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Communication

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 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(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.

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 metallaphotoredox 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 ($k_{disproportionation} \approx 10^5$ 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

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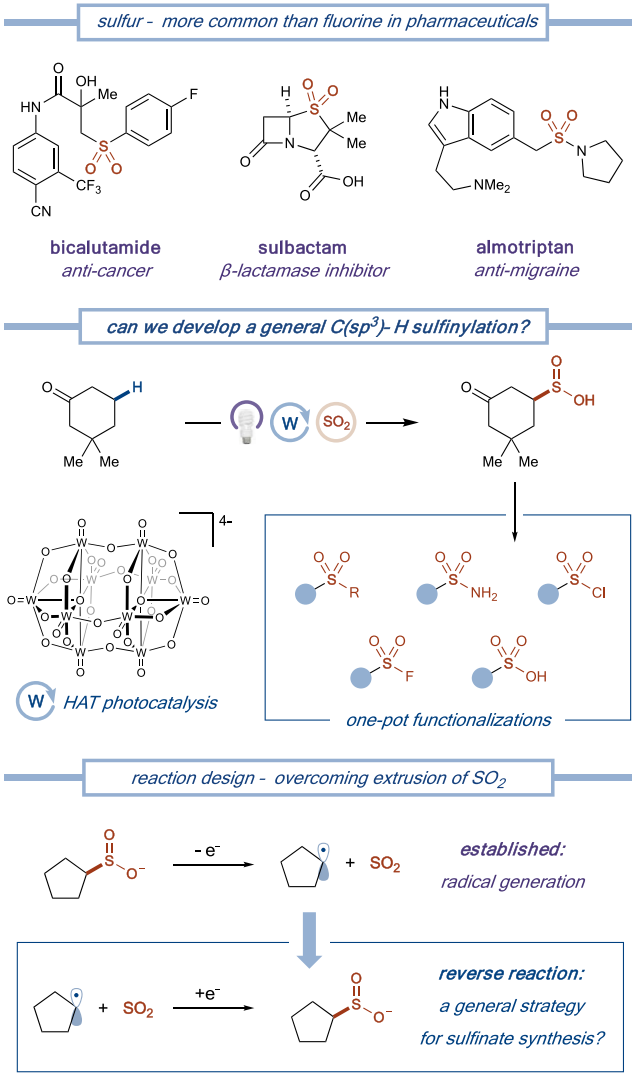


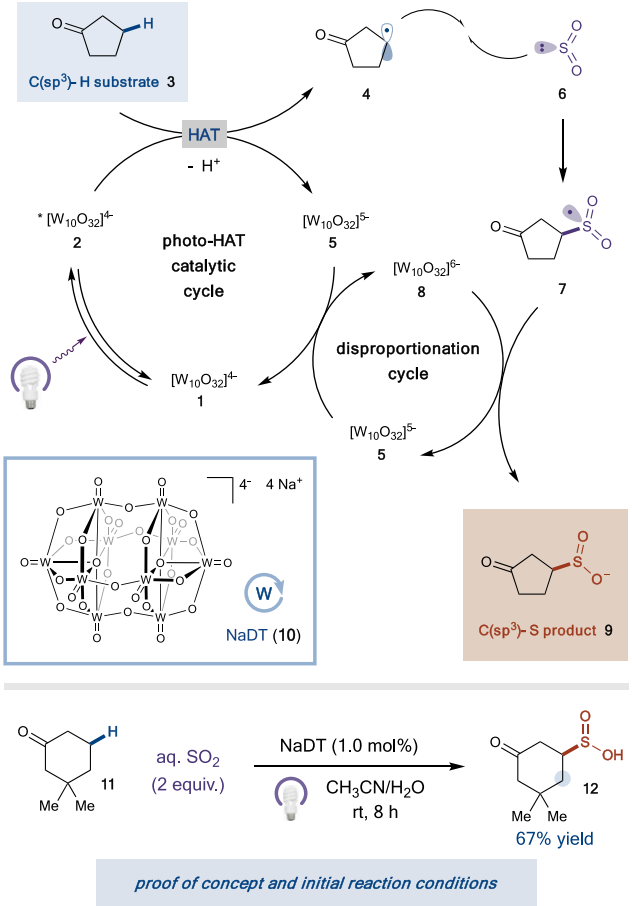
Figure 1. Development of a general C(sp^3)−H sulfinylation.

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

Scheme 1. Proposed Photocatalytic Cycle and Initial Conditions



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.

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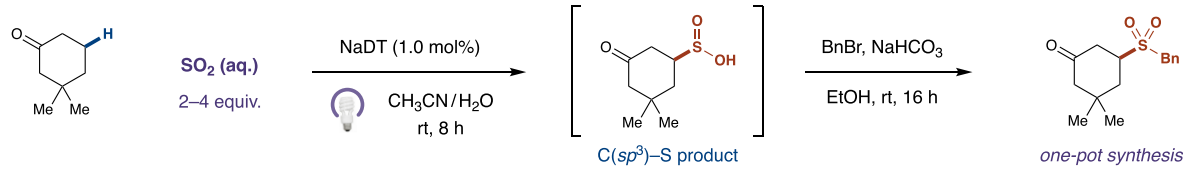
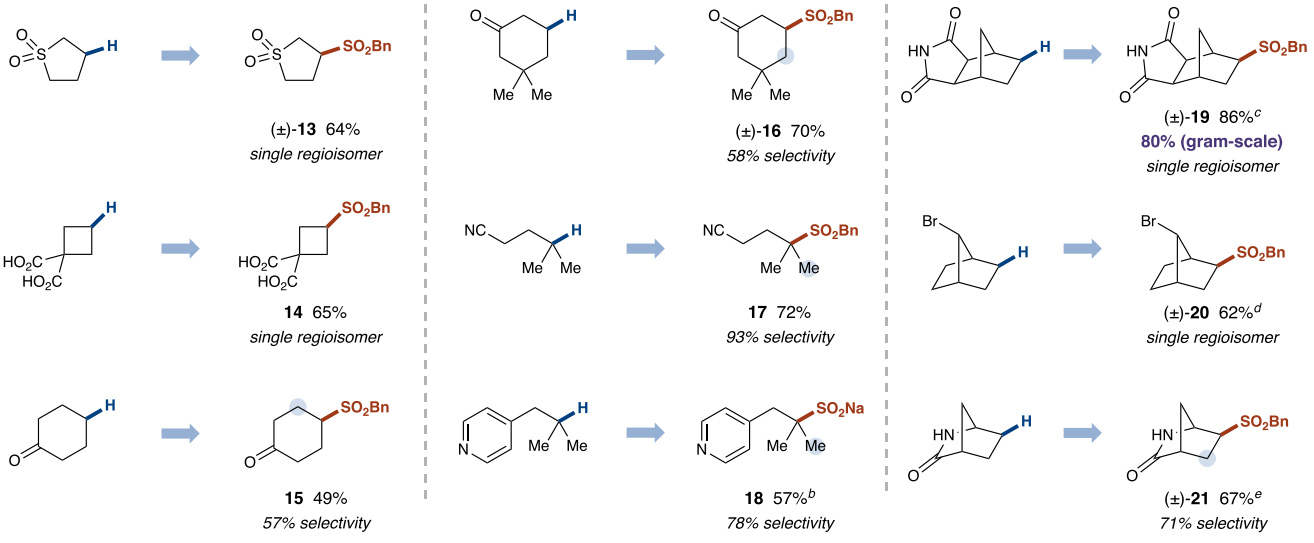
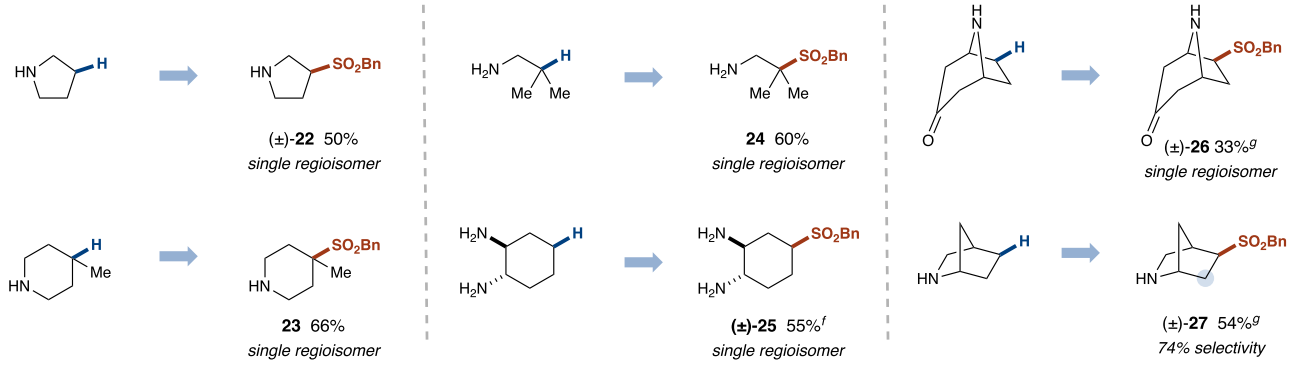
Table 1. Scope of C(sp)^3–H Sulfinylation[a]



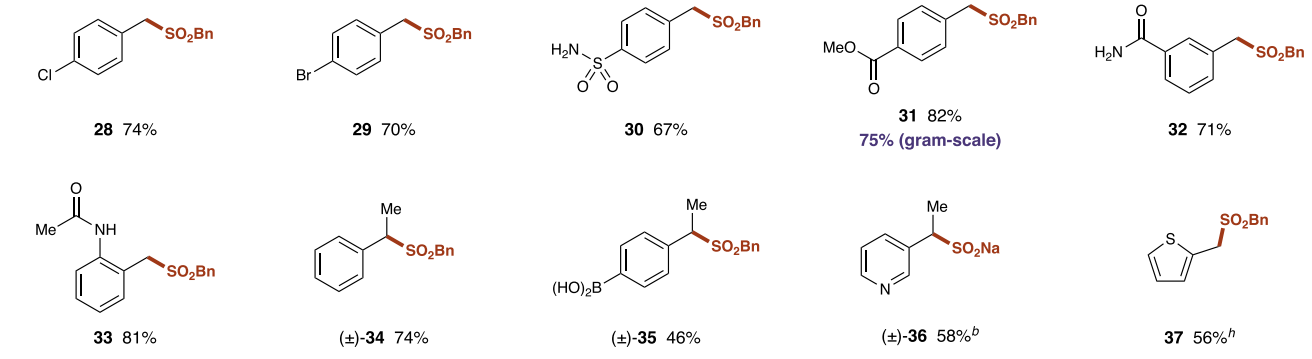
unactivated substrates = minor regioisomer



free amine substrates



benzylic substrates



[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 ^{1}H 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.

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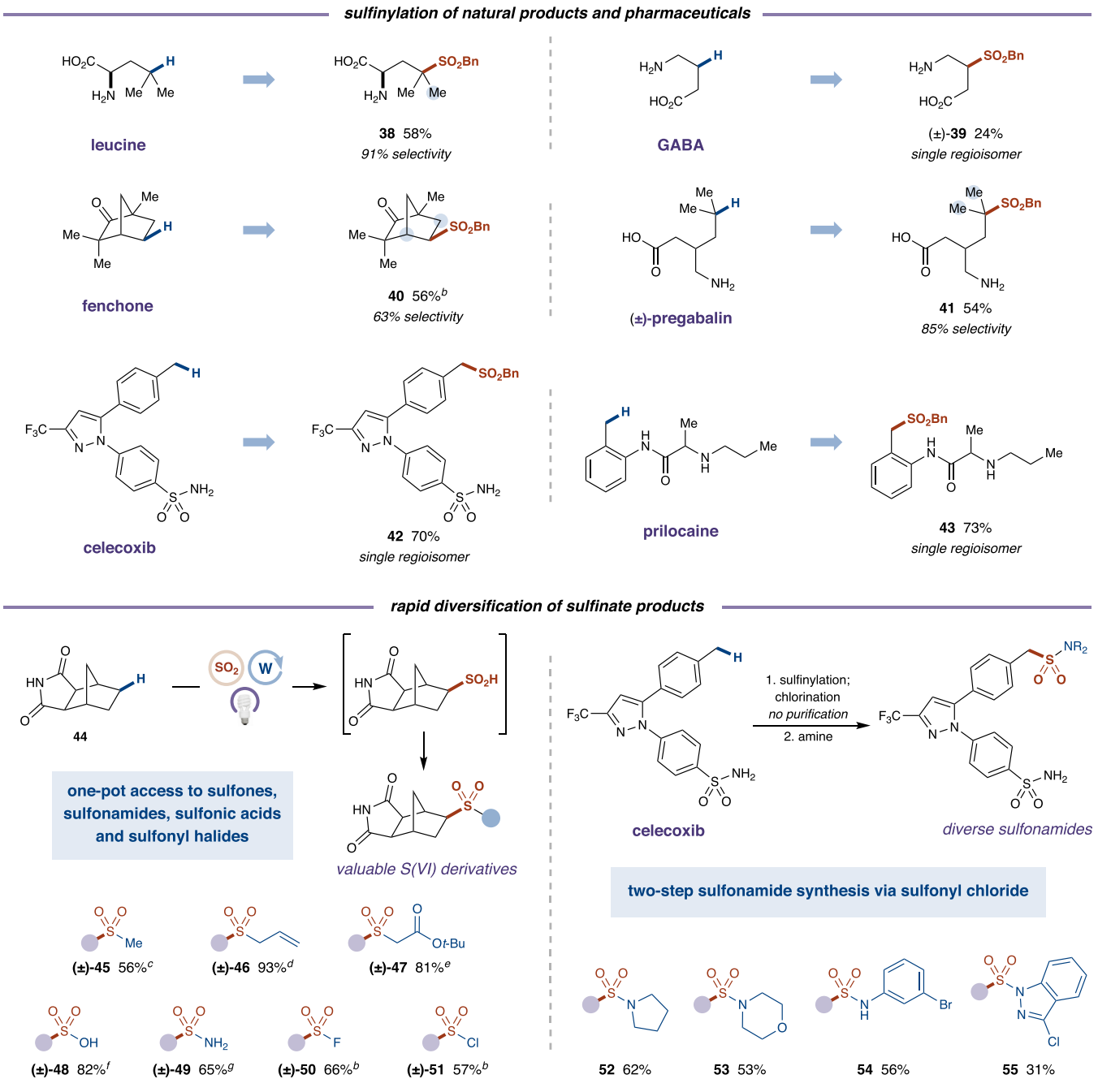
Table 2. Sulfinylation of Natural Product and Pharmaceutical Substrates and One-Pot Diversification of Alkyl Sulfinates[a]



[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.

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

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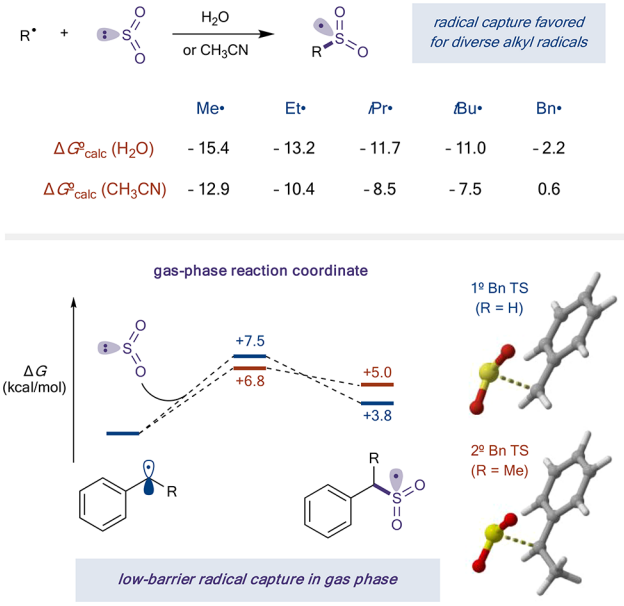
C−H bond dissociation energies render the initial HAT step facile, the stability of the resultant radical led us to initially question the favorability of its reaction with sulfur dioxide. Gratifyingly, toluene derivatives were highly effective in this transformation, producing the expected benzylic 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.

Scheme 2. Computational Study of Radical Addition to SO_2



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.

■ 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.

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■ REFERENCES

(1) Kheirieh, S.; Asghari, M.; Afsari, M. Application and modification of polysulfone membranes. *Rev. Chem. Eng.* **2018**, *34*, 657−693.

(2) Devendar, P.; Yang, G.-F. Sulfur-Containing Agrochemicals. *Top. Curr. Chem.* **2017**, *375*, 82.

(3) (a) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, *376*, 5. (b) 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.

(4) Ertl, P.; Altmann, E.; McKenna, J. M. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J. Med. Chem.* **2020**, *63*, 8408−8418.

(5) Smith, B. R.; Eastman, C. M.; Njardarson, J. T. Beyond C, H, O, and N! Analysis of the Elemental Composition of U.S. FDA Approved Drug Architectures. *J. Med. Chem.* **2014**, *57*, 9764−9773.

(6) (a) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. Recent advances in C-S bond formation via C-H bond functionalization and decarboxylation. *Chem. Soc. Rev.* **2015**, *44*, 291−314. (b) Liu, J.; Zheng, L. Recent Advances in Transition-Metal-Mediated Chelation-Assisted Sulfonylation of Unactivated C-H Bonds. *Adv. Synth. Catal.* **2019**, *361*, 1710−1732. (c) Shaaban, S.; Liang, S.; Liu, N.-W.; Manolikakes, G. Synthesis of sulfones via selective C-H-functionalization. *Org. Biomol. Chem.* **2017**, *15*, 1947−1955. (d) Ferguson, R. R.; Crabtree, R. H. Mercury-Photosensitized Sulfination, Hydrosulfination, and Carbonylation of Hydrocarbons: Alkane and Alkene Conversion to Sulfonic Acids, Ketones, and Aldehydes. *J. Org. Chem.* **1991**, *56*, 5503−5510. (e) Ishii, Y.; Matsunaka, K.; Sakaguchi, S. The First Catalytic Sulfoxidation of Saturated Hydrocarbons with SO2/O2 by a Vanadium Species. *J. Am. Chem. Soc.* **2000**, *122*, 7390−7391. (f) Kamijo, S.; Hirota, M.; Tao, K.; Watanabe, M.; Murafuji, T. Photoinduced sulfonylation of cyclic ethers. *Tetrahedron Lett.* **2014**, *55*, 5551−5554. (g) Swarnkar, S.; Ansari, M. Y.; Kumar, A. Visible-Light-Induced Tertiary C(sp3)-H Sulfonylation: An Approach to Tertiary Sulfones. *Org. Lett.* **2021**, *23*, 1163−1168. (h) Cao, S.; Hong, W.; Ye, Z.; Gong, L. Photocatalytic three-component asymmetric sulfonylation via direct C(sp3)-H functionalization. *Nat. Commun.* **2021**, *12*, 2377.

(7) Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. Alkyl Sulfinates: Radical Precursors Enabling Drug Discovery. *J. Med. Chem.* **2019**, *62*, 2256−2264.

(8) (a) Good, A.; Thynne, J. C. J. Reaction of free radicals with sulphur dioxide. *Trans. Faraday Soc.* **1967**, *63*, 2708−2719. (b) Good, A.; Thynne, J. C. J. Reaction of free radicals with Sulphur dioxide. Part 2.-Ethyl Radicals. *Trans. Faraday Soc.* **1967**, *63*, 2720−2727. (c) Horowitz, A. Liquid phase kinetic study of the formation and decomposition of methylsulfonyl and cyclohexylsulfonyl radicals in the cyclohexane-MeSO2Cl-SO2 system at 150°. *Int. J. Chem. Kinet.* **1975**, *7*, 927−942. (d) Horowitz, A. Radiolytic decomposition of methanesulfonyl chloride in liquid cyclohexane. *Int. J. Chem. Kinet.* **1976**, *8*, 709−723.

(9) (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) Meng, Y.; Wang, M.; Jiang, X. Multicomponent Reductive Cross-Coupling of an Inorganic Sulfur Dioxide Surrogate: Straightforward Construction of Diversely Functionalized Sulfones. *Angew. Chem., Int. Ed.* **2020**, *59*, 1346−1353. (e) Li, Y.; Chen, S.; Wang, M.; Jiang, X. Sodium Dithionite-Mediated Decarboxylative Sulfonylation: Facile Access to Tertiary Sulfones. *Angew. Chem., Int. Ed.* **2020**, *59*, 8907−8911.

(10) For reviews on the use of sulfinates as synthetic intermediates, see: (a) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701−8780. (b) Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. Sulfinate derivatives: dual and versatile partners in organic synthesis. *Org. Biomol. Chem.* **2014**, *12*, 9743−9759. (c) Willis, M. C. New catalytic reactions using sulfur dioxide. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 654−657. (d) Aziz, J.; Hamze, A. An update on the use of sulfinate derivatives as versatile coupling partners in organic chemistry. *Org. Biomol. Chem.* **2020**, *18*, 9136−9159. (e) Reddy, R. J.; Kumari, A. H. Synthesis and applications of sodium sulfinates (RSO2Na): a powerful building block for the synthesis of organo-sulfur compounds. *RSC Adv.* **2021**, *11*, 9130−9221.

(11) (a) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363. (c) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7*, 2563−2575. (d) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166. (e) Narayanam, J. M. R.; Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102−113. (f) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects for Visible Light Photocatalysis. *Science* **2014**, *343*, 1239176. (g) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A. Photocatalysis. A multi-faceted concept for green chemistry. *Chem. Soc. Rev.* **2009**, *38*, 1999−2011.

(12) (a) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056−2071. (b) Capaldo, L.; Quadri, L. L.; Ravelli, D. Photocatalytic hydrogen atom transfer: the philosopher's stone for late-stage functionalization? *Green Chem.* **2020**, *22*, 3376−3396.

(13) De Waele, V.; Poizat, O.; Fagnoni, M.; Bagno, A.; Ravelli, D. Unraveling the Key Features of the Reactive State of Decatungstate Anion in Hydrogen Atom Transfer (HAT) Photocatalysis. *ACS Catal.* **2016**, *6*, 7174−7182.

(14) Tzirakis, M. D.; Lykakis, I. N.; Orfanopoulos, M. Decatungstate as an efficient photocatalyst in organic chemistry. *Chem. Soc. Rev.* **2009**, *38*, 2609−2621.

(15) (a) Schultz, D. M.; Lévesque, F.; DiRocco, D. A.; Reibarkh, M.; Ji, Y.; Joyce, L. A.; Dropinski, J. F.; Sheng, H.; Sherry, B. D.; Davies, I. W. Oxyfunctionalization of the Remote C-H Bonds of Aliphatic Amines by Decatungstate Photocatalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 15274−15278. (b) Laudadio, G.; Govaerts, S.; Wang, Y.; Ravelli, D.; Koolman, H. F.; Fagnoni, M.; Djuric, S. W.; Noël, T. Selective (Csp3)-H Aerobic Oxidation Enabled by Decatungstate Photocatalysis in Flow. *Angew. Chem., Int. Ed.* **2018**, *57*, 4078−4082.
(16) West, J. G.; Huang, D.; Sorensen, E. J. Acceptorless dehydrogenation of small molecules through cooperative base metal catalysis. *Nat. Commun.* **2015**, *6*, 10093.
(17) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. A Convenient Photocatalytic Fluorination of Unactivated C-H Bonds. *Angew. Chem., Int. Ed.* **2014**, *53*, 4690−4693.
(18) (a) Dondi, D.; Fagnoni, M.; Albini, A. Tetrabutylammonium Decatungstate-Photosensitized Alkylation of Electrophilic Alkenes: Convenient Functionalization of Aliphatic C-H Bonds. *Chem. - Eur. J.* **2006**, *12*, 4153−4163. (b) Ravelli, D.; Protti, S.; Fagnoni, M. Decatungstate Anion for Photocatalyzed "Window Ledge" Reactions. *Acc. Chem. Res.* **2016**, *49*, 2232−2242.
(19) Yahata, K.; Sakurai, S.; Hori, S.; Yoshioka, S.; Kaneko, Y.; Hasegawa, K.; Akai, S. Coupling Reactions between Aldehydes and Non-Activated Hydrocarbons via the Reductive Radical-Polar Crossover Pathway. *Org. Lett.* **2020**, *22*, 1199−1203.
(20) (a) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct arylation of strong aliphatic C-H bonds. *Nature* **2018**, *560*, 70−75. (b) Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; DiRocco, D. A.; Lam, Y.; Sherer, E. C.; MacMillan, D. W. C. The merger of decatungstate and copper catalysis to enable aliphatic C(sp3)-H trifluoromethylation. *Nat. Chem.* **2020**, *12*, 459−467. (c) Fan, P.; Lan, Y.; Zhang, C.; Wang, C. Nickel/Photo-Cocatalyzed Asymmetric Acyl-Carbamoylation of Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 2180−2186. (d) Wang, L.; Wang, T.; Cheng, G.-J.; Li, X.; Wei, J.-J.; Guo, B.; Zheng, C.; Chen, G.; Ran, C.; Zheng, C. Direct C-H Arylation of Aldehydes by Merging Photocatalyzed Hydrogen Atom Transfer with Palladium Catalysis. *ACS Catal.* **2020**, *10*, 7543−7551.
(21) For decatungstate-catalyzed conversion of aldehydes into fluorinated thioesters, see: (a) Dong, J.; Yue, F.; Wang, X.; Song, H.; Liu, Y.; Wang, Q. Light-Mediated Difluoromethylthiolation of Aldehydes with a Hydrogen Atom Transfer Photocatalyst. *Org. Lett.* **2020**, *22*, 8272−8277. (b) Wang, X.; Dong, J.; Liu, Y.; Song, H.; Wang, Q. Decatungstate as a direct hydrogen atom transfer photocatalyst for synthesis of trifluromethylthioesters from aldehydes *Chin. Chem. Lett.*, Article ASAP. DOI: 10.36106/ijar10.1016/j.cclet.2021.03.070.
(22) (a) Duncan, D. C.; Netzel, T. L.; Hill, C. L. Early-Time Dynamics and Reactivity of Polyoxometalate Excited States. Identification of a Short-Lived LMCT Excited State and a Reactive Long-Lived Charge-Transfer Intermediate following Picosecond Flash Excitation of [W10O32]4- in Acetonitrile. *Inorg. Chem.* **1995**, *34*, 4640−4646. (b) Duncan, D. C.; Fox, M. A. Early Events in Decatungstate Photocatalyzed Oxidations: A Nanosecond Laser Transient Absorbance Reinvestigation. *J. Phys. Chem. A* **1998**, *102*, 4559−4567. (c) Texier, I.; Delaire, J. A.; Giannotti, C. Reactivity of the charge transfer excited state of sodium decatungstate at the nanosecond time scale. *Phys. Chem. Chem. Phys.* **2000**, *2*, 1205−1212. (d) Tanielian, C.; Lykakis, I. N.; Seghrouchni, R.; Cougnon, F.; Orfanopoulos, M. Mechanism of decatungstate photocatalyzed oxygenation of aromatic alcohols: Part 1. Continuous photolysis and laster flash photolysis studies. *J. Mol. Catal. A: Chem.* **2007**, *262*, 170−175. (e) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A.; Bagno, A. Electronic and EPR spectra of the species involved in [W10O32]4- photocatalysis. A relativistic DFT investigation. *Phys. Chem. Chem. Phys.* **2013**, *15*, 2890−2896.
(23) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C-H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018**, *8*, 701−713.
(24) Yamase, T.; Usami, T. Photocatalytic dimerization of olefins by decatungstate(VI), [W10O32]4-, in acetonitrile and magnetic resonance studies of photoreduced species. *J. Chem. Soc., Dalton Trans.* **1988**, 183−190.
(25) Meyer, A. U.; Straková, K.; Slanina, T.; König, B. Eosin Y (EY) Photoredox-Catalyzed Sulfonylation of Alkenes: Scope and Mechanism. *Chem. - Eur. J.* **2016**, *22*, 8694−8699.
(26) Nematollahi, D.; Joudaki, M.; Khazalpour, S.; Pouladi, F. Electrochemical Oxidation of Sulfinic Acids: Efficient Oxidative Synthesis of Diaryl Disulfones. *J. Electrochem. Soc.* **2017**, *164*, G65−G70.
(27) Alternatively, HAT between protonated **8** and sulfonyl radical **7** could directly afford protonated **9**.
(28) 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.
(29) $223/2 kg (Millipore Sigma, June 2021).
(30) 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.
(31) Yamada, K.; Okada, M.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. Photocatalyzed Site-Selective C-H to C-C Conversion at Aliphatic Positions. *Org. Lett.* **2015**, *17*, 1292−1295.
(32) Fukuyama, T.; Nishikawa, T.; Yamada, K.; Ravelli, D.; Fagnoni, M.; Ryu, I. Photocatalyzed Site-Selective C(sp3)-H Functionalization of Alkylpyridines at Non-Benzylic Positions. *Org. Lett.* **2017**, *19*, 6436−6439.
(33) (a) Lee, M.; Sanford, M. S. Palladium-Catalyzed, Terminal-Selective C(sp3)-H Oxidation of Aliphatic Amines. *J. Am. Chem. Soc.* **2015**, *137*, 12796−12799. (b) Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. Remote Oxidation of Aliphatic C-H Bonds in Nitrogen-Containing Molecules. *J. Am. Chem. Soc.* **2015**, *137*, 14590−14593. (c) Salamone, M.; Giammarioli, I.; Bietti, M. Tuning hydrogen atom abstraction from the aliphatic C-H bonds of basic substrates by protonation. *Control over selectivity by C-H deactivation. Chem. Sci.* **2013**, *4*, 3255−3262.
(34) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **2018**, *10*, 383−394.

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