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Decatungstate-Catalyzed C(sp^3)-H Sulfinylation: Rapid Access to Diverse Organosulfur Functionality

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Abstract

Here we report the direct conversion of strong, aliphatic C(sp^3)–H bonds into the corresponding alkyl sulfinic acids via decatungstate photocatalysis. This transformation has been applied to a diverse range of C(sp^3)-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 medicinally relevant functional groups have been developed.

Sulfonamides, sulfones, and sulfides are widely employed functional groups that are broadly found in modem 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(sp^3)–H bonds into alkylsulfonyl groups.[6] Intriguingly, recent studies involving alkyl sulfinates have instead focused on the inverse transform, namely C(sp^3)–SO_2 bond cleavage via the oxidative conversion of sulfinates to alkyl radicals with concomitant extrusion of SO_2.[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 SO_2 trapping and subsequent reduction, a pathway that if successful would generate C(sp^3)-rich, sulfonyl-containing adducts from simple aliphatic substrates.

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Supporting Information

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

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c04722

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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 kinetic[8] and synthetic[9] studies support the feasibility of C(sp^3) radical capture by SO_2 (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(sp^3)–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)-sulfinylation 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(sp^3)–H functionalization.[12] Among photo-HAT catalysts, the decatungstate anion ($[W_{10}O_{32}]^{4-}$) 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-laphotoredox reactions.[20] Despite this scope of previous work, methods for the formation of C(sp^3)–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 $*[W_{10}O_{32}]^{4-}$ (**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 ($[W_{10}O_{32}]^{5-}$, **5**).[23] Rapid radical capture of **4** by sulfur dioxide (**6**) would then generate sulfonyl radical **7**, forming the key C(sp^3)–S bond. Based on literature precedent ($k_{\text{disproportionation}} \approx 10^5\ M^{-1}\ s^{-1}$)[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** ($E_{pa}(RSO_2^-/RSO_2^\bullet) \approx 0.46$ V in acetonitrile,[25] 0.8 V in water,[26] both vs SCE for related alkyl sulfinates) by **8** ($E_{1/2}^{red}([W_{10}O_{32}]^{5-}/[W_{10}O_32]^{6-}) = -1.48$ 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 ($\Delta G^{\ddagger}_{calc} > 22$ 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 SO_2 sources such as DABSO[28] 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. SO_2, $0.12/mmol)[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(sp^3)–S bond-forming reaction (Table 1). To ensure uniformity and applicability within a medicinal chemistry setting, all experiments were performed using a commercial integrated photoreactor[30] including numerous examples at gram-scale. While isolation of the crude alkyl sulfinates 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(sp^3)–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(sp^3)–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-cyano[31] and heterobenzylic[32] C(sp^3)– 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 bicylic 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(sp^3)–H functionalization-based approaches.

Given the acidic nature of the aqueous SO_2 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(sp^3)–H bonds both stronger and less hydridic, enabling selective abstraction of distal C–H bonds.[15a,33] Thus, pyrrolidine was sulfinylated 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(sp^3)–H bonds, with 4-methylpiperidine and isobutylamine affording the corresponding C(sp^3)–S products in good yields and complete regioselectivity (**23** and **24**, 66% and 60% yield, respectively). By further increasing the amount of aqueous SO_2, *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 monoterpenoid 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 sulfinylation 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)-ωB97XD/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 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 SO_2 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 SO_2 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(sp^3)–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.

Supplementary Material

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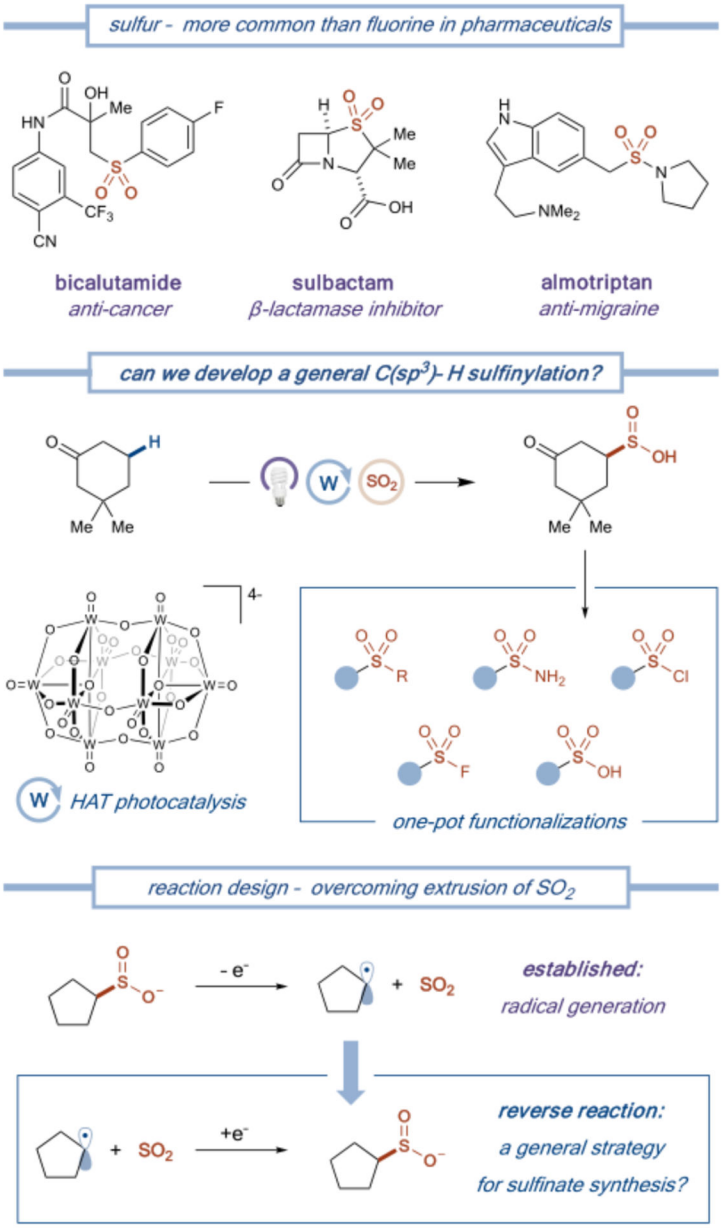
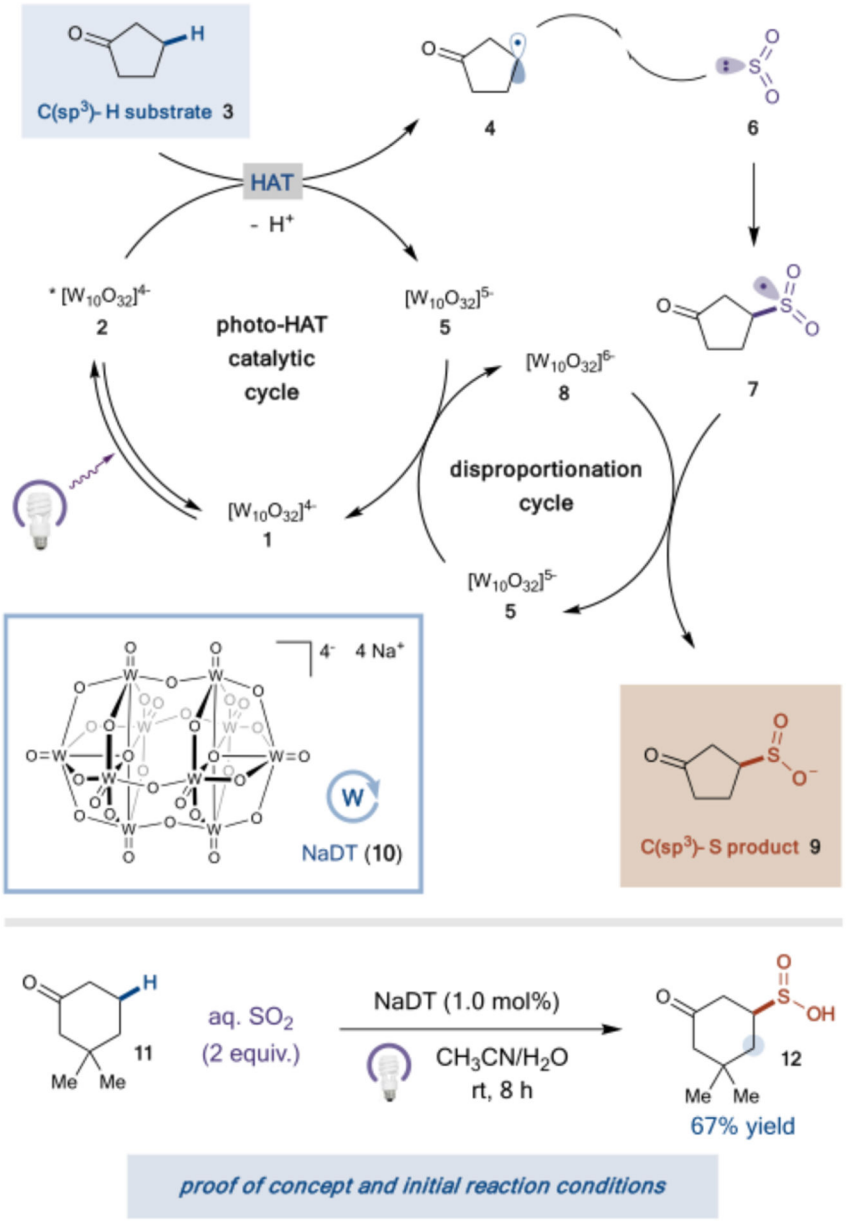
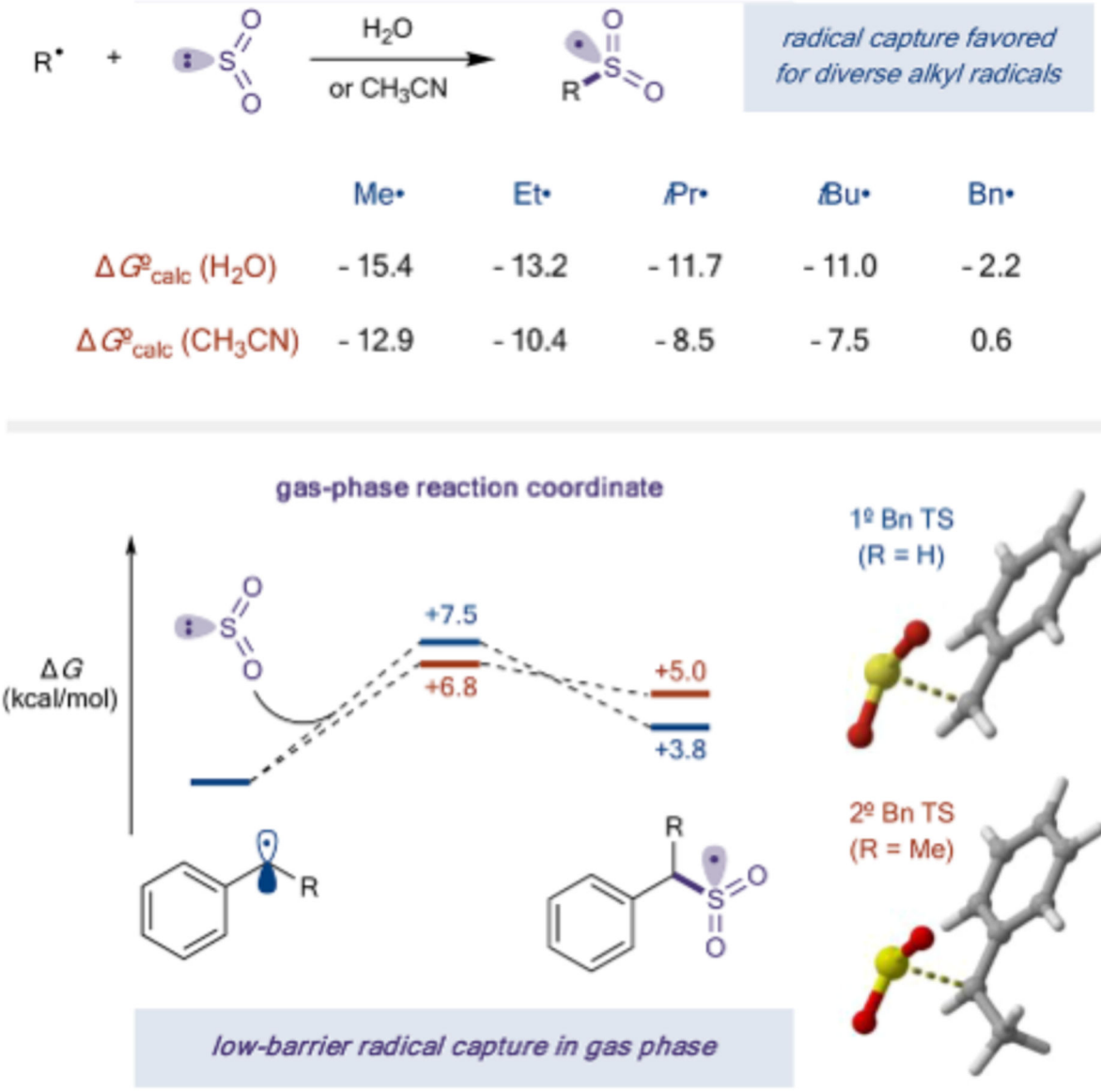


Figure 1.
Development of a general C(sp^3)–H sulfinylation.



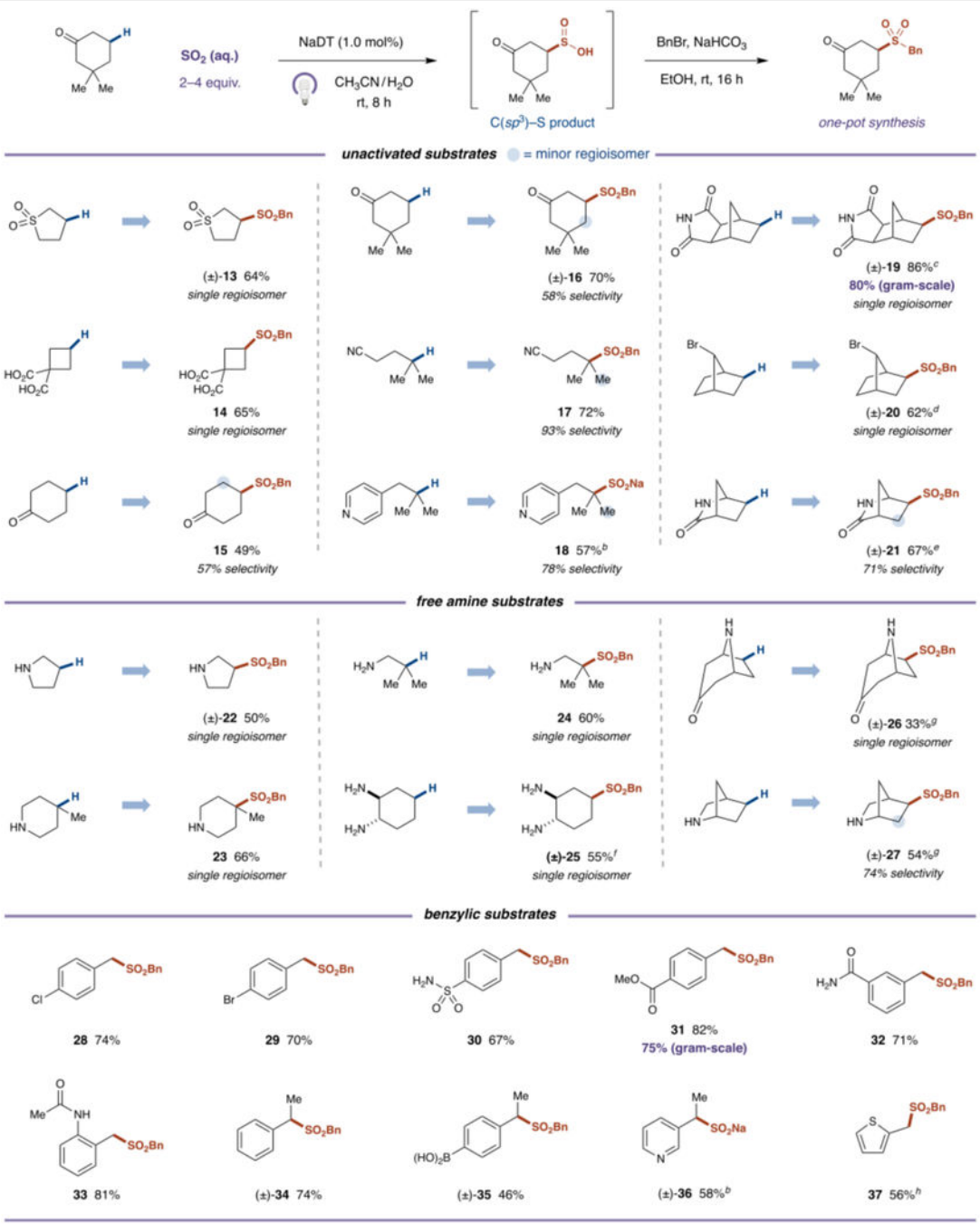
Scheme 1.
Proposed Photocatalytic Cycle and Initial Conditions



Scheme 2.
Computational Study of Radical Addition to SO_2

Table 1.

Scope of C(sp)^3–H Sulfinylation[a]



[a]All yields are isolated. Performed with substrate (1.0 equiv, 0.5 mmol), SO_2 (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 $NaHCO_3$ (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.

[b]Yield of crude sodium sulfinate by ^1H NMR.

[c]11:1 dr.

[d]5:1 dr.

[e]3.9:1 dr (major), > 20:1 dr (minor).

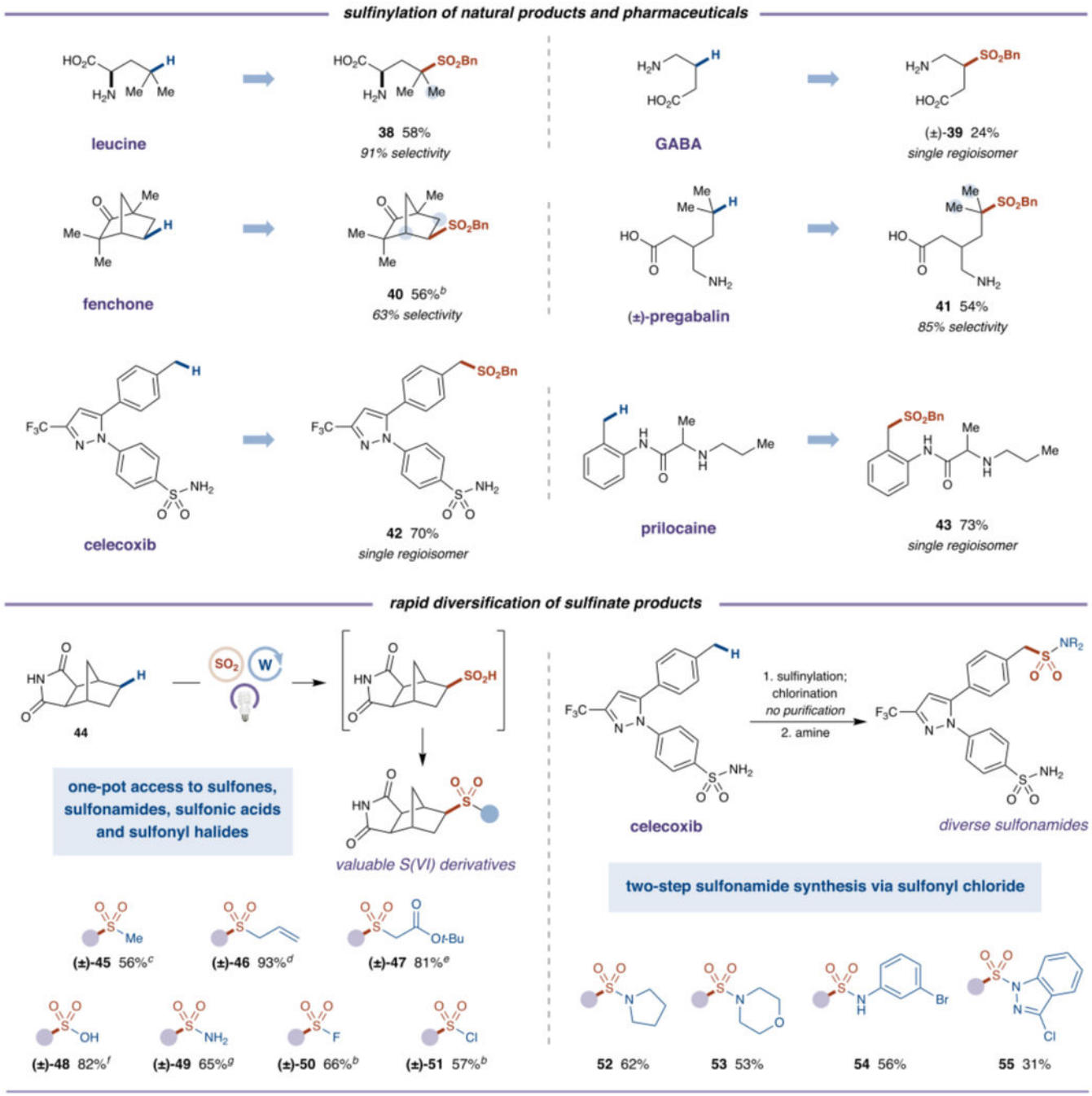
[f]1:1 dr.

[g]>20:1 dr.

[h]5 mol % NaDT.

Table 2.

Sulfinylation of Natural Product and Pharmaceutical Substrates and One-Pot Diversification of Alkyl Sulfinates[a]



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[a] All yields are isolated. See SI for complete experimental details.

[b] >20:1 dr.

[c] 6.0:1 dr.

[d] 6.5:1 dr.

[e] 9.1:1 dr.

[f] 5.0:1 dr.

[g] 11:1 dr.