using Selectfluor as both the single electron oxidant and fluorine atom source, slightly elevated copper loadings of 50 mol %, and an increased concentration of 0.5 M (see SI for experimental details).

With the optimized conditions in hand, we evaluated the scope of the decarboxylative chlorosulfonylation reaction (Figure 3). To demonstrate that electronically and sterically unbiased substrates are capable of this reaction, benzoic acid was converted to benzenesulfonamide (**1**, 63% yield). Gratifyingly, electron deficient acids (**2**−**7**, 61−85% yield) proceeded with good to excellent efficiencies. Notably, these examples were successfully functionalized with diverse amines, providing efficient access to primary, secondary, tertiary, and anilinic sulfonamides, all in near quantitative yield from the intermediate sulfonyl chlorides. Ortho-substitution was also found to be well tolerated (**8** and **9**, 58 and 75% yield, respectively). Additionally, *O*−heteroatom substituents could be effectively introduced around the arene periphery (**10** and **11**, 71 and 61% yield, respectively), as well as electron donating alkyl substituents (**12** and **13**, 59 and 61% yield, respectively). Finally, other sulfur-containing functionalities such as trifluoromethyl thioethers (**14**, 75% yield) and sulfonyl fluorides (**15**, 69% yield) were successfully tolerated, highlighting an opportunity to introduce distinct sulfur-containing functionalities of variable oxidation states on the same arene.

We were eager to evaluate the scope of heteroaryl sulfonyl chlorides accessible via this sequence, as these scaffolds are desirable in medicinal chemistry programs despite the challenges presented by their high electrophilicity and susceptibility to hydrolysis. We were delighted to find that our method proceeded in good efficiency on a range of differentially substituted, electron-deficient pyridines, including picolinic (**16**−**18**, 45−64% yield), nicotinic (**19**−**22**, 45−55% yield) and isonicotinic (**23**, 63% yield) acids across a diverse set of amines.

We next attempted to extend our method beyond (hetero)arenes and toward the functionalization of other medicinally relevant *s*-rich acids, such as cyclopropanes and bicyclo[1.1.1]pentanes (BCPs), which have found widespread adoption as arene bioisosteres.[38] An inexpensive and commercially available BCP substrate, 3-(methoxycarbonyl)-BCP-1-carboxylic acid, was efficiently converted to the corresponding sulfonamide (**24**, 63% yield). While BCPs bearing a sulfonamide exit vector have been reported in the literature, they previously have been accessed via a 5-step

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196

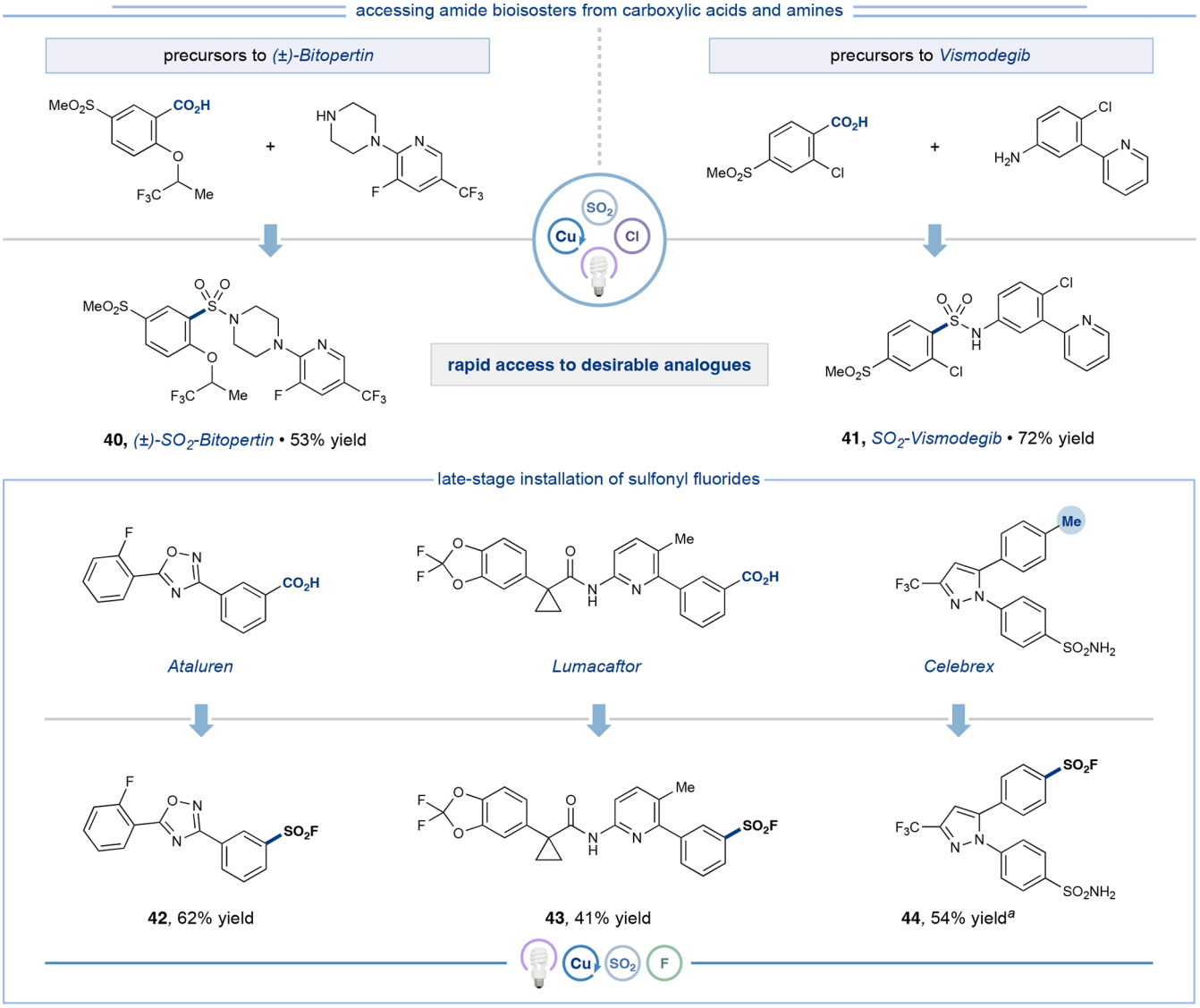


Figure 5. Late stage functionalization via Cu-LMCT halosulfonylation. All yields isolated. See SI for experimental details. [a]After two-step benzylic oxidation and decarboxylative fluorosulfonylation. Yield given is for the fluorosulfonylation step.

synthetic sequence.[39] Beyond this BCP scaffold, cyclopropanes were also readily functionalized in high yield (**25**, 64% yield, see SI for additional examples and limitations).

While each of the acid starting materials that appear in Figure 3 are inexpensive and commercially available,[40] the corresponding sulfonyl chlorides are in many cases either not commercial (designated by NC) or are prohibitively expensive (>$100 per gram and >18× more expensive per gram than the acid starting material, designated by PE).[41] As such, this procedure to convert bench-stable acids to desirable sulfonamides via a one-pot protocol alleviates a significant limitation associated with sulfonamide preparation.

Next, we evaluated the scope of the decarboxylative fluorosulfonylation (Figure 4). This reaction tolerates both electron-deficient (**26**−**28**, 50−82% yield) and electron-rich (**29** and **30**, 50 and 53% yield, respectively) acids. Additionally, highly activated aryl bromides (**31**, 56% yield) are well tolerated. This method also extends to a similarly desirable selection of electron deficient isonicotinic (**32**−**34**, 51−61%) and nicotinic acids (**35**, 59% yield). While picolinic acids did not proceed in the standard protocol with high efficiencies, a one-pot, two step procedure for their synthesis from the intermediate sulfonyl chloride was developed (**36**, 53% yield). Though more challenging, other heteroarenes, such as pyridazines (**37**, 40%), were also successful.

To demonstrate the differentiated reactivity of sulfonyl chlorides and fluorides, we subjected 2-chloro-6-(trifluoromethyl)nicotinic acid to both sets of halosulfonylation conditions, followed by an identical one-pot amination. These two sequences gave different products: the sulfonyl chloride was converted exclusively to the expected sulfonamide product (**38**, 65% yield) while the sulfonyl fluoride gave exclusively the S_NAr product (**39**, 71% yield). This selectivity is due to the attenuated electrophilicity of sulfonyl fluorides and can allow for programmable S_NAr/sulfonamide formation sequences.

To exemplify the utility of these methods in drug discovery programs, we undertook the synthesis of sulfonamide analogues for amide-containing biologically active molecules (Figure 5). Sulfonamide analogues of (±)-Bitopertin and Vismodegib could be synthesized in high yields directly from their amide coupling partners (**40** and **41**, 53 and 72% yield,

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196

respectively). Additionally, native carboxylate pharmacophores could be directly converted into sulfonyl fluoride-containing chemical probes potentially capable of forming covalent linkages in the binding sites of their target proteins.[18] Specifically, Ataluren and Lumacaftor were converted into their sulfonyl fluoride analogues in good yield (**42** and **43**, 62 and 41% yield, respectively). Finally, the tolyl group of Celebrex was converted to an aryl sulfonyl fluoride in a two-step sequence involving benzylic oxidation and subsequent decarboxylative fluorosulfonylation (**44**, 54% yield).

In summary, we have developed an approach for aromatic decarboxylative halosulfonylation that is amenable to a one-pot synthesis of sulfonamides from traditional amide coupling partners. We anticipate that these reactions will be of value to the medicinal chemistry community by assisting in the rapid synthesis of diverse organosulfur products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c08218.

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

■ AUTHOR INFORMATION

Corresponding Author

David W. C. MacMillan − *Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States;* orcid.org/0000-0001-6447-0587; Email: dmacmill@princeton.edu

Authors

P. Scott Pedersen − *Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544, United States*

David C. Blakemore − *Worldwide Research and Development, Pfizer, Inc., Groton, Connecticut 06340, United States*

Gary M. Chinigo − *Worldwide Research and Development, Pfizer, Inc., Groton, Connecticut 06340, United States*

Thomas Knauber − *Worldwide Research and Development, Pfizer, Inc., Groton, Connecticut 06340, United States;* orcid.org/0000-0002-3354-3322

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c08218

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.

■ ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under Award R35GM134897-03), the Princeton Catalysis Initiative, and kind gifts from Pfizer, MSD, Janssen, Bristol-Myers Squibb and Genentech. P. S. P. acknowledges Princeton University, E. C. Taylor and the Taylor family for an Edward C. Taylor Fellowship and the National Science Foundation (NSF) for a predoctoral fellowship (Award DGE-2039656). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS. The authors thank R. Lambert for assistance in preparing this manuscript and T. Chen, P. Sarver, and C. Oswood for helpful scientific discussions.

■ REFERENCES

(1) (a) Varenikov, A.; Shapiro, E.; Gandelman, M. Decarboxylative Halogenation of Organic Compounds. *Chem. Rev.* **2021**, *121* (1), 412−484. (b) Beil, S. B.; Chen, T. Q.; Intermaggio, N. E.; MacMillan, D. W. C. Carboxylic Acids as Adaptive Functional Groups in Metallaphotoredox Catalysis. *Acc. Chem. Res.* **2022**, *55* (23), 3481−3494.

(2) Wang, Y.; Haight, I.; Gupta, R.; Vasudevan, A. What Is in Our Kit? An Analysis of Building Blocks Used in Medicinal Chemistry Parallel Libraries. *J. Med. Chem.* **2021**, *64* (23), 17115−17122.

(3) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the Medicinal Chemistry Synthetic Toolbox. *Nat. Rev. Drug Discovery* **2018**, *17* (10), 709−727.

(4) For examples of alternative couplings of carboxylic acids and amines, see: (a) Zhang, Z.; Cernak, T. The Formal Cross-Coupling of Amines and Carboxylic Acids to Form sp^3−sp^3 Carbon−Carbon Bonds. *Angew. Chem., Int. Ed.* **2021**, *60* (52), 27293−27298. (b) McGrath, A.; Zhang, R.; Shafiq, K.; Cernak, T. Repurposing amine and carboxylic acid building blocks with an automatable esterification reaction. *Chem. Commun.* **2023**, *59*, 1026−1029. (c) Wang, J.; Ehehalt, L. E.; Huang, Z.; Beleh, O. M.; Guzei, I. A.; Weix, D. J. Formation of $C(sp^2)$−$C(sp^3)$ Bonds Instead of Amide C−N Bonds from Carboxylic Acid and Amine Substrate Pools by Decarbonylative Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2023**, *145* (18), 9951−9958. (d) Douthwaite, J. L.; Zhao, R.; Shim, E.; Mahjour, B.; Zimmerman, P. M.; Cernak, T. Formal Cross-Coupling of Amines and Carboxylic Acids to Form sp^3−sp^2 Carbon−Carbon Bonds. *J. Am. Chem. Soc.* **2023**, *145* (20), 10930−10937.

(5) Mahjour, B.; Shen, Y.; Liu, W.; Cernak, T. A map of the amine−carboxylic acid coupling system. *Nature.* **2020**, *580*, 71−75.

(6) Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, *63* (21), 12290−12358.

(7) Ecker, A. K.; Levorse, D. A.; Victor, D. A.; Mitcheltree, M. J. Bioisostere Effects on the EPSA of Common Permeability-Limiting Groups. *ACS Med. Chem. Lett.* **2022**, *13*, 964−971.

(8) Hirayama, F.; Koshio, H.; Ishihara, T.; Watanuki, S.; Hachiya, S.; Kaizawa, H.; Kuramochi, T.; Katayama, N.; Kurihara, H.; Taniuchi, Y.; Sato, K.; Sakai-Moritani, Y.; Kaku, S.; Kawasaki, T.; Matsumoto, Y.; Sakamoto, S.; Tsukamoto, S. Design, Synthesis and Biological Activity of YM-60828 Derivatives: Potent and Orally-Bioavailable Factor Xa Inhibitors Based on Naphthoanilide and Naphthalensulfonanilide Templates. *Bioorg. Med. Chem.* **2002**, *10* (8), 2597−2610.

(9) Alegre-Requena, J. V.; Grijalvo, S.; Sampedro, D.; Mayr, J.; Saldías, C.; Marrero-Tellado, J. J.; Eritja, R.; Herrera, R. P.; Díaz, D. D. Sulfonamide as amide isostere for fine-tuning the gelation properties of physical gels. *RSC Adv.* **2020**, *10* (19), 11481−11492.

(10) Mondal, S.; Malakar, S. Synthesis of Sulfonamide and Their Synthetic and Therapeutic Applications: Recent Advances. *Tetrahedron* **2020**, *76* (48), 131662.

(11) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54* (10), 3451−3479.

(12) Mondal, S. Recent Developments in the Synthesis and Application of Sultones. *Chem. Rev.* **2012**, *112* (10), 5339−5355.

(13) Hell, S. M.; Meyer, C. F.; Misale, A.; Sap, J. B.; Christensen, K. E.; Willis, M. C.; Trabanco, A. A.; Gouverneur, V. Hydrosulfonylation of Alkenes with Sulfonyl Chlorides under Visible Light Activation. *Angew. Chem., Int. Ed.* **2020**, *132* (28), 11717−11723.

(14) (a) Whitmore, F. C.; Hamilton, F. H. SODIUM p-TOLUENESULFINATE. *Org. Synth.* **1922**, *2*, 89−90. (b) Kulka, M. Derivatives of p-Chlorobenzenesulfonic Acid. *J. Am. Chem. Soc.* **1950**, *72*, 1215−1218.

(15) Akamanchi, K.; Bellale, E.; Chaudhari, M. A Simple, Fast and Chemoselective Method for the Preparation of Arylthiols. *Synthesis* **2009**, *2009*, 3211−3213.

(16) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem., Int. Ed.* **2014**, *53* (36), 9430−9448.
(17) Lou, T. S.-B.; Willis, M. C. Sulfonyl Fluorides as Targets and Substrates in the Development of New Synthetic Methods. *Nat. Rev. Chem.* **2022**, *6* (2), 146−162.
(18) (a) Grimster, N. P.; Connelly, S.; Baranczak, A.; Dong, J.; Krasnova, L. B.; Sharpless, K. B.; Powers, E. T.; Wilson, I. A.; Kelly, J. W. Aromatic Sulfonyl Fluorides Covalently Kinetically Stabilize Transthyretin to Prevent Amyloidogenesis While Affording a Fluorescent Conjugate. *J. Am. Chem. Soc.* **2013**, *135* (15), 5656−5668. (b) Mukherjee, H.; Debreczeni, J.; Breed, J.; Tentarelli, S.; Aquila, B.; Dowling, J. E.; Whitty, A.; Grimster, N. P. A Study of the Reactivity of S(VI)−F Containing Warheads with Nucleophilic Amino-Acid Side Chains under Physiological Conditions. *Org. Biomol. Chem.* **2017**, *15* (45), 9685−9695.
(19) Chinthakindi, P. K.; Kruger, H. G.; Govender, T.; Naicker, T.; Arvidsson, P. I. On-Water Synthesis of Biaryl Sulfonyl Fluorides. *J. Org. Chem.* **2016**, *81* (6), 2618−2623.
(20) (a) Shreiber, S. T.; Molander, G. A. Alkyl (Het)Arylsulfones from SuFEx Reagents via Photochemical S−F Bond Activation. *Org. Lett.* **2023**, *25* (12), 2084−2087. (b) Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; am Ende, C. W.; Ball, N. D. Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **2018**, *20* (13), 3943−3947. (c) Han, B.; Khasnavis, S. R.; Nwerem, M.; Bertagna, M.; Ball, N. D.; Ogba, O. M. Calcium Bistriflimide-Mediated Sulfur(VI)−Fluoride Exchange (SuFEx): Mechanistic Insights toward Instigating Catalysis. *Inorg. Chem.* **2022**, *61* (25), 9746−9755.
(21) (a) Magre, M.; Cornella, J. Redox-Neutral Organometallic Elementary Steps at Bismuth: Catalytic Synthesis of Aryl Sulfonyl Fluorides. *J. Am. Chem. Soc.* **2021**, *143* (51), 21497−21502. (b) Lo, P. K.; Chen, Y.; Willis, M. C. Nickel(II)-Catalyzed Synthesis of Sulfinates from Aryl and Heteroaryl Boronic Acids and the Sulfur Dioxide Surrogate DABSO. *ACS Catal.* **2019**, *9* (12), 10668−10673. (c) Debergh, J. R.; Niljianskul, N.; Buchwald, S. L. Synthesis of Aryl Sulfonamides via Palladium-Catalyzed Chlorosulfonylation of Aryl Boronic Acids. *J. Am. Chem. Soc.* **2013**, *135* (29), 10638.
(22) (a) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. One-Pot Palladium-Catalyzed Synthesis of Sulfonyl Fluorides from Aryl Bromides. *Chem. Sci.* **2017**, *8* (2), 1233−1237. (b) Tribby, A. L.; Rodríguez, I.; Shariffudin, S.; Ball, N. D. Pd-Catalyzed Conversion of Aryl Iodides to Sulfonyl Fluorides Using SO_2 Surrogate DABSO and Selectfluor. *J. Org. Chem.* **2017**, *82* (4), 2294−2299. (c) Lou, T. S.; Kawamata, Y.; Ewing, T.; Correa-Otero, G. A.; Collins, M. R.; Baran, P. S. Scalable, Chemoselective Nickel Electrocatalytic Sulfinylation of Aryl Halides with SO_2. *Angew. Chem., Int. Ed.* **2022**, *61* (37), No. e2022080.
(23) (a) Liu, Y.; Yu, D.; Guo, Y.; Xiao, J.-C.; Chen, Q.-Y.; Liu, C. Arenesulfonyl Fluoride Synthesis via Copper-Catalyzed Fluorosulfonylation of Arenediazonium Salts. *Org. Lett.* **2020**, *22* (6), 2281−2286. (b) Zhong, T.; Pang, M.-K.; Chen, Z.-D.; Zhang, B.; Weng, J.; Lu, G. Copper-Free Sandmeyer-Type Reaction for the Synthesis of Sulfonyl Fluorides. *Org. Lett.* **2020**, *22* (8), 3072−3078. (c) Májek, M.; Neumeier, M.; Jacobi von Wangelin, A. Aromatic Chlorosulfonylation by Photoredox Catalysis. *ChemSusChem* **2017**, *10* (1), 151−155.
(24) (a) Gómez-Palomino, A.; Cornella, J. Selective Late-stage Sulfonyl Chloride Formation from Sulfonamides Enabled by Pyry-BF_4. *Angew. Chem., Int. Ed.* **2019**, *58* (50), 18235−18239. (b) Laudadio, G.; Bartolomeu, A. de; Verwijlen, L. M.; Cao, Y.; de Oliveira, K. T.; Noël, T. Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride. *J. Am. Chem. Soc.* **2019**, *141* (30), 11832−11836. (c) Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. N-Halogeno Compounds. Part 18. 1-Alkyl-4-Fluoro-1,4-Diazoniabicyclo[2.2.2]Octane Salts: User-Friendly Site-Selective Electrophilic Fluorinating Agents of the N-Fluoroammonium Class. *J. Chem. Soc., Perkin Trans.* **1996**, *1* (16), 2069−2076.
(25) Nguyen, V. T.; Haug, G. C.; Nguyen, V. D.; Vuong, N. T.; Karki, G. B.; Arman, H. D.; Larionov, O. V. Functional Group Divergence and the Structural Basis of Acridine Photocatalysis Revealed by Direct Decarboxysulfonylation. *Chem. Sci.* **2022**, *13* (14), 4170−4179.
(26) Xu, P.; López-Rojas, P.; Ritter, T. Radical Decarboxylative Carbometalation of Benzoic Acids: A Solution to Aromatic Decarboxylative Fluorination. *J. Am. Chem. Soc.* **2021**, *143* (14), 5349−5354.
(27) 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. A Unified Approach to Decarboxylative Halogenation of (Hetero)Aryl Carboxylic Acids. *J. Am. Chem. Soc.* **2022**, *144* (18), 8296−8305.
(28) Dow, N. W.; Pedersen, P. S.; Chen, T. Q.; Blakemore, D. C.; Dechert-Schmitt, A.-M.; Knauber, T.; MacMillan, D. W. C. Decarboxylative Borylation and Cross-Coupling of (Hetero)Aryl Acids Enabled by Copper Charge Transfer Catalysis. *J. Am. Chem. Soc.* **2022**, *144* (14), 6163−6172.
(29) Su, W.; Xu, P.; Ritter, T. Decarboxylative Hydroxylation of Benzoic Acids. *Angew. Chem., Int. Ed.* **2021**, *60* (45), 24012−24017.
(30) Xu, P.; Su, W.; Ritter, T. Decarboxylative Sulfoximination of Benzoic Acids Enabled by Photoinduced Ligand-to-Copper Charge Transfer. *Chem. Sci.* **2022**, *13* (45), 13611−13616.
(31) For recent reviews on the applications of open-shelled intermediates generated via LMCT, see: (a) Juliá, F. Ligand-to-Metal Charge Transfer (LMCT) Photochemistry at 3D-Metal Complexes: An Emerging Tool for Sustainable Organic Synthesis. *ChemCatChem* **2022**, *14* (19), No. e202200916. (b) Abderrazak, Y.; Bhattacharyya, A.; Reiser, O. Visible-light-induced Homolysis of Earth-abundant Metal-substrate Complexes: A Complementary Activation Strategy in Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60* (39), 21100−21115.
(32) (a) Qiu, G.; Zhou, K.; Gao, L.; Wu, J. Insertion of sulfur dioxide via a radical process: an efficient route to sulfonyl compounds. *Org. Chem. Front.* **2018**, *5*, 691−705. (b) Ye, S.; Li, X.; Xie, W.; Wu, J. Photoinduced Sulfonylation Reactions Through the Insertion of Sulfur Dioxide. *Eur. J. Org. Chem.* **2020**, *2020*, 1274−1287. (c) Hofman, K.; Liu, N.-W.; Manolikakes, G. Radicals and Sulfur Dioxide: A Versatile Combination for the Construction of Sulfonyl Containing Molecules. *Chem. - Eur. J.* **2018**, *24*, 11852−11863. (d) Sarver, P. J.; Bissonnette, N. B.; MacMillan, D. W. C. Decatungstate-Catalyzed C(*sp*3)−H Sulfinylation: Rapid Access to Diverse Organosulfur Functionality. *J. Am. Chem. Soc.* **2021**, *143* (26), 9737−9743. (e) Jin, S.; Haug, G. C.; Trevino, R.; Nguyen, V. D.; Arman, H. D.; Larionov, O. V. Photoinduced C(*sp*3)−H Sulfination Empowers the Direct and Chemoselective Introduction of the Sulfonyl Group. *Chem. Sci.* **2021**, *12* (41), 13914−13921.
(33) (a) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. Spectroscopic and kinetic characteristics of aroyloxyl radicals. 1. The 4-methoxybenzoyloxyl radical. *J. Am. Chem. Soc.* **1988**, *110*, 2877−2885. (b) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. Spectroscopic and kinetic characteristics of aroyloxyl radicals. 2. Benzoyloxyl and ring-substituted aroyloxyl radicals. *J. Am. Chem. Soc.* **1988**, *110*, 2886−2893. (c) Misawa, H.; Sawabe, K.; Takahara, S.; Sakuragi, H.; Tokumaru, K. Decarboxylation Rates of Benzoyloxyl Radicals as Determined by Laser Flash Photolysis. Further Insight into the Mechanism for Photodecomposition of Dibenzoyl Peroxides. *Chem. Lett.* **1988**, *17*, 357−360. (d) Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551. (e) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. Visible-Light-Promoted Activation of Unactivated C-(*sp*3)−H Bonds and Their Selective Trifluoromethylthiolation. *J. Am. Chem. Soc.* **2016**, *138* (50), 16200−16203.
(34) Le, C. C.; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. A General Small-Scale Reactor to Enable Standardization and Acceleration of Photocatalytic Reactions. *ACS Cent. Sci.* **2017**, *3*, 647−653.

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196

(35) For reviews on the incorporation of SO_2 and SO_2 surrogates, see: (a) Blum, S. P.; Hofman, K.; Manolikakes, G.; Waldvogel, S. R. Advances in Photochemical and Electrochemical Incorporation of Sulfur Dioxide for the Synthesis of Value-Added Compounds. *Chem. Commun.* **2021**, *57* (67), 8236−8249. (b) Emmett, E. J.; Willis, M. C. The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry. *Asian J. Org. Chem.* **2015**, *4* (7), 602−611. (c) Liu, G.; Fan, C.; Wu, J. Fixation of Sulfur Dioxide into Small Molecules. *Org. Biomol. Chem.* **2015**, *13* (6), 1592−1599. (d) Ye, S.; Qiu, G.; Wu, J. Inorganic Sulfites as the Sulfur Dioxide Surrogates in Sulfonylation Reactions. *Chem. Commun.* **2019**, *55* (8), 1013−1019.

(36) For an additional recent example employing stock solutions of SO_2 in an electrocatalytic reaction, see: Blum, S. P.; Schäffer, L.; Schollmeyer, D.; Waldvogel, S. R. Electrochemical Synthesis of Sulfamides. *Chem. Commun.* **2021**, *57* (39), 4775−4778.

(37) Amines and SO_2 are known to react readily to form Lewis adducts: (a) Hata, T.; Kinumaki, S. Reactions of Ammonia and Aliphatic Amines with Sulphur Dioxide. *Nature.* **1964**, *203*, 1378−1379. (b) Douglas, J. E.; Kollman, P. A. Trimethylamine-SO_2, the Prototype Strong Charge-Transfer Complex. *J. Am. Chem. Soc.* **1978**, *100* (16), 5226−5227.

(38) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752−6756. (b) Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; La Vecchia, L.; Briard, E. Improving Nonspecific Binding and Solubility: Bicycloalkyl Groups and Cubanes as *Para*-Phenyl Bioisosteres. *ChemMedChem.* **2017**, *12* (8), 590−598. (c) Talele, T. T. The "Cyclopropyl Fragment" Is a Versatile Player That Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59* (19), 8712−8756.

(39) Bär, R. M.; Gross, P. J.; Nieger, M.; Bräse, S. Sodium Bicyclo[1.1.1]Pentanesulfinate: A Bench-stable Precursor for Bicyclo[1.1.1]Pentylsulfones and Bicyclo- [1.1.1]-Pentanesulfonamides. *Chem.—Eur. J.* **2020**, *26* (19), 4242−4245.

(40) In the context of commercial prices for acid starting materials, inexpensive was defined as less than $30 per 1 gram across all commercial vendors using the *Reaxys* database. *Reaxys*; Elsevier. https://www.reaxys.com/#/search/quick (accessed 2023-06-30).

(41) Sulfonyl chlorides were classified as prohibitively expensive if their price exceeded $100 per 1 gram across all commercial vendors using the *Reaxys* database. *Reaxys*; Elsevier. https://www.reaxys.com/#/search/quick (accessed 2023-06-30).

https://doi.org/10.1021/jacs.3c08218
J. Am. Chem. Soc. 2023, 145, 21189−21196