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Letter

Site-Selective C–H Functionalization–Sulfination Sequence to Access Aryl Sulfonamides

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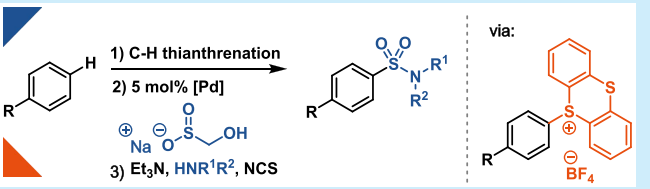
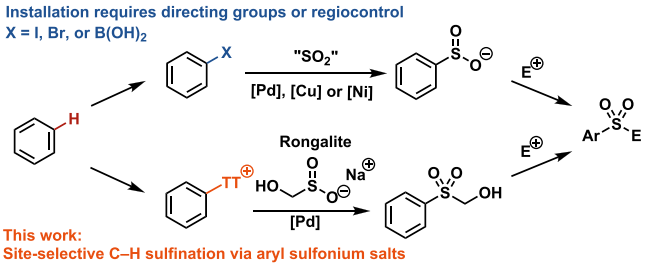
ABSTRACT: Aryl sulfinates are precursors to a diverse number of sulfonyl-derived arenes, which are common motifs in pharmaceuticals and agrochemicals. Here, we report a site-selective two-step C–H sulfination sequence via aryl sulfonium salts to access aryl sulfonamides. Combined with site-selective aromatic thianthrenation, an operationally simple one-pot palladium-catalyzed protocol introduces the sulfonyl group using sodium hydroxymethylsulfinate (Rongalite) as a source of SO_2^{2-}. The hydroxymethyl sulfone intermediate generated from the catalytic process can be employed as a synthetic handle to deliver a variety of sulfonyl-containing compounds.



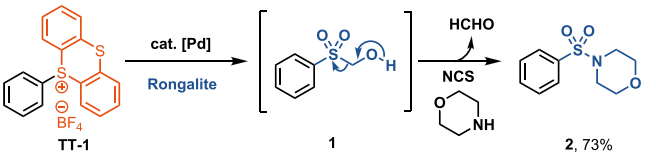
Sulfur occurs in several different oxidation states; the most stable hexavalent organosulfur compounds such as sulfonamides, sulfones, and sulfonyl fluorides are abundant motifs in pharmaceuticals and agrochemicals.[1] Commonly, sulfonyl functionality is introduced into arenes by electrophilic aromatic substitution with reagents such as chlorosulfuric acid.[2] The limitations of such transformations are the formation of constitutional isomers and the low functional group tolerance.[3] Synthetically valuable sulfonyl-containing molecules can be obtained by using aryl sulfinates as versatile intermediates, which can be formed from prefunctionalized arenes such as aryl halides,[4] aryl boronic acids,[5,6] aryl Grignard reagents,[7,8] or aryl iodonium salts[9] in the presence of sulfur dioxide surrogates.[10] Additionally, primary[11,12] and secondary[13] sulfonamides can generate sulfinates *in situ* acting as terminal functional groups. However, the site selectivity of the synthesis of the starting materials remains a challenge for many of those substrates.[14−16] Here, we present a two-step C–H sulfination sequence of site-selectively formed aryl thianthrenium salts under the action of a palladium catalyst and the inexpensive industrial reagent sodium hydroxymethanesulfinate (Rongalite) to synthetically access the sulfinate salt precursor, hydroxymethylsulfone. Subsequent electrophilic trapping of the sulfinate can be useful for functional group diversification (Scheme 1).

Given that sulfinates can often be difficult to purify, strategies for accessing sulfonamides among other valuable sulfonyl-containing groups entail a two-step one-pot procedure by using the aryl sulfinate in a subsequent transformation.[17−23] Aryl sulfinates can be obtained from the reaction of aryl nucleophiles with SO_2, which is a toxic gas and is therefore frequently replaced with solid SO_2 surrogates such as the adduct of SO_2 with DABCO, called DABSO.[24] Suitable aryl nucleophiles are Grignard reagents,[7] aryl-zinc compounds,[8] and arylboronic acids,[5,6] all of which react well with DABSO. The generation of arylsulfinates from aryl electrophiles such as aryl halides[4] and SO_2 (surrogates) is also possible when using an additional

Scheme 1. Synthetic Approaches to Aryl Sulfonyl Groups



Scheme 2. Formation of Phenyl Hydroxymethyl Sulfone en Route to a Sulfonamide[a]



[a]Two-step yield of the sulfonylation. Reaction conditions: (i) sulfonium salt (0.2 mmol), Pd(dppf)Cl_2 (5 mol %), Rongalite (1.5 equiv), i-PrOH (0.2 M), 60 °C, 12 h; (ii) Et_3N (2.0 equiv), morpholine (2.0 equiv), NCS (2.0 equiv), 25 °C, 1 h.

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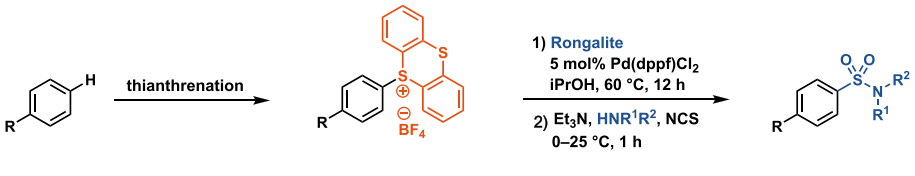
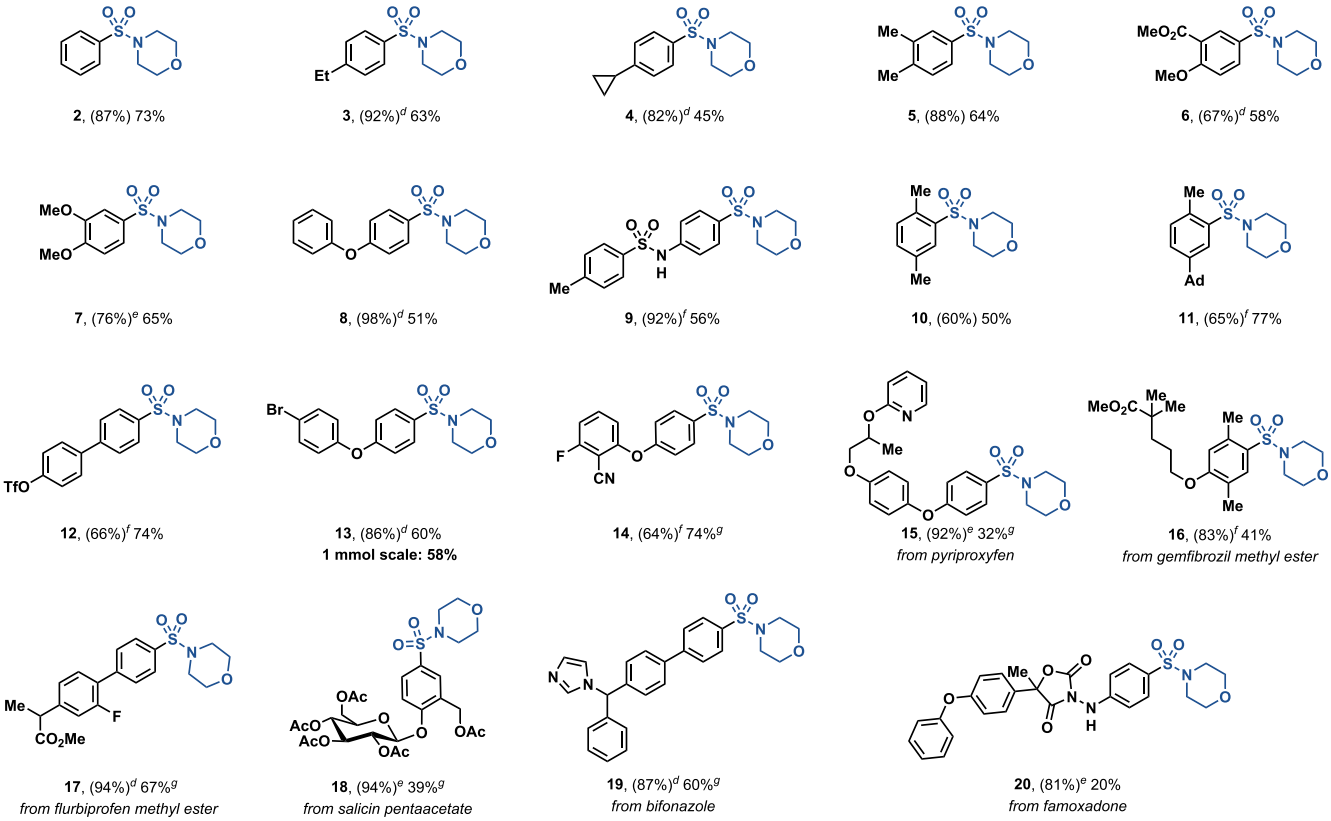
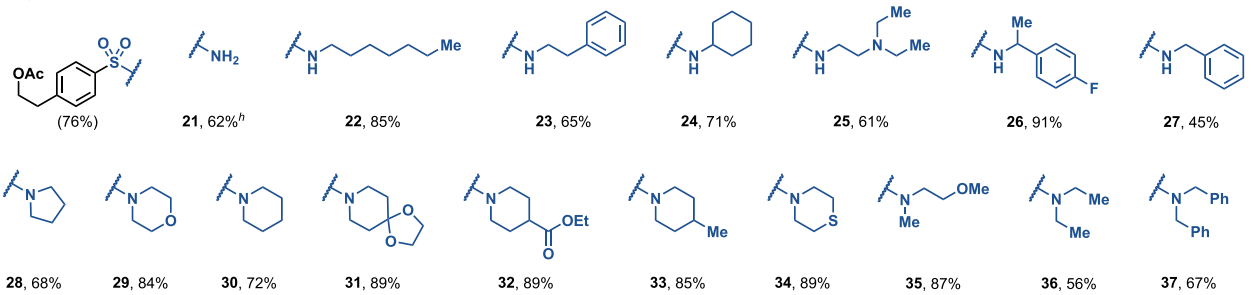
Scheme 3. Evaluation of Thianthrenium Salts for the Palladium-Catalyzed Coupling with Rongalite toward the Synthesis of Sulfonamides[a]



A) Scope of arylsulfoniums:



B) Scope of amines:



[a]Reaction conditions: (1) sulfonium salt (0.1−0.2 mmol), Pd(dppf)Cl_2 (5 mol %), Rongalite (1.5 equiv), i-PrOH (0.2 M), 60 °C, 12 h; (2) Et_3N (2.0 equiv), R^1R^2NH (2.0 equiv), NCS (2.0 equiv), 25 °C, 1 h. [b]Yield of thianthrenation. [c]Two-step yield of sulfonylation. [d]Yield of the thianthrenation from ref 28. [e]Yield of the thianthrenation from ref 27. [f]Yield of the thianthrenation from ref 29. [g]MeCN was used as a co-solvent. [h]Two-step yield of the sulfonylation with (2) hydroxylamine-*O*-sulfonic acid (4.0 equiv) and sodium acetate (7.0 equiv), at 25 °C for 1 h, instead of Et_3N and NCS.

reducing agent.[19] An alternative route for generating sulfinates from aryl electrophiles, without the need for an exogenous reducing reagent, would be the reaction with a source of SO_2^{2-}, such as Rongalite (sodium hydroxymethylsulfinate), an industrial bleaching and reducing reagent.[25] While alkyl halides have been converted to alkyl sulfinates by reaction with Rongalite,[26] methods for achieving aromatic sulfinylation with Rongalite remain unexplored. Although previous methods for making aryl sulfinates are practical when synthetic handles already exist, selective installation of halo or boryl substituents

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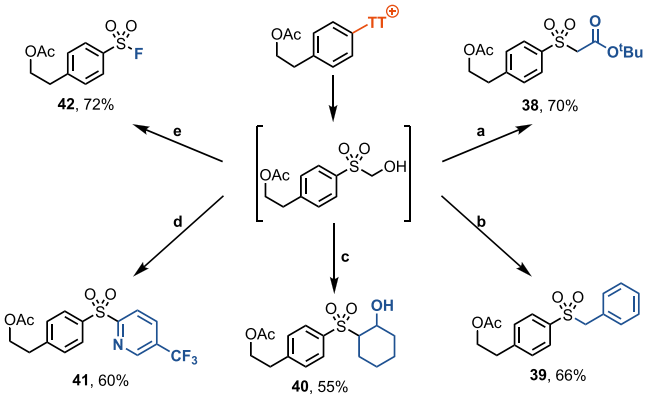
Scheme 4. Functional Group Diversification via an Aryl Hydroxymethyl Sulfone[a]



[a]For detailed experimental procedures, see the Supporting Information. The corresponding electrophiles were reacted: (a) α-bromo *tert*-butyl acetate, (b) benzyl bromide, (c) cyclohexene oxide, (d) 2-chloro-5-(trifluoromethyl)pyridine, and (e) *N*-fluorobenzenesulfonimide.

at a late stage can be challenging.[14−16] The combination of site-selective thianthrenation and the first example of a palladium-catalyzed C−S bond forming reaction using Rongalite grants access to aryl hydroxymethyl sulfones, masked sulfinates that undergo a base-mediated fragmentation to release aryl sulfinates.

In our previous work,[27] we capitalized on the exquisite selectivity of aromatic C−H thianthrenation for subsequent site-selective functionalization in a two-step process to access various functional groups via palladium or photoredox catalysis.[28−31] In this study, we envisioned a synthetic strategy for installing a masked sulfinate via a cross-coupling between aryl sulfonium salts and Rongalite. In contrast to our previous sulfone synthesis,[27] the sulfinate precursor can be used *in situ* for further derivatization.[32]

We developed reaction conditions to synthesize aryl hydroxymethyl sulfones [**1** (Scheme 2)] from aryl thianthrenium salts via a palladium-catalyzed C−S bond formation by employing $Pd(dppf)Cl_2$ as the catalyst and Rongalite as the coupling partner in iPrOH at 60 °C. The structure of **1** was confirmed by NMR spectroscopy and high-resolution mass spectrometry (see the Supporting Information). In the presence of a base, intermediate **1** loses formaldehyde, and the aryl sulfinate is generated *in situ*. The oxidative amination of the resulting aryl sulfinate with Et_3N (2.0 equiv), morpholine (2.0 equiv), and *N*-chlorosuccinimide (NCS) (2.0 equiv) at 25 °C for 1 h resulted in sulfonamide **2** in 73% yield from the corresponding aryl sulfonium salt **TT-1** (Scheme 2).

The optimal reaction conditions proved to be effective for generating a variety of structurally diverse sulfonamides with respect to the sulfonium salts, using morpholine as a representative amine component (Scheme 3A). Alkyl-substituted aryl sulfonamides (**3**−**5**) were obtained in 45−64% yields. A range of electron-rich arenes reacted under our conditions, providing aryl sulfonamides (**6**−**9**) in 51−65% yields. *ortho*-Substituted sulfonamides **10** and **11** were obtained in 50% and 77% yields, respectively. The hydrodefunctionalized compound was identified as the major side product for these substrates. Under our coupling conditions, the reactivity of sulfonium salts exceeds the reactivity of standard palladium cross-coupling partners, bromo and triflate groups, and compounds **12** and **13** were obtained in 74% and 60% yields, respectively. As a further demonstration of the utility of this methodology, late-stage functionalization of several active pharmaceuticals and agrochemicals was performed. For these more complex sulfonium salts (**15**−**20**), the solubility in isopropanol was low and proved to be an obstacle to achieving full conversion. However, when using the polar aprotic acetonitrile as a co-solvent, conversion improved and the morpholino sulfonyl compounds were obtained in 20−67% yields.

We tested our two-step one-pot procedure with a set of primary (**22**−**25**), benzylic (**26** and **27**), and secondary (**28**−**37**) amines (Scheme 3B), resulting in 45−91% yields. In addition, the ammonia-derived sulfonamide **21** could be obtained in 62% yield with hydroxylamine-*O*-sulfonic acid in the presence of sodium acetate.

Finally, we evaluated several common electrophiles in the synthesis of sulfone derivatives via the hydroxymethyl sulfone intermediate (Scheme 4). The reaction with alkyl electrophiles, such as alkyl bromides or epoxides, afforded the alkylaryl sulfones (**38**−**40**) in 55−70% yields. Trapping with a heteroaryl electrophile in a nucleophilic aromatic substitution reaction yielded an aryl-heteroaryl sulfone (**41**) in 60% yield. Sulfonyl fluoride (**42**) can be obtained in 72% yield by reaction with the electrophilic fluorinating reagent *N*-fluorobenzenesulfonimide.[33]

In conclusion, we have identified the readily available and inexpensive SO_2^{2-} source, Rongalite, as a coupling partner in the palladium-catalyzed sulfination of aryl sulfonium salts. Besides a highly selective C−H functionalization, the two-step sequence grants access to valuable sulfinate precursors that can subsequently be unmasked and afford sulfonamides, which are important functional motifs in pharmaceuticals and agrochemicals among sulfones and sulfonyl fluorides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00982.

Detailed experimental procedures and spectroscopic characterization (PDF)

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Author Contributions

E.M.A. and M.B.P. developed the sulfination reaction. E.M.A. optimized follow-up transformations. All authors wrote the manuscript. T.R. directed the project.

Notes

The authors declare the following competing financial interest(s): A patent application (EP18204755.5, Germany) dealing with the use of thianthrene and its derivatives for CH functionalization has been filed, and F.B. and T.R. may benefit from royalty payments.

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■ REFERENCES

(1) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200−1216.
(2) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific and Technical, 1989; p 877.
(3) Bassin, J. P.; Cremlyn, R. J.; Swinbourne, F. J. Review. Chlorosulfonation of Aromatic and Hetero-Aromatic Systems. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *56*, 245−275.
(4) Deeming, A. S.; Russell, C. J.; Willis, M. C. Palladium(II)-Catalyzed Synthesis of Sulfinates from Boronic Acids and DABSO: A Redox-Neutral, Phosphine-Free Transformation. *Angew. Chem., Int. Ed.* **2016**, *55*, 747−750.
(5) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-Catalyzed Synthesis of Ammonium Sulfinates from Aryl Halides and a Sulfur Dioxide Surrogate: A Gas- and Reductant-Free Process. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204−10208.
(6) 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*, 10638−10641.
(7) Deeming, A. S.; Russell, C. J.; Hennessy, A. J.; Willis, M. C. DABSO-Based, Three Component, One-Pot Sulfone Synthesis. *Org. Lett.* **2014**, *16*, 150−153.
(8) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. Synthesis of Sulfones from Organozinc Reagents, DABSO, and Alkyl Halides. *Org. Lett.* **2014**, *16*, 154−157.
(9) Zhang, W.; Luo, M. Iron-catalyzed synthesis of arylsulfinates through radical coupling reaction. *Chem. Commun.* **2016**, *52*, 2980−2983.
(10) Emmett, E. J.; Willis, M. C. The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry. *Asian J. Org. Chem.* **2015**, *4*, 602−611.
(11) Fier, P. S.; Maloney, K. M. NHC-Catalyzed Deamination of Primary Sulfonamides: A Platform for Late-Stage functionalization. *J. Am. Chem. Soc.* **2019**, *141*, 1441−1445.
(12) Gómez-Palomino, A.; Cornella, J. Selective Late-Stage Sulfonyl Chloride Formation from Sulfonamides Enabled by Pyry-BF_4. *Angew. Chem., Int. Ed.* **2019**, *58*, 18235−18239.
(13) Fier, P. S.; Kim, S.; Maloney, K. M. Reductive Cleavage of Secondary Sulfonamides: Converting Terminal Functional Groups into Versatile Synthetic Handles. *J. Am. Chem. Soc.* **2019**, *141*, 18416−18420.
(14) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002**, *124*, 390−391.
(15) Saito, Y.; Segawa, Y.; Itami, K. *para*-C-H Borylation of Benzene Derivatives by a Bulky Iridium Catalysts. *J. Am. Chem. Soc.* **2015**, *137*, 5193−5198.
(16) Tang, R.-J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol. *J. Org. Chem.* **2018**, *83*, 930−938.
(17) Deeming, A. S.; Emmett, E. J.; Richards-Taylor, C. S.; Willis, M. C. Rediscovering the Chemistry of Sulfur Dioxide: New developments in Synthesis and Catalysis. *Synthesis* **2014**, *46*, 2701−2710.
(18) Chen, Y.; Willis, M. C. Copper (I)-Catalyzed Sulfonylative Suzuki-Miyaura Cross-Coupling. *Chem. Sci.* **2017**, *8*, 3249−3253.
(19) Anderson, K. K. In *Sulfonic Acids and Their Derivatives in Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Jones, D. N., Eds.; Pergamon Press: Oxford, U.K., 1979; Vol. 3, pp 331− 350.
(20) Deeming, A. S.; Russell, C. J.; Willis, M. C. Combining Organometallic Reagents, the Sulfur Dioxide Surrogate DABSO, and Amines: A One-Pot Preparation of Sulfonamides, Amenable to Array Synthesis. *Angew. Chem., Int. Ed.* **2015**, *54*, 1168−1171.
(21) Zhu, H.; Shen, Y.; Deng, Q.; Huang, C.; Tu, T. One-Pot Bimetallic Pd/Cu-Catalyzed Synthesis of Sulfonamides from Boronic Acids, DABSO and *O*-Benzoyl Hydroxylamines. *Chem. - Asian J.* **2017**, *12*, 706−712.
(22) Flegeau, E. F.; Harrison, J. M.; Willis, M. C. One-Pot Sulfonamide Synthesis Exploiting the Palladium Catalyzed Sulfination of Aryl Iodides. *Synlett* **2015**, *27*, 101−105.
(23) Lo, P. K. T.; 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*, 10668−10673.
(24) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. DABCO-*Bis*(sulfur dioxide), DABSO, as a Convenient Source of Sulfur Dioxide for Organic Synthesis: Utility in Sulfonamide and Sulfamide preparation. *Org. Lett.* **2011**, *13*, 4876−4878.
(25) Kotha, S.; Khedkar, P. Rongalite: A Useful Green Reagent in Organic Synthesis. *Chem. Rev.* **2012**, *112*, 1650−1680.
(26) Shavnya, A.; Coffey, S. B.; Hesp, K. D.; Ross, S. C.; Tsai, A. S. Reaction of Alkyl Halides with Rongalite: One-Pot and Telescoped Synthesis of Aliphatic Sulfonamides, Sulfonyl Fluorides and Unsymmetrical Sulfones. *Org. Lett.* **2016**, *18*, 5848−5851.
(27) Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Site-selective and versatile aromatic C−H functionalization by thianthrenation. *Nature* **2019**, *567*, 223−228.
(28) Engl, P. S.; Häring, A. P.; Berger, F.; Berger, G.; Peréz-Bitrián, A.; Ritter, T. C-N Cross-Couplings for Site-Selective Late-Stage Diversification via Aryl Sulfonium Salts. *J. Am. Chem. Soc.* **2019**, *141*, 13346−13351.
(29) Ye, F.; Berger, F.; Jia, H.; Ford, J.; Wortman, A.; Borgel, J.; Genicot, C.; Ritter, T. Aryl Sulfonium Salts for Site-Selective Late-Stage Trifluoromethylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 14615−14619.
(30) Sang, R.; Korkis, S.; Su, W.; Ye, F.; Engl, P.; Berger, F.; Ritter, T. Site-Selective C-H Oxygenation via Aryl Sulfonium Salts. *Angew. Chem., Int. Ed.* **2019**, *58*, 16161−16166.
(31) Li, J.; Chen, J.; Sang, R.; Ham, W.-S.; Plutschack, M. B.; Berger, F.; Chabbra, S.; Schnegg, A.; Genicot, C.; Ritter, T. Photoredox catalysis with aryl sulfonium salts enables site-selective late-stage fluorination. *Nat. Chem.* **2020**, *12*, 56−62.
(32) Willis, M. C. New catalytic reactions using sulfur dioxide. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 654−657.
(33) 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*, 1233−1237.

https://dx.doi.org/10.1021/acs.orglett.0c00982
Org. Lett. 2020, 22, 4593−4596