

Decatungstate-Catalyzed C(sp³)–H Sulfonylation: Rapid Access to Diverse Organosulfur Functionality

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Cite This: *J. Am. Chem. Soc.* 2021, 143, 9737–9743

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ABSTRACT: Here we report the direct conversion of strong, aliphatic C(sp³)–H bonds into the corresponding alkyl sulfinic acids via decatungstate photocatalysis. This transformation has been applied to a diverse range of C(sp³)-rich scaffolds, including natural products and approved pharmaceuticals, providing efficient access to complex sulfur-containing products. To demonstrate the broad potential of this methodology for the divergent synthesis of pharmaceutically relevant molecules, procedures for the diversification of the sulfinic acid products into a range of medically relevant functional groups have been developed.

Sulfonamides, sulfones, and sulfides are widely employed functional groups that are broadly found in modern materials,¹ agrochemicals,² and pharmaceuticals.³ The importance of these ubiquitous motifs is underscored by their abundance in bioactive molecules,⁴ with sulfur being more commonly found than fluorine or phosphorus in approved drugs.⁵ Despite the well-established importance of organosulfur compounds and many advances in C–H functionalization, there remain few catalytic technologies for the conversion of C(sp³)–H bonds into alkylsulfonyl groups.⁶ Intriguingly, recent studies involving alkyl sulfinates have instead focused on the inverse transform, namely C(sp³)–SO₂ bond cleavage via the oxidative conversion of sulfinates to alkyl radicals with concomitant extrusion of SO₂.⁷ With this in mind, we questioned whether this open-shell pathway might be reverse engineered to selectively deliver the opposite transformation. More specifically, we considered the formation of alkyl radicals from C–H bonds prior to SO₂ trapping and subsequent reduction, a pathway that if successful would generate C(sp³)-rich, sulfonyl-containing adducts from simple aliphatic substrates.

Given the current body of open shell coupling processes that rely on the oxidative extrusion of sulfur dioxide to access alkyl radicals, it is surprising to consider that previous kinetic⁸ and synthetic⁹ studies support the feasibility of C(sp³) radical capture by SO₂ (effectively the inverse process to extrusion). On this basis, we hypothesized that a sulfur dioxide alkyl radical trapping mechanism might be readily married with C(sp³)–H functionalization using a photo-HAT catalyst: a pathway that would expand the range of potential sulfur-containing feedstocks and, at the same time, provide a new strategy for the divergent, late-stage functionalization of pharmaceuticals. Herein, we report the successful execution of these ideals and present a hydrogen atom transfer (HAT)-sulfonylation protocol that employs aqueous sulfur dioxide, light, and an inexpensive catalyst to rapidly deliver sulfones, sulfonamides, and other sulfurous functionality (Figure 1).¹⁰

Advances in photoredox catalysis over the past decade have facilitated the development of powerful methods for the

conversion of abundant functional groups, such as alcohols and carboxylic acids, into a broad range of valuable products under mild conditions.¹¹ A number of recent studies have provided further improvements to synthetic efficiency via photoredox approaches to HAT-mediated C(sp³)–H functionalization.¹² Among photo-HAT catalysts, the decatungstate anion ([W₁₀O₃₂]^{4−}) has been widely investigated due to its ability to catalytically cleave strong C–H bonds following excitation with near-UV light.¹³ Given these uniquely valuable properties, decatungstate has been utilized in a range of synthetically valuable transformations,¹⁴ including oxidations,¹⁵ dehydrogenations,¹⁶ fluorinations,¹⁷ conjugate additions,¹⁸ chromium-mediated additions to aldehydes,¹⁹ and several novel metal-lathotoredox reactions.²⁰ Despite this scope of previous work, methods for the formation of C(sp³)–S bonds via decatungstate photocatalysis have not previously been reported.²¹

A depiction of our reaction design appears in Scheme 1. Near-UV excitation of the decatungstate anion (1) followed by rapid relaxation is known to afford the reactive excited state *[W₁₀O₃₂]^{4−} (2).^{13,22} Due to the electrophilic nature of the oxygen-centered hole present in 2, selective HAT at the more electron-rich β-position of cyclopentanone (3) would yield alkyl radical 4 and reduced decatungstate ([W₁₀O₃₂]^{5−}, 5).²³ Rapid radical capture of 4 by sulfur dioxide (6) would then generate sulfonyl radical 7, forming the key C(sp³)–S bond. Based on literature precedent (*k*_{disproportionation} ≈ 10⁵ M^{−1} s^{−1})²⁴ and UV/vis studies of the reaction mixture at partial conversion (Figure S6), the cycle would close via disproportionation of 5 to afford doubly reduced decatungstate (8) followed by single-electron reduction of 7 (*E*_{pa}(RSO₂[−]/RSO₂[•]) ≈ 0.46 V in acetonitrile,²⁵ 0.8 V in water,²⁶ both vs SCE for

Received: May 6, 2021

Published: June 23, 2021



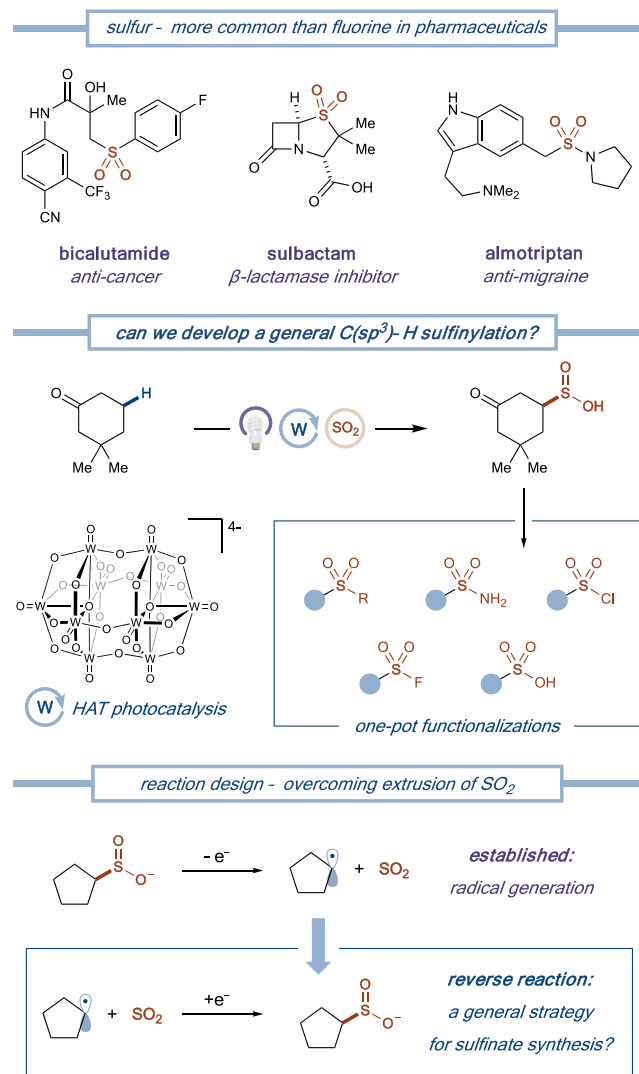


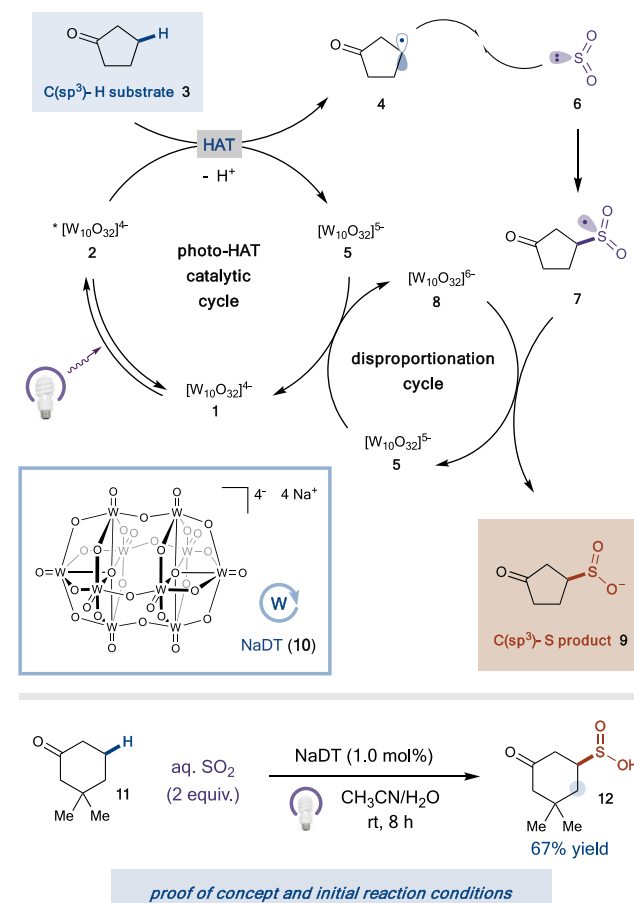
Figure 1. Development of a general C(sp³)-H sulfinylation.

related alkyl sulfonates) by **8** ($E_{1/2}^{\text{red}}([\text{W}_{10}\text{O}_{32}]^{5-}/[\text{W}_{10}\text{O}_{32}]^{6-}) = -1.48$ V in acetonitrile,^{20a} -0.38 V in water,^{20b} both vs SCE) to afford the corresponding sulfinate (**9**). Under sufficiently acidic conditions, subsequent protonation would afford the sulfinic acid.²⁷ An alternative radical chain mechanism, in which sulfonyl radical **7** undergoes chain-propagating HAT from **3** to afford the sulfinic acid product and regenerate alkyl radical **4**, appears unlikely based on computed reaction barriers ($\Delta G_{\text{calc}}^{\ddagger} > 22$ kcal/mol, Table S9).

Our initial investigations began by irradiating a solution of 3,3-dimethylcyclohexanone (**11**) and sodium decatungstate (NaDT, **10**) in acetonitrile/water with PR160 40 W Kessil 390 nm lights in the presence of a range of convenient sulfur dioxide surrogates. While commonly employed SO₂ sources such as DABSO²⁸ and metabisulfite salts failed to generate the corresponding sulfinic acid under a range of conditions, use of inexpensive aqueous sulfur dioxide (“sulfurous acid,” 6 wt % aq. SO₂, \$0.12/mmole)²⁹ afforded the desired product (**12**) in 67% yield (Table S1). Importantly, control experiments indicated that both decatungstate and light are required for reactivity (Table S4).

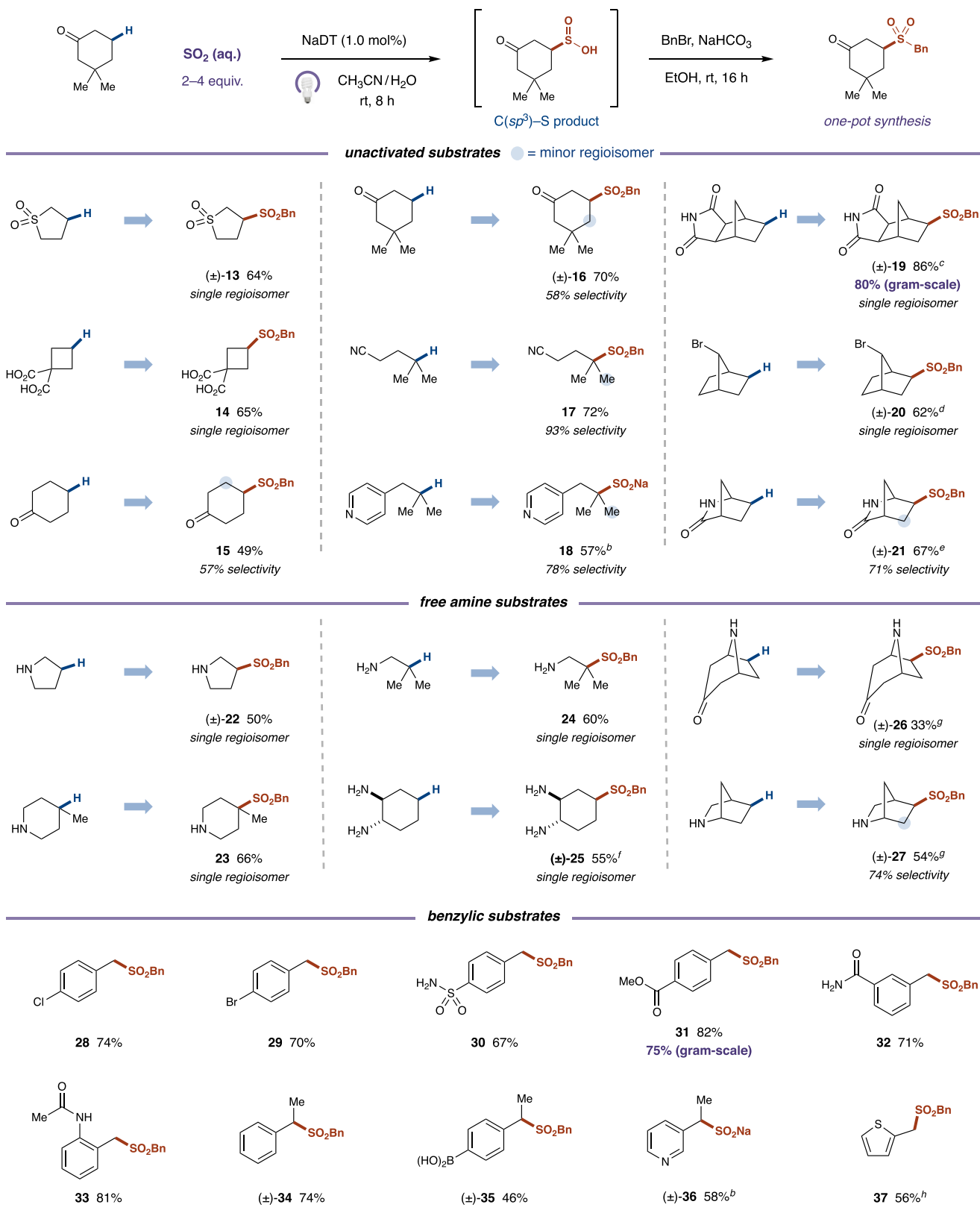
With optimized conditions in hand, we sought to evaluate the scope of this new C(sp³)-S bond-forming reaction (Table 1). To ensure uniformity and applicability within a medicinal

Scheme 1. Proposed Photocatalytic Cycle and Initial Conditions



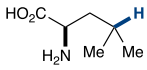
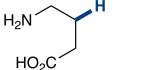
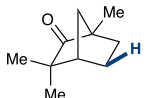
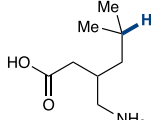
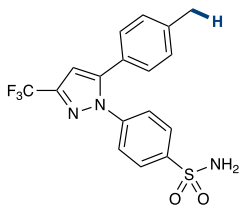
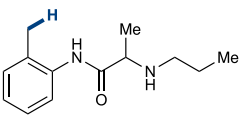
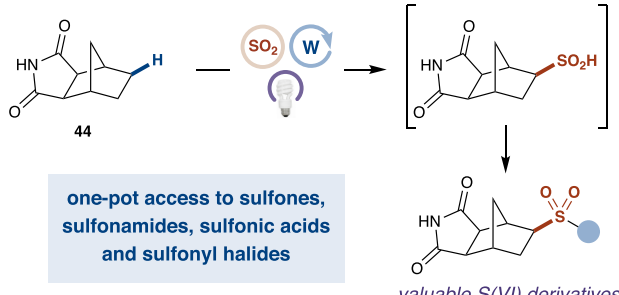
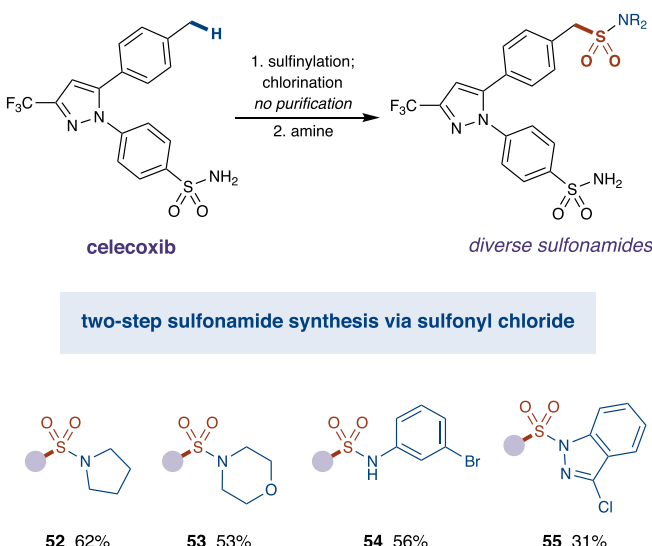
chemistry setting, all experiments were performed using a commercial integrated photoreactor³⁰ including numerous examples at gram-scale. While isolation of the crude alkyl sulfonates was possible (e.g., **18**, **36**, S13), a one-pot procedure to convert the intermediate sulfinic acid into the corresponding benzyl sulfone was employed to facilitate convenient isolation and characterization of the C(sp³)-S products. We first examined a range of cyclic hydrocarbons bearing electron-withdrawing groups such as sulfones (**13**, 64% yield), carboxylic acids (**14**, 65% yield), and ketones (**15** and **16**, 49 and 70% yield, 57% and 58% selectivity, respectively). In all cases, excellent selectivity was observed for the more electron-rich, sterically accessible positions.²³ Consistent with the hydridic nature of tertiary C(sp³)-H bonds, **17** and **18** were generated in good yield (72% and 57%, respectively) and excellent tertiary selectivity despite the presence of weak (but electron-poor) α-cyano³¹ and heterobenzylic³² C(sp³)-H bonds.

We next turned our attention to medicinally relevant bicyclic scaffolds. A tricyclic imide and brominated norbornane derivative were sulfinylated at the most accessible, electron-rich position as a single regioisomer in both cases (**19** and **20**, 86% and 62% yield, respectively). Heterobicyclic scaffolds also proved to be effective substrates for this transformation, with a bicyclic amide affording the corresponding benzyl sulfone (**21**, 67% yield, 71% selectivity). This ability to efficiently and selectively modify complex bicyclic scaffolds clearly illustrates the benefits of C(sp³)-H functionalization-based approaches.

Table 1. Scope of C(sp³)-H Sulfinylation^a

^aAll yields are isolated. Performed with substrate (1.0 equiv, 0.5 mmol), SO₂ (2.0–4.0 equiv, 6 wt % aq.), and NaDT (1 mol %) in acetonitrile/water, irradiating for 4–8 h with 365 nm LEDs followed by addition of NaHCO₃ (1.5–2.0 equiv), EtOH (1 mL), and BnBr (1.2–1.5 equiv), stirring at room temperature for 16 h. See SI for complete experimental details. ^bYield of crude sodium sulfinate by ¹H NMR. ^c11:1 dr. ^d5:1 dr. ^e3.9:1 dr (major), > 20:1 dr (minor). ^f1:1 dr. ^g>20:1 dr. ^h5 mol % NaDT.

Table 2. Sulfonylation of Natural Product and Pharmaceutical Substrates and One-Pot Diversification of Alkyl Sulfonates^a

sulfonylation of natural products and pharmaceuticals	
 <p>leucine</p> <p>38 58% 91% selectivity</p>	 <p>GABA</p> <p>(±)-39 24% single regioisomer</p>
 <p>fenchone</p> <p>40 56%^b 63% selectivity</p>	 <p>(±)-pregabalin</p> <p>41 54% 85% selectivity</p>
 <p>celecoxib</p> <p>42 70% single regioisomer</p>	 <p>prilocaine</p> <p>43 73% single regioisomer</p>
rapid diversification of sulfonate products	
 <p>44</p> <p>one-pot access to sulfones, sulfonamides, sulfonic acids and sulfonyl halides</p> <p>valuable S(VI) derivatives</p> <p>(±)-45 56%^c (±)-46 93%^d (±)-47 81%^e</p> <p>(±)-48 82%^f (±)-49 65%^g (±)-50 66%^b (±)-51 57%^b</p>	 <p>1. sulfonylation; chlorination no purification 2. amine</p> <p>celecoxib</p> <p>diverse sulfonamides</p> <p>two-step sulfonamide synthesis via sulfonyl chloride</p> <p>52 62% 53 53% 54 56% 55 31%</p>

^aAll yields are isolated. See SI for complete experimental details. ^b>20:1 dr. ^c6.0:1 dr. ^d6.5:1 dr. ^e9.1:1 dr. ^f5.0:1 dr. ^g11:1 dr.

Given the acidic nature of the aqueous SO₂ employed under our optimized conditions, we hypothesized that adding an additional equivalent of this reagent should enable direct functionalization of unprotected amines. Protonation of amines renders the adjacent C(sp³)-H bonds both stronger and less hydridic, enabling selective abstraction of distal C-H bonds.^{15a,33} Thus, pyrrolidine was sulfonylated under our standard conditions to afford the expected β-benzyl sulfone as a single regioisomer (**22**, 50% yield). Excellent selectivity was observed in the case of amines bearing tertiary C(sp³)-H bonds, with 4-methylpiperidine and isobutylamine affording the corresponding C(sp³)-S products in good yields and

complete regioselectivity (**23** and **24**, 66% and 60% yield, respectively). By further increasing the amount of aqueous SO₂, *trans*-1,2-cyclohexanediamine was selectively functionalized at the position furthest from the amines (**25**, 55% yield, single regioisomer). Bicyclic amines were also effective substrates for this transformation, with nortropanone and a [2.2.1] bicycle functionalized at the most sterically accessible, electron-rich positions (**26** and **27**, 33% and 54% yield, respectively, single regioisomer and 74% selectivity, respectively).

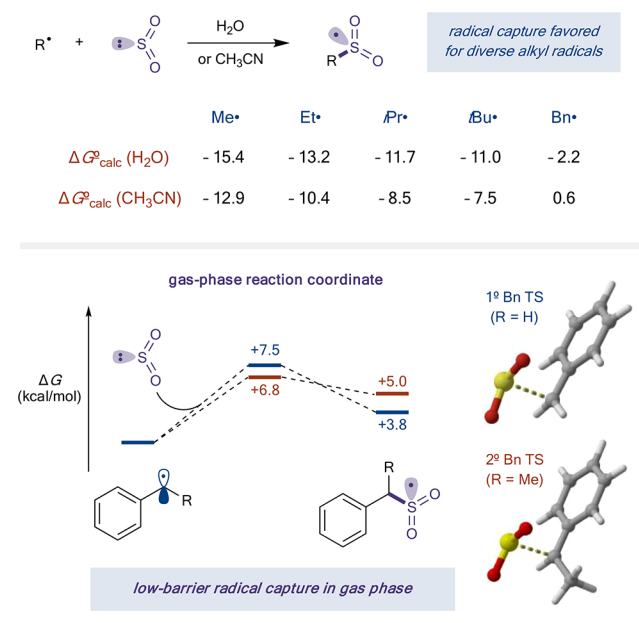
Finally, this reaction was applied to an electronically diverse range of benzylic substrates. While the relatively low benzylic

C–H bond dissociation energies render the initial HAT step facile, the stability of the resultant radical led us to initially question the favorability of its reaction with sulfur dioxide. Gratifyingly, toluene derivatives were highly effective in this transformation, producing the expected benzylic sulfinic acids in good yields across a broad range of aryl functionality (**28**–**33**, 67–82% yield), including *ortho* substitution (**33**, 81% yield). Despite greater stabilization of the resultant radical, secondary benzylic substrates also performed well in this transformation (**34** and **35**, 74% and 46% yield, respectively). Notably, many of these benzylic substrates contain protic functional groups, such as sulfonamides (**30**), amides (**32** and **33**), and boronic acids (**35**), which prove problematic for traditional approaches requiring a strong base or organometallic nucleophiles.³⁴ Further investigation revealed that heterobenzylic substrates were also effective in this reaction, with selectivity observed for functionalization at the (hetero)-benzylic C–H bonds (**36** and **37**, 58% and 56% yield, respectively).

To demonstrate the utility of this methodology for late-stage functionalization, natural products and pharmaceuticals were converted to the corresponding sulfinates in a single step (Table 2). Notably, natural amino acids leucine and GABA afforded the corresponding benzyl sulfones in synthetically useful yields and excellent selectivity (**38** and **39**, 58% and 24% yield, respectively, 91% selective and single regioisomer, respectively). The monoterpene fenchone was functionalized with good selectivity for the most electron-rich, sterically accessible C–H bond (**40**, 56% yield, 63% selectivity), and pregabalin was converted to the corresponding benzyl sulfone with excellent regioselectivity for the tertiary position (**41**, 54% yield, 85% selectivity). Finally, two drugs bearing benzylic C–H bonds, celecoxib and prilocaine, were derivatized with complete selectivity observed for functionalization at the benzylic position (**42** and **43**, 70% and 73% yield, respectively).

As an illustration of the broad utility of this platform for the synthesis of diverse organosulfur compounds, a range of one-pot procedures for the divergent functionalization of tricyclic imide **44** were developed. As shown in Table 2, the sulfinic acid intermediate was successfully converted to a range of alkyl sulfone derivatives (**45**–**47**, 56–93% yield). Introduction of heteroatoms also proved facile, with the corresponding sulfonic acid (**48**, 82% yield), primary sulfonamide (**49**, 65% yield), sulfonyl fluoride (**50**, 66% yield), and sulfonyl chloride (**51**, 57% yield) all generated with good efficiency. Additionally, two-pot protocols were developed for the conversion of celecoxib to a diverse range of sulfonamides via the intermediacy of a sulfonyl chloride, generated via chlorination of the C–H sulfonylation product without intermediate purification. Alkyl amines (**52** and **53**, 62% and 53% yield, respectively), anilines (**54**, 56% yield), and *N*-heterocycles (**55**, 31% yield) all reacted to afford the desired sulfonamide products.

As a preliminary investigation into the mechanism of this transformation, we computationally studied the coupling of a range of alkyl radicals with sulfur dioxide (Scheme 2). Notably, with aliphatic radicals, a significant negative free energy of reaction was observed for this trapping in water ((U)- ω B97XD/6-31+G(d,p), SMD solvent model). Moreover, efforts to identify a transition state in the case of unstabilized aliphatic radicals proved unsuccessful, with stretching of the C–S bond of the sulfonyl radical product resulting in a

Scheme 2. Computational Study of Radical Addition to SO₂

continuous increase in energy, possibly indicating a barrierless process (Figure S7). In order to further investigate the nature of the C–S bond-forming step, we calculated the transition state energies for the addition of a series of stabilized radicals (e.g., benzylic) into SO₂ in the gas phase, conditions under which sulfonyl radical formation is predicted to be markedly less favorable than in the presence of polar solvent. Remarkably, however, low barriers to radical capture with SO₂ were determined (7.5 and 6.8 kcal/mol for primary and secondary benzylic, respectively), consistent with the observed efficiencies in experiments involving aliphatic radicals and sulfur dioxide.

In summary, we have developed a perfectly atom-economical protocol for the photocatalytic conversion of C(sp³)–H bonds into the corresponding alkyl sulfinic acids, thereby enabling unprecedented access to a broad array of valuable organosulfur products. Furthermore, these studies clearly illustrate the importance of sulfur dioxide as an efficient reagent for the formation of C–S bonds from a diverse range of aliphatic radicals and, as such, should inform the development of related transformations that proceed via this key elementary step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c04722>.

Experimental and characterization data, UV/vis and computational studies, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful for financial support provided by the National Institute of General Medical Sciences (NIGMS), the NIH (under Award R35GM134897-01), the Princeton Catalysis Initiative, and kind gifts from Merck, Janssen, BMS, Genentech, Celgene, and Pfizer. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS. P.J.S. thanks Bristol-Myers Squibb for a graduate fellowship.

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