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Communication

Photoredox Catalysis-Enabled Sulfination of Alcohols and Bromides

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ABSTRACT: Sulfinates are important lynchpin intermediates in pharmaceutical production; however, their synthesis via photoredox catalysis is challenging because of their facile oxidation. We herein disclose a photocatalytic strategy for the direct conversion of alcohols and alkyl bromides into alkyl sulfinates. These transformations are enabled by the utilization of easily oxidized radical precursors—namely, alcohol *N*-heterocyclic carbene adducts and *N*-adamantyl aminosupersilane—that facilitate efficient synthesis of the oxidatively labile sulfinate products. A broad range of functional groups are amenable to the reported transformations, providing rapid access to sulfonamides, sulfonyl halides, sulfones, and sulfonic acids. The utility of these methods is further demonstrated via the late-stage diversification of natural products and drugs into pharmaceutically relevant sulfonamides and "clickable" sulfonyl fluorides. In summary, this work illustrates the potential of novel radical precursors to expand the breadth of photoredox transformations.

Organosulfur compounds are ubiquitous in agrochemicals,[1] materials,[2] fine chemicals, and pharmaceuticals.[3] Indeed, sulfur is more prevalent in approved drugs than both fluorine and phosphorus.[4] In drug discovery, sulfur(VI) derivatives, such as sulfonic acids, sulfonamides, and sulfones, are of high value because they are often utilized as bioisosteres for carboxylic acids, amides, and esters.[5−7] Given the diverse heteroatom connectivity that sulfonyl-containing functional groups can adopt, the accession of desirable organosulfur products generally requires step-intensive *de novo* synthesis. Recently, sulfinates ($R-SO_2^-$) have emerged as useful lynchpin intermediates that can access a wide variety of important sulfur compounds.[8] As such, new methods for the synthesis of sulfinates are coveted by numerous chemical industries.

Despite the value of sulfinates, their synthesis via a redox manifold remains challenging (Figure 1). Their exceedingly low oxidation potential ($E_{pa}[R-SO_2^-/R-SO_2^\bullet]$ = +0.5 V vs SCE)[9] renders sulfinate oxidation a facile process, a property that has been leveraged for the generation of sulfonyl radicals[10,11] and aliphatic radicals through subsequent extrusion of SO_2.[12] Given the sulfinate's ease of oxidation, only a handful of approaches have been reported for the reverse transformation, namely, the construction of alkyl sulfinates from radicals. To avoid sulfinate oxidation, these transformations employ net-reductive conditions,[13−15] proton-coupled electron transfer (PCET),[16] or hydrogen-atom transfer (HAT).[17,18] However, these approaches limit the functional groups that can be employed in sulfinate synthesis. To this point, we became interested in oxidative radical generation modes other than HAT that might enable the direct conversion of abundant functionality to alkyl sulfinates. This would allow for a site-specific, redox-neutral means to access a novel sulfur-based chemical space, thereby affording a range of valuable products while also avoiding intractable mixtures of undesired isomers. We considered established oxidative radical generation methods that might facilitate this transformation. However, many conventional methods for oxidative radical generation, such as carboxylate or oxalate oxidation followed by CO_2 extrusion[19,20] ($E_{pa}[R-CO_2^-/R-CO_2^\bullet]$ and $E_{pa}[R-C_2O_4^-/R-C_2O_4^\bullet]$ = +1.2 V vs SCE)[21] or oxidation of supersilanol (SiOH) followed by radical Brook rearrangement and halide abstraction ($E_{pa}[SiOH/SiO^\bullet]$ = +1.54 V vs SCE),[22] require single-electron transfers with activated substrates that are themselves more thermodynamically challenging to oxidize than alkyl sulfinates.

To overcome this issue, we envisioned developing a photoredox-neutral synthesis of alkyl sulfinates that features a mild radical generation mode from abundant functional groups to facilitate activation of the substrate and minimize competing oxidation of the sulfinate product. Alcohols are the most prevalent native functional group, with over 61% of natural products containing at least one hydroxy group.[23] Recently, our group disclosed a method for the radical deoxygenative arylation of alcohols,[24] which features the *N*-heterocyclic carbene−alcohol adduct (NHC-OR), an activated alcohol species that is formed under mild conditions without purification. Notably, this activated alcohol has an oxidation potential significantly lower than other oxidative methods for generating alkyl radicals from alcohols ($E_{pa}[NHC-OR/NHC-OR^{+\bullet}]$ = +0.9 V vs SCE). Additionally, Stern−Volmer quenching studies reveal that the NHC−alcohol adduct significantly outcompetes zinc and sodium sulfinates, as well as cesium oxalates, in photocatalyst quenching (Scheme 1, top). For this reason, we hypothesized that this NHC−alcohol

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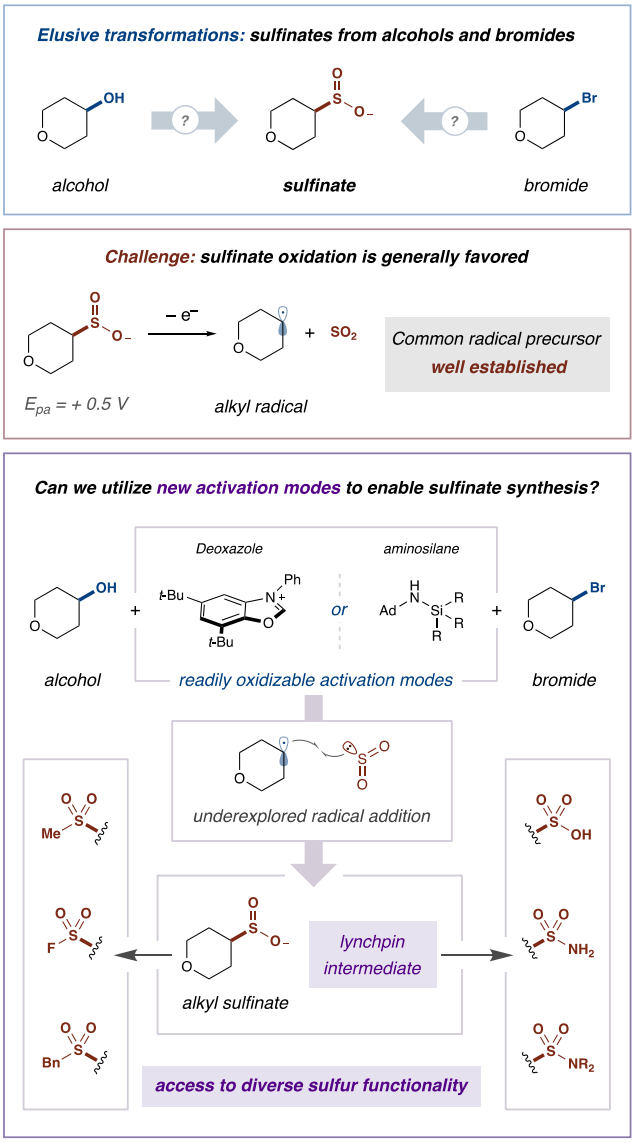
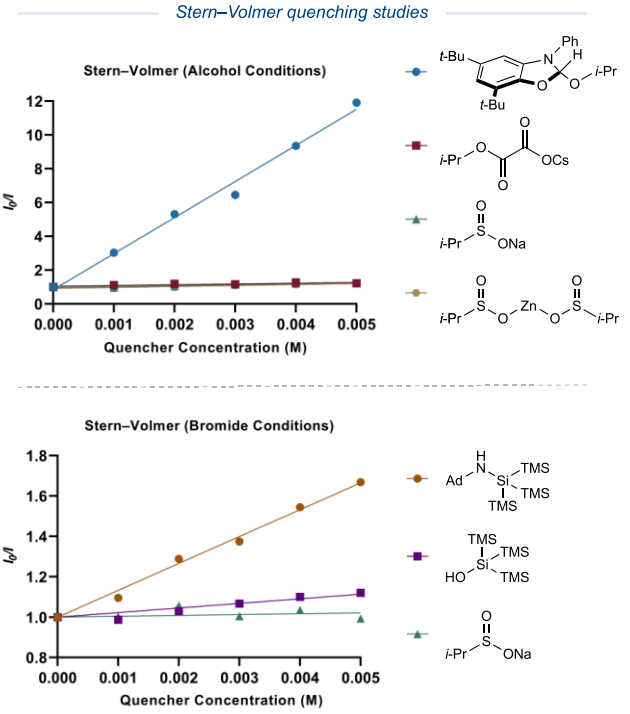


Figure 1. Development of a general C(sp^3)–OH and C(sp^3)–Br sulfination.

adduct, in conjunction with a suitable SO_2 surrogate and photocatalyst, could provide a broadly applicable method to convert alcohols to their corresponding sulfinates—an elusive reaction to date.

In considering additional functional handles that might be targeted for radical sulfination, we became interested in alkyl bromides. In particular, we were intrigued by the recently reported *N*-adamantyl aminosupersilane reagent (Si–NHAd), which was used in the development of a broadly applicable cross-electrophile coupling of unactivated chlorides.[25] Though the initial report of this reagent emphasized the effect of the nitrogen atom's π-donation to the silyl radical, thereby generating a more nucleophilic species capable of performing challenging halide abstractions, cyclic voltammetry studies also showed that this reagent is oxidized at much lower potentials (E_{pa}[Si–NHAd/Si–NHAd$^{+\bullet}$] = +0.75 V vs SCE) than related silyl radical precursors. Moreover, Stern–Volmer quenching studies showed that this reagent outcompetes supersilanol and sodium sulfinate in photocatalyst quenching (Scheme 1, bottom). We, thus, postulated that this activation mode

Scheme 1. Stern–Volmer Quenching Studies[a]



[a]See the Supporting Information for complete experimental details.

would be well suited for the direct conversion of alkyl bromides to alkyl sulfinates, a transformation that generally relies on either sensitive organometallic reagents or lengthy synthetic sequences.[12,26,27] We hypothesized that these radical generation strategies would enable the functionalization of highly abundant chemical feedstocks—alcohols and bromides—to valuable organosulfur products. Moreover, we believe that the envisioned transformations would highlight the value of developing reagents that afford radicals via mild electron transfer, thus, expanding the range of products accessible by photoredox catalysis to include even those that are themselves susceptible to oxidation or reduction.

The proposed reaction mechanisms for both the debrominative and deoxygenative sulfination of bromides and alcohols are included in the Supporting Information. In the alcohol sulfination reaction, the NHC–alcohol adduct is oxidized by an excited Ir(III) photocatalyst, {Ir[dF(CF_3)ppy]$_2$ (dtbbpy)}-PF_6 ($E^{III*/II}$ = +1.21 V vs SCE in MeCN),[28] and deprotonated to arrive at an NHC radical, which, upon β-scission, furnishes the alkyl radical that is captured by SO_2 to form the alkyl sulfonyl radical. In the bromide reaction, an excited Ir(III) photocatalyst {Ir[dF(CF_3)ppy]$_2$ (5,5′-dCF_3bpy)}PF_6 ($E^{III*/II}$ = +1.68 V vs SCE in MeCN)[29] oxidizes the aminosupersilane via single-electron transfer (SET). The silyl-centered radical formed after radical *aza*-Brook rearrangement[30−32] abstracts a bromine atom from the alkyl bromide to generate an alkyl radical, which is captured by SO_2 to form the alkyl sulfonyl radical. To close the photocatalytic cycle in both proposed mechanisms, the reduced ground-state photocatalysts reduce the alkyl sulfonyl radicals via SET (E_{pa} [R–SO_2^-/R–$SO_2^{\bullet}$] ≈ 0.46 V in MeCN vs SCE),[9] thereby generating the alkyl sulfinate product.

Optimization of key reaction parameters on a model alcohol substrate furnished the desired sulfinate in excellent isolated

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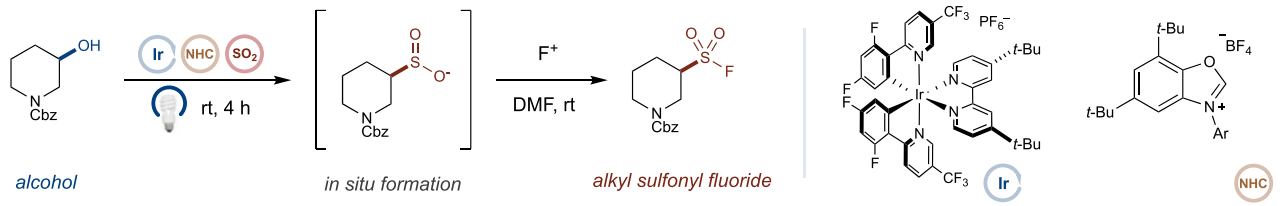
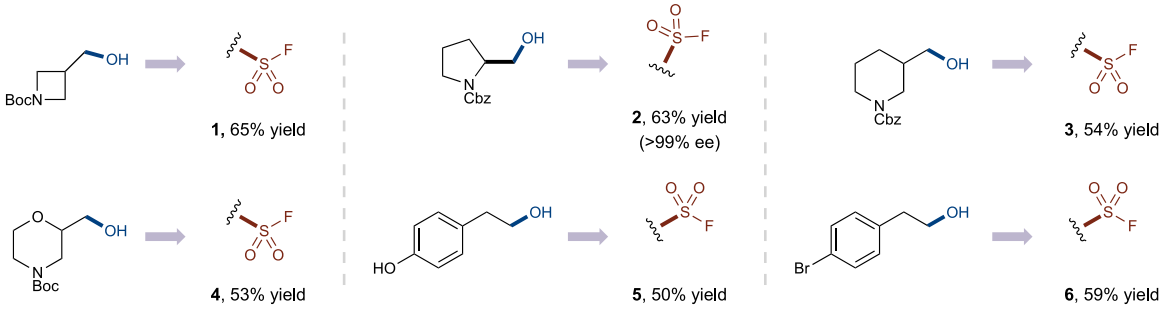
Table 1. Scope of Deoxygenative Sulfination of Alcohols[a]



primary



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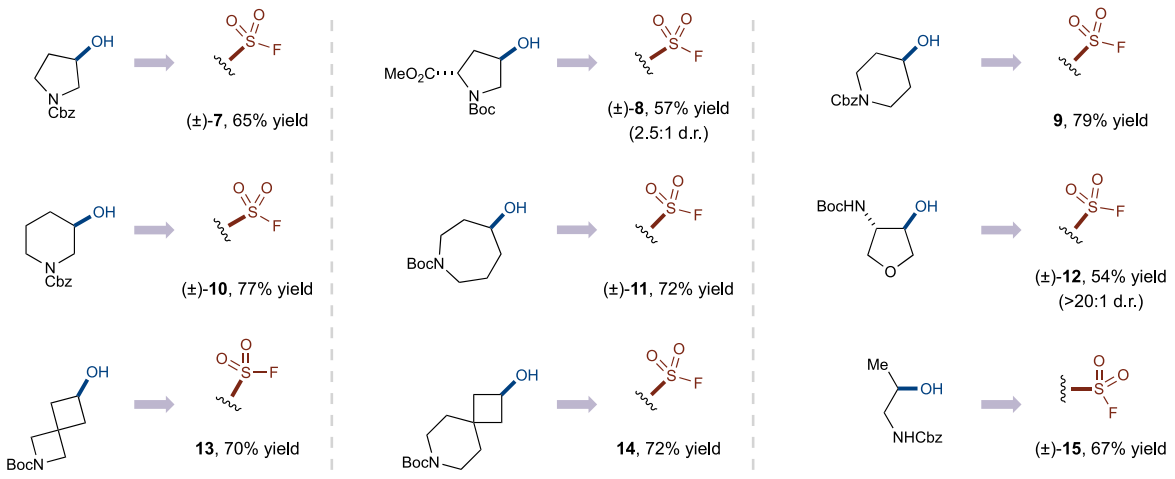
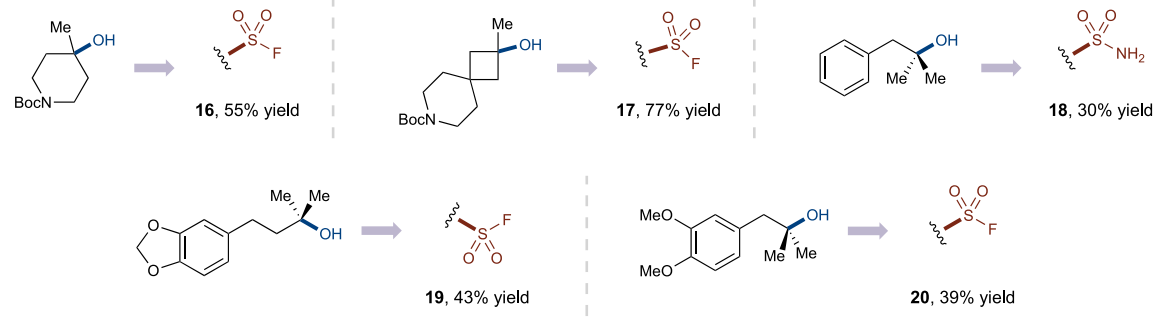


tertiary



additional examples in SI

[a]All yields are isolated. Reaction performed with substrate (1.0 equiv, 0.5 mmol), NHC (1.2 equiv), and pyridine (1.2 equiv) in TBME with stirring at room temperature for 30 min. Then, $K_2S_2O_5$ (2.0 equiv), {Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)}PF$_6$ (1 mol %), Zn(OAc)$_2$ (4 equiv), TBACl (2 equiv), and water (40 equiv) in DMF/TBME and are irradiated for 4 h with 450 nm LEDs followed by addition of Selectfluor I (2 equiv) or hydroxylamine-*O*-sulfonic acid (3 equiv); then, it is stirred at room temperature for 16 h. See the Supporting Information for complete experimental details. TBME: tert-butyl methyl ether.

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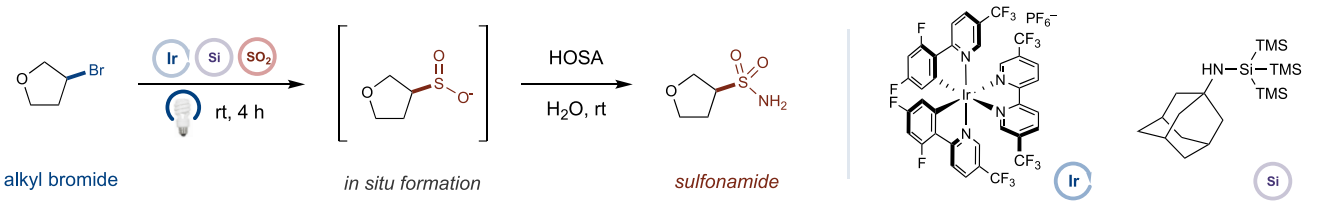
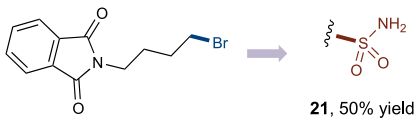
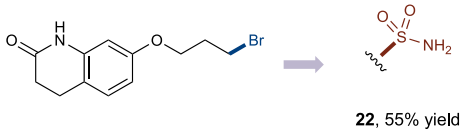
Table 2. Scope of Debrominative Sulfination[a]



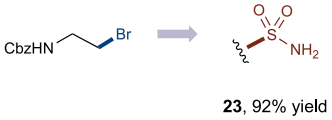
primary



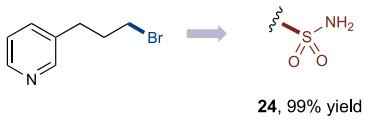
21, 50% yield



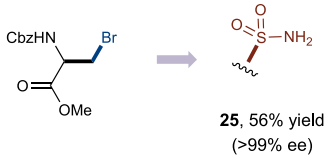
22, 55% yield



23, 92% yield

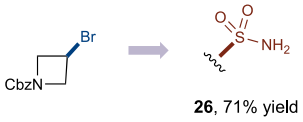


24, 99% yield

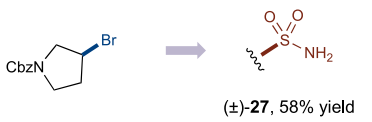


25, 56% yield
(>99% ee)

secondary



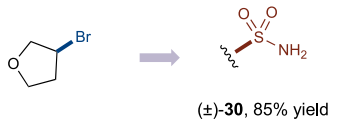
26, 71% yield



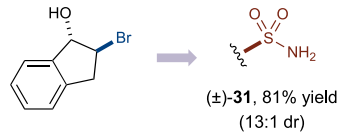
(±)-**27**, 58% yield

28, 51% yield

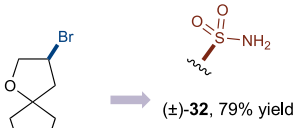
29, 58% yield



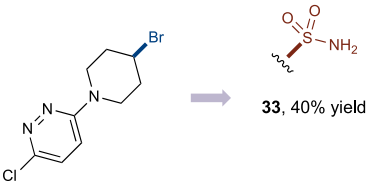
(±)-**30**, 85% yield



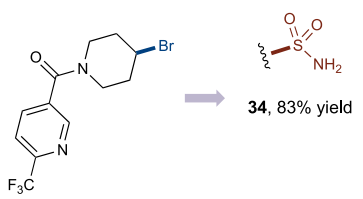
(±)-**31**, 81% yield
(13:1 dr)



(±)-**32**, 79% yield

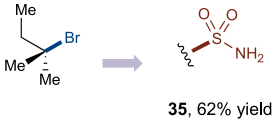


33, 40% yield

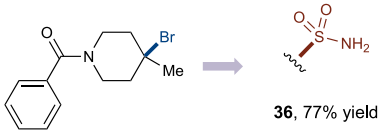


34, 83% yield

tertiary



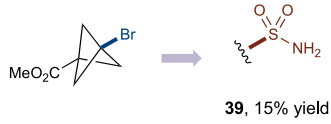
35, 62% yield



36, 77% yield

37, 74% yield

38, 50% yield



39, 15% yield

additional examples in SI

[a]All yields are isolated. Reaction performed with substrate (1.0 equiv, 0.5 mmol), $Na_2S_2O_5$ (3.0 equiv), {Ir[dF(CF_3)ppy]$_2$(5,5′-dCF_3bpy)}PF_6 (1 mol %), aminosupersilane (1.2 equiv), and NaOAc (2 equiv) in trifluorotoluene (or acetonitrile) and water and irradiated for 4 h with 450 nm LEDs followed by addition of hydroxylamine-*O*-sulfonic acid (5 equiv) with stirring at room temperature for 16 h. See the Supporting Information for complete experimental details.

yield (see the Supporting Information). Notably, attempts to identify conditions to effect the same transformation employing independently synthesized cesium oxalate afforded no product, which is consistent with the hypothesized importance

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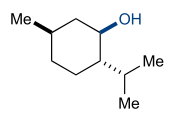
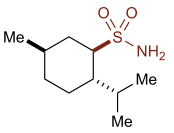
Table 3. Sulfination of Natural Product and Pharmaceutical Substrates[a]

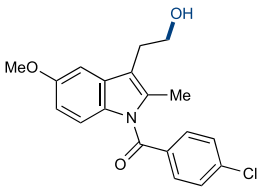
Late-stage Functionalization of Drugs and Bio-relevant Molecules



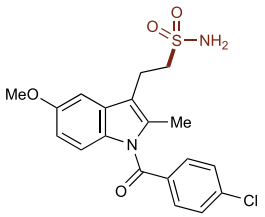
(–)-menthol



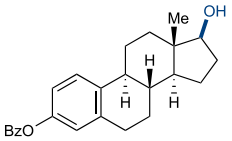
40, 48% yield
(19:1 d.r.)



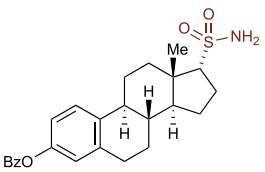
indomethacin analogue



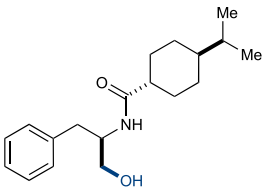
43, 59% yield



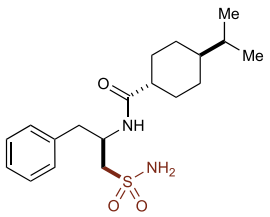
estradiol benzoate



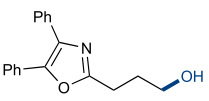
41 54% yield
(>20:1 d.r.)



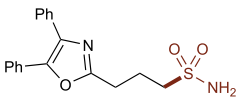
nateglinide analogue



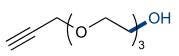
44, 43% yield



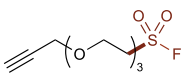
oxaprozin analogue



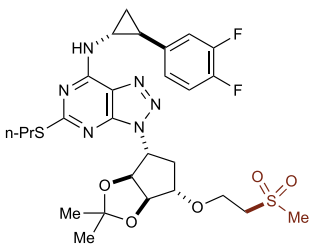
42, 27% yield



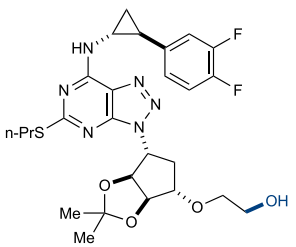
alkyne-PEG3-alcohol



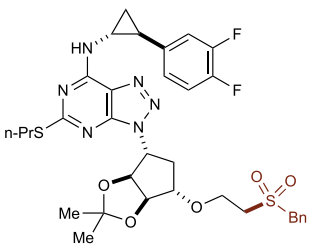
45, 42% yield



46, 50% yield

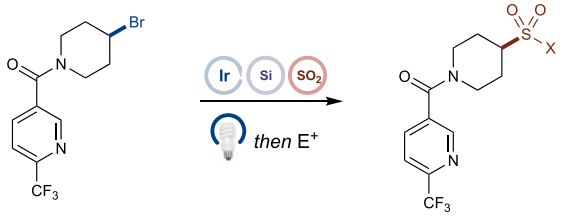


Ticagrelor acetonide



47, 50% yield

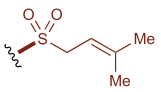
Diversification of Sulfinate



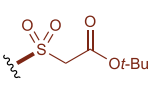
48, 90% yield

49, 84% yield

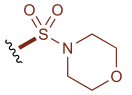
50, 74% yield



51, 58% yield



52, 66% yield



53, 51% yield

[a]All yields are isolated. See the Supporting Information for complete experimental details.

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of readily oxidized radical precursors. With the optimized conditions in hand, we next evaluated the scope for the deoxysulfination of alcohols (Table 1). Following the generation of sulfinate, Selectfluor was added to the reaction vial to provide a convenient synthesis of sulfonyl fluorides. Sulfonyl fluorides are privileged motifs in organic chemistry because they are known to engage in sulfur(VI)−fluoride exchange (SufFEx) click chemistry, which has growing applications in drug discovery, bioconjugation, and materials science.[33−41] Concerning the scope of this reaction, primary alcohols bearing saturated heterocyclic scaffolds ranging from four- to six-membered rings were converted to their sulfonyl fluoride analogues in good yields (**1**−**4**). Notably, unprotected phenols (**5**, 50% yield), as well as aryl bromides (**6**, 59% yield), were well tolerated, which offers the opportunity for further diversification. Secondary alcohols were also productive substrates. Saturated heterocyclic scaffolds, including pyrrolidines, piperidines, azepane, and tetrahydrofuran cores, were transformed to the corresponding sulfonyl fluorides in good to great yields (**7**−**12**). Additionally, spirocyclic motifs are amenable to the reaction conditions (**13** and **14**). This methodology was also extended to an acyclic framework, which generated **15** in a good yield (67% yield). Gratifyingly, this methodology allows for the facile conversion of tertiary alcohols to their highly elusive tertiary sulfonyl fluorides in fair to great yields (**16**−**20**); fewer than 60 examples of this motif have been reported in the literature to date. In summary, the ubiquitous alcohol functional handle can now be transformed in a single step to the corresponding sulfinate; facile one-pot fluorination provides accelerated access to the highly privileged alkyl sulfonyl fluoride motif, which can engage in important "click" functionalizations.

We next evaluated the scope of the debrominative sulfination (Table 2). Although the sulfinate can be isolated directly (see the Supporting Information), to demonstrate the value of the reaction in the synthesis of pharmaceutically important products, the alkyl sulfinates were converted in one pot to the primary sulfonamide ($R-SO_2NH_2$) via the addition of aqueous hydroxylamine-*O*-sulfonic acid (HOSA) after irradiation.[42] Sulfonamides are widely found in pharmaceuticals and comprise 8% of the top 200 bestselling drugs in 2018.[43] Concerning primary bromides, the reaction tolerated phthalimide (**21**, 50% yield) and dihydroquinalinone (**22**, 55% yield) scaffolds. A primary alkyl bromide with β-amine functionality was converted to its sulfonamide in excellent yield (**23**, 92% yield). Pyridines are also tolerated under the reaction conditions to yield the corresponding sulfonamide in quantitative yield (**24**, 99% yield). Moreover, a modified amino acid can be converted to the sulfonamide with good efficiency and complete retention of enantiopurity (**25**, 56% yield, >99% ee). With respect to secondary alkyl bromides, four-, five-, and six-membered saturated heterocycles were transformed to the target sulfonamides in good to great yields (**26**−**30**). Notably, alcohol-containing alkyl bromides can be converted to their primary sulfonamides in excellent yields and high diastereomeric ratios, thereby providing access to useful intermediates for further deoxygenative diversification (**31**, 81% yield, 13:1 dr). A spirocyclic alkyl bromide was functionalized with great efficiency (**32**, 79% yield). Despite the use of a highly oxidizing photocatalyst, an alkyl bromide containing a readily oxidizable tertiary amine afforded the desired product in a fair yield (**33**, 40% yield), further illustrating the value of employing easily oxidized radical precursors. Pyridine-containing secondary alcohols are also amendable to the reaction conditions (**34**, 83% yield). This methodology additionally enables the efficient conversion of a range of tertiary alkyl bromides to sterically hindered primary sulfonamides (**35**−**38**), which are difficult to synthesize via conventional transition metal catalysis or closed-shell reaction strategies. Lastly, the privileged medicinal scaffold bicyclo[1.1.1]pentane was converted to a previously inaccessible sulfonamide in synthetically useful yields (**39**, 15% yield).

Having evaluated the scope of these methods, we next sought to demonstrate their application to the late-stage diversification of bioactive and biologically relevant molecules (Table 3). Under the reaction conditions, (−)-menthol and estradiol benzoate were directly converted to sulfonamide analogues (**40** and **41**, 48% and 54% yield). Similarly, analogues of oxaprozin, indomethacin, and nateglinide were transformed to their sulfonamide congeners in one sequence with this novel methodology (**42**, **43**, and **44**). Considering the benefits of SufFEx, a commercially available, terminal-alkyne-containing PEG-3 alcohol was converted to the sulfonyl fluoride, which allowed for the installation of orthogonal click-chemistry handles for rapid incorporation into complex biological systems (**45**, 42% yield). Pleasingly, ticagrelor acetonide, notably bearing a thioether, can be divergently converted to either its methyl or benzyl sulfone under this methodology (**46** and **47**, 50% and 50% yield).

To further illustrate the utility of these methods, a variety of sulfur(VI) products were generated beyond the sulfonyl fluoride and the primary sulfonamide (Table 3). Because of the versatile nature of the sulfinate, a host of electrophiles could be intercepted to expediently generate a diverse library of sulfur(VI)-containing molecules. Starting from a pyridine-containing secondary alkyl bromide, it was possible to generate a sulfonic acid (**48**, 90% yield) and two alkyl sulfones (**49** and **50**, 84% and 74% yield) with excellent efficiency. Using an azaspirocylic alcohol, an allyl sulfone (**51**, 58% yield) and an ester-containing β-keto sulfone (**52**, 66% yield) were constructed in good yield. Excitingly, tertiary sulfonamides can be produced from the alcohol with an operationally simple workup of the sulfonyl fluoride followed by treatment with nucleophile and a Lewis acid (**53**, 51% yield);[44] thus, this procedure allows for the rapid conversion of alcohols to medicinally relevant substituted sulfonamides.[45]

In conclusion, general methods for debrominative and deoxygenative sulfination have been realized through photoredox catalysis. Despite proceeding via an easily oxidizable sulfinate intermediate, these transformations can provide excellent yields when employing readily oxidized NHC−alcohol adduct and aminosupersilane activation modes. The developed methods are amenable to a wide range of functional groups and allow for the rapid generation of a host of biologically relevant sulfur(VI) analogues, many of which are highly coveted across numerous chemical enterprises. Beyond the inherent value in generating important products, these transformations clearly illustrate the potential for photoredox catalysis to provide efficient access to products that are, themselves, prone to undergo single-electron chemistry, thereby further expanding the scope of this enabling catalytic paradigm.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c08216.

Experimental, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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