

# Sulfamyl Radicals Direct Photoredox-Mediated Giese Reactions at Unactivated C(3)–H Bonds

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Supporting Information Placeholder

**ABSTRACT:** Herein described, alcohol-derived anchors guide the alkylation of aliphatic C(3)–H bonds. The disclosed method relies on photoredox catalysts to drive the oxidation of alcohol-anchored sulfamate esters to sulfamyl radicals. These sulfamyl radicals template otherwise rare 1,6-hydrogen-atom transfer (HAT) processes via seven-membered transition states to enable C(3)–H functionalization during Giese reactions. The transformation proceeds directly from N–H bonds with a catalytic oxidant, a contrast to prior sulfamate ester guided methods, which have required pre-oxidation of the reactive nitrogen center, or employed stoichiometric amounts of strong oxidants. Consequently, this reaction manifold tolerates a range of functional groups that are sensitive to oxidation. The developed reaction proceeds with predictable selectivity using enantioenriched radical acceptors, and within complex small molecule substrates. Surprisingly, this transformation affects position-selective alkylation of tertiary *and* secondary C(sp<sup>3</sup>) centers with synthetically useful efficiencies.

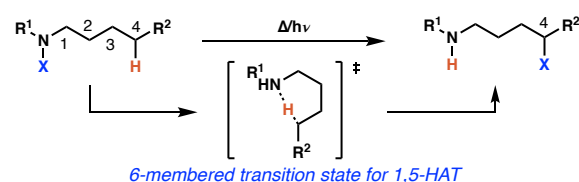
## INTRODUCTION

Nitrogen-centered radicals are an important and versatile class of chemical intermediates.<sup>1</sup> Yet, nitrogen-centered radicals remain underutilized, as most methods for their generation rely on harsh conditions to oxidize the nitrogen center to facilitate radical generation. Recently, photocatalytic strategies have been developed as mild processes to form nitrogen-centered radicals,<sup>2, 3, 4, 5, 6</sup> however, only amides, carbamates, and sulfonamides have served as precursors to neutral nitrogen-centered radicals.<sup>4, 5, 6</sup> These groups template position-selective C–H functionalization technologies, transforming C(4)–H bonds through 1,5-HAT processes (Figure 1A).<sup>7</sup> As a complement to these guided methods, sulfamate esters are attractive directing groups because they derive from alcohols, which are ubiquitous in biologically active small molecules. Additionally, sulfamate esters guide functionalization to C(3) centers through otherwise rare 1,6-HAT processes (Figure 1B), providing complementary positional selectivity to established processes.<sup>8, 9, 10, 11, 12, 13, 14, 15, 16</sup> To date, protocols templated by sulfamate ester substrates require the use of strong stoichiometric oxidants to access nitrogen-centered sulfamyl radicals.<sup>14, 15</sup> As such, a strategy to facilitate sulfamyl radical formation under mild conditions would enhance the substrate tolerance of these directing motifs, and could also enable previously unrealized synthetic disconnections.<sup>17, 18</sup> Herein disclosed is the first catalytic process to access sulfamyl free radicals directly from N–H bonds. These sulfamyl radicals have been engaged in Giese reactions, in the only

examples of C(3)–H alkylation reactions guided by alcohol surrogates (Scheme 1C, **1** → **2**).

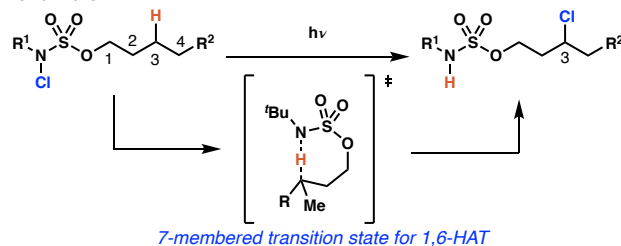
## Scheme 1. Sulfamate esters offer complementary site selectivity to developed templates for C–H alkylation reactions

(a) HLF reactions rely on 1,5-HAT processes to dictate site-selectivity, traditionally

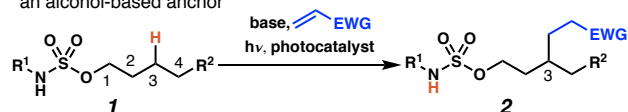


(b) Sulfamyl radicals engage in 1,6-HAT processes

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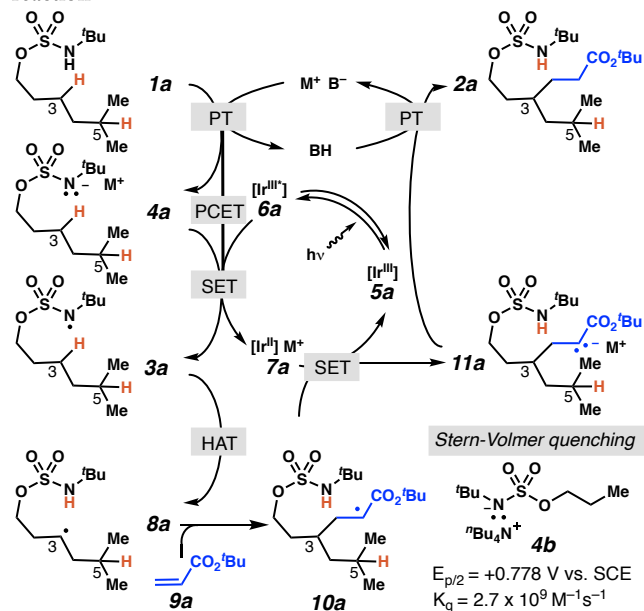
(c) These investigations: First net C(3)–H alkylation reaction templated by an alcohol-based anchor



## RESULTS AND DISCUSSION

At the outset of these investigations, we sought conditions that would facilitate oxidation of sulfamate ester **1a** to sulfamyl radical **3a**. We envisioned that this could occur through an initial deprotonation to provide sulfamate ester anion **4a**. Anion **4a** could undergo single electron oxidation to generate sulfamyl radical **3a**, with concurrent reduction of the excited iridium catalyst **6a** (Figure 2). Consistent with this proposal, in acetonitrile, sodiated 5-methylhexyl *N*-tert-butyl sulfamate ester anion **4a** has a half-peak potential ( $E_{p/2}$ ) of +0.753 V versus saturated calomel electrode (SCE), indicating that oxidation of the anion by a strongly oxidizing and broadly used iridium(III) photocatalyst [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (**6a**,  $E_{1/2}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21$  V versus SCE, dF(CF<sub>3</sub>)ppy = 2-(2,4-difluorophenyl)-3-trifluoromethylpyridine, dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine) is thermodynamically feasible.<sup>19</sup> Stern-Volmer analysis of the related sulfamate ester anion **4b** quenches **6a**.<sup>19</sup> Based on this data, reductive quenching of [Ir<sup>III</sup>] **6a** to [Ir<sup>II</sup>] **7a** by an in situ generated sulfamate ester anion, such as **4a**, can furnish sulfamyl radical **3a**. Alternatively, oxidation could occur through a concerted proton-coupled electron transfer (PCET) event. Presently, we cannot exclude the possibility that electron transfer could proceed through a concerted PCET event.

### Scheme 1. Proposed mechanism for sulfamate ester directed Giese reaction



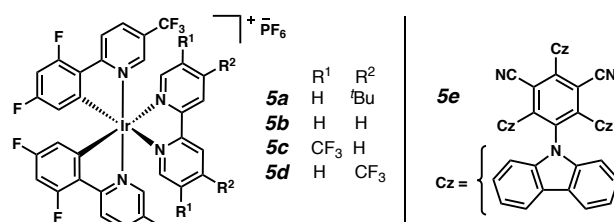
By analogy to previously reported sulfamyl radical-mediated C–H functionalization reactions,<sup>14, 15</sup> **3a** is poised to guide an intramolecular 1,6-HAT process to furnish carbon-centered radical **8a**. Nucleophilic radical **8a** engages electron-deficient olefin **9a** in a Giese reaction. At this point, reduction of an ester stabilized radical ( $E^{\circ}[\text{R}\cdot/\text{R}^-] \approx -0.63$  V versus SCE),<sup>20</sup> such as **10a**, by strong reductant **7a** ( $E_{1/2}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37$  V versus SCE)<sup>19</sup> to furnish carbon anion **11a** should be thermodynamically favorable. Finally, anion protonation would provide C(3)-alkylated product **2a**.

To develop this guided Giese reaction, we employed *tert*-butyl acrylate (**9a**) as an electrophile, and 5-methylhexyl *N*-*tert*-butylsulfamate ester (**1a**, Table 1). With this system, we could probe

the ability of this process to overcome the innate position-selectivity that dictates the site of unguided C–H functionalization reactions. In undirected processes, functionalization would be expected to proceed preferentially at the weakest, electron-rich C–H bond in the molecule, which would be the distal tertiary C–H center (bond dissociation energy (BDE)  $\approx 96$  kcal/mol).<sup>21</sup> The targeted C(3)–H bond is expected to be stronger (BDE  $\approx 98$  kcal/mol), and thus less likely to engage in unguided functionalization. Nevertheless, the directed Giese reaction proceeds in the presence of light, photocatalyst **5a**, and K<sub>2</sub>CO<sub>3</sub> to afford desired **2a** in 77% yield over 48 hours (entry 1). Using a range of strongly oxidizing excited state photocatalysts **5a–5e**, those that become stronger reductants prove more efficient in this transformation (entries 1, 2, 5). Consistent with mechanistic hypotheses, control experiments confirm that the photocatalyst, light, base, and inert atmosphere are required for product formation.

**Table 1. Photocatalysts that are stronger reductants upon initial quenching are more efficient**

entry <sup>a</sup>	photocatalyst	$E^{1/2}(\text{PC}^+/\text{PC}^-)$ [V] <sup>b</sup>	$E^{1/2}(\text{PC}/\text{PC}^-)$ [V] <sup>b</sup>	<b>1a</b> [%] <sup>c</sup>	yield <b>2a</b> [%] <sup>d</sup>
1	<b>5a</b>	+1.21	-1.37	17	77
2	<b>5b</b>	+0.97	-1.23	46	44
3	<b>5c</b>	+1.68	-0.69	98	nd <sup>e</sup>
4	<b>5d</b>	+1.65	-0.79	96	nd <sup>e</sup>
5	<b>5e</b>	+1.37	-1.21	12	34

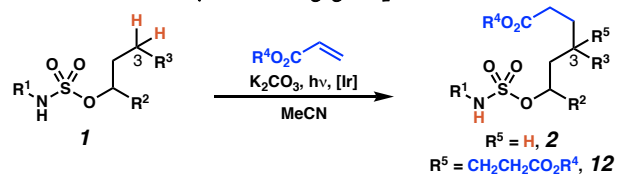


<sup>a</sup>General reaction conditions: 1.0 equiv sulfamate ester, 2.2 equiv *tert*-butyl acrylate, two 34 W blue Kessil lamps, photocatalyst (1.0 mol %), 1.0 equiv K<sub>2</sub>CO<sub>3</sub>, MeCN (0.2 M), 900 mot/min stirring, 21–28 °C, 48 h. <sup>b</sup>V versus SCE. <sup>5,19, 22</sup> <sup>c</sup>Recovered 1. <sup>d</sup>Isolated yields. <sup>e</sup>Not detected in <sup>1</sup>H NMR of the crude reaction mixture.

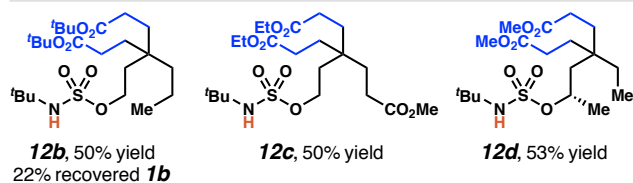
Under the optimized reaction conditions, the methylene center in sulfamate ester **1a** engages selectively in a single alkylation event to furnish Giese product **2a**, which incorporates a tertiary C(5)–H bond. This tertiary C–H bond is weaker than the secondary C(3)–H bond in substrate **1a**, and might be expected to be more susceptible to further alkylation to furnish fully-substituted **12**. To explain this selectivity, we hypothesize that the newly generated tertiary C(3)–H bond may prove too sterically hindered to engage in further functionalization. Consistent with this hypothesis, we found that less sterically encumbered **1b–1d** undergo initial monoalkylation with *tert*-butyl acrylate, followed by a second Giese

reaction to generate fully-substituted **12b–d** (Scheme 3). Furthermore, compounds with distal branching patterns (i.e. **1e–h**) react to furnish exclusive monoalkylated products **2e–h**.

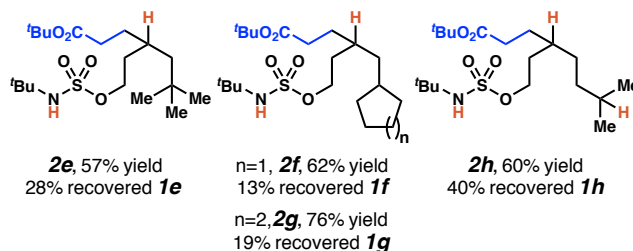
### Scheme 3. Secondary centers engage in productive Giese reactions<sup>a</sup>



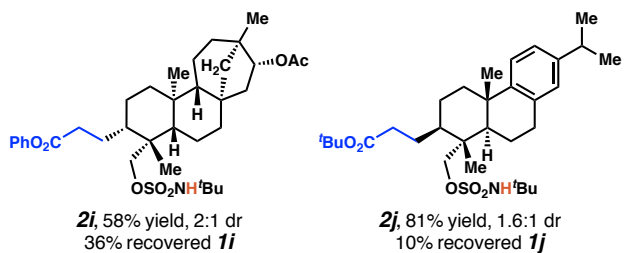
bisalkylation is feasible with unencumbered alkyl substrates



monoalkylation occurs with more sterically encumbered substrates



complex scaffolds induce diastereoselectivity



<sup>a</sup> General reaction conditions: 1.0 equiv sulfamate ester, 2.2 equiv electrophile, two 34 W blue Kessil lamps, photocatalyst (1.0 mol %), 1.0 equiv  $\text{K}_2\text{CO}_3$ , MeCN (0.2 M), 900 mot/min stirring, 21–28 °C, 48h.

<sup>b</sup> Isolated yields. <sup>c</sup> 11 days, additional 2.2 equiv acrylate added after 142 h. <sup>d</sup> 144 h, 4.4 equiv ethyl acrylate, and additional 4.4 equiv methyl acrylate added after 48 and 96 h.

In more complex substrates, C(3)-methylene centers react with substrate-induced site- and diastereoselectivity (Scheme 3). To our delight, the reaction of isosteviol derivative **1i** gives product **2i** as a 2:1 mixture of diastereomers in 58% isolated yield. Furthermore, while many electron-rich aryl groups are oxidatively labile, these conditions are sufficiently mild to affect functionalization of dehydroabietyl-derived **1j**. Indeed, **1j** provides alkylated products **2j** as a 1.6:1 mixture of diastereomers in a remarkable 81% isolated yield. These are the first documented cases of sulfamate ester-guided process where the radical-containing intermediate unambiguously induces a diastereoselective reaction.<sup>23</sup>

In spite of sensitivity to steric hindrance, sulfamate esters guide Giese reactions at tertiary centers (Scheme 4). While the electron densities of the C(5)–H and C(8)–H bonds of menthol-derived **13a**

are predicted to be similar,<sup>24</sup> this Giese reaction functionalizes solely the C(8)–H bond. Analogous site-selectivity is displayed in sulfamate ester-guided chlorination<sup>14</sup> and bromination<sup>15</sup> reactions, as well as in iron- and manganese-mediated intramolecular amination reactions.<sup>10d, 10g</sup> Presumably, the C(8)–H bond is geometrically disposed to interact with the directing groups that guide these reactions. By comparison, unguided intermolecular oxidation<sup>24</sup> and amination<sup>25</sup> processes engage the more sterically accessible C(5)–H bond selectively.

Furthermore, this directed reaction surmounts electronically-induced preferences for functionalization. In undirected processes, inductively electron-withdrawing groups can deactivate proximal C–H bonds to oxidation. When 3,7-dimethyloctanol is masked with an electron withdrawing group, it undergoes preferential oxidation at C(7) in fluorination,<sup>26</sup> oxygenation,<sup>27</sup> amination,<sup>28</sup> azidation,<sup>29</sup> and trifluoromethylthiolation<sup>30</sup> reactions. By contrast, this sulfamate ester guided reaction installs new carbon–carbon bonds predictably and selectively at C(3).

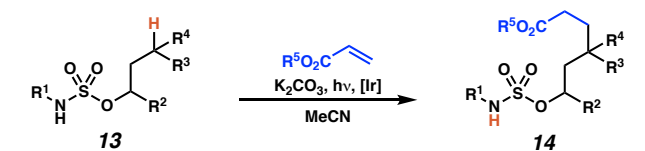
Additional fully-substituted C(3) centers can be generated from unactivated acyclic or cyclic tertiary C(sp<sup>3</sup>)–H bonds, or ethereal centers (i.e. **13c–g**). Remarkably, while ethereal **13e** features more sterically accessible and electronically activated C–H bonds, the reaction occurs selectively at the C(3)–H site.

Notably, optically active **13h** is converted to racemic **14h**, such that the generated radical must have a sufficient lifetime to epimerize. Nevertheless, remaining substrate is recovered without detectable epimerization, which suggests that the C–H abstraction is not reversible on a time scale that would allow for epimerization.

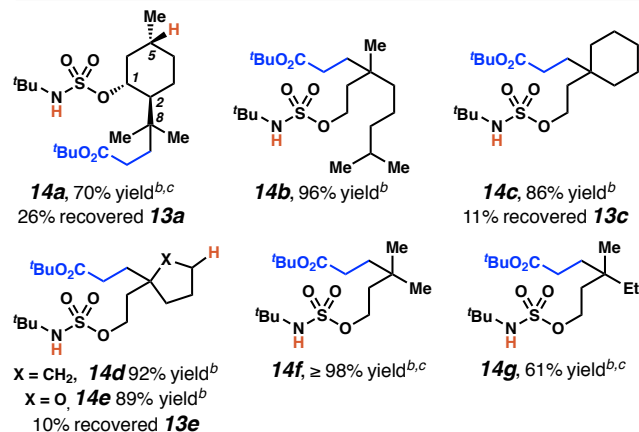
While tertiary and secondary C–H bonds engage in productive Giese reactions, primary centers, and secondary benzylic centers do not. Additionally, while racemic substrate **13g** reacts productively in this transformation, analogue **13k** is ineffective, providing further evidence that the reaction is sensitive to steric encumbrance. To date, the efficient transformation is highly dependent on nitrogen substitution. Unfortunately, *N*-*iso*-propyl, *N*-(1,1,1-trifluoro-2-methylpropyl), and *N*-2-(2-phenylpropyl) sulfamate esters (**13l–n**) guide the Giese reaction less effectively than *N*-*tert*-butyl sulfamate esters.

A wide range of electron-deficient olefins engage in this directed Giese reaction (Table 2). Alkyl, aryl, allyl, and alkynyl acrylates react in good to excellent yields (entries 1–4). This is remarkable, as many aryl, allyl, and alkynyl groups would undergo deleterious processes under more oxidizing conditions. Furthermore, as alkynes are well-developed as handles to facilitate structure-activity-relationship or mode-of-action studies, incorporation of an alkyne-bearing trapping agent suggests that this Giese reaction could be applied to complex small molecules to generate chemical probes.<sup>31</sup>

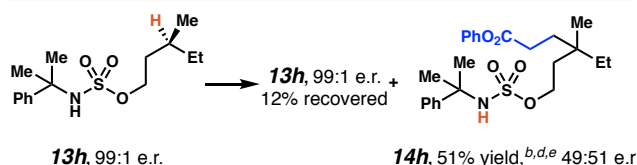
**Scheme 4. Reactions can form fully-substituted centers and tolerate *N*-substituent variations<sup>a</sup>**



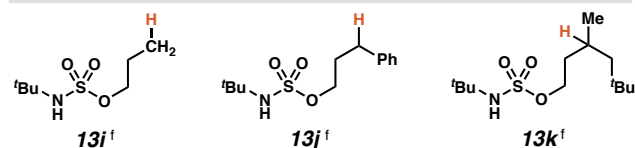
variations of *O*-alkyl substituents



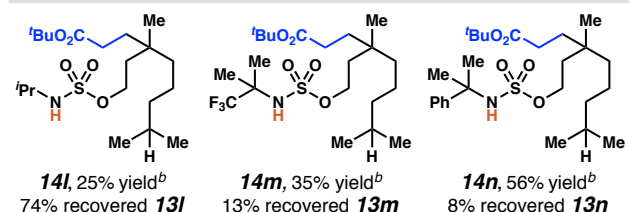
carbon-centered radical is generated irreversibly



limitations on *O*-alkyl substitution



variations of *N*-substitution



<sup>a</sup> General reaction conditions: 1.0 equiv sulfamate ester, 2.2 equiv electrophile, two 34 W blue Kessil lamps, photocatalyst (1.0 mol %), 1.0 equiv K<sub>2</sub>CO<sub>3</sub>, MeCN (0.2 M), 900 mot/min stirring, 21–28 °C, 48h. <sup>b</sup> Isolated yields. <sup>c</sup> 16 h. <sup>d</sup> 24 h. <sup>e</sup> Yield as average of two trials. <sup>f</sup> Product not detected by <sup>1</sup>H NMR of the crude reaction.

Despite the documented challenges with substrate steric encumbrance, bulky radical trapping agents engage effectively, including 2-substituted acrylates, a dehydroalanine derivative, and dimethyl fumarate, which contains an internal olefin (entries 5–8). More electrophilic radical trapping agents also react effectively, including α,β-unsaturated ketones that are cyclic, acyclic, or aryl-substituted, and with acrolein (entries 9–12). Finally, nitrogen-

containing electrophiles are competent in the reaction (entries 13–15).

**Table 2. Reaction traps various electron deficient electrophiles**

entry <sup>a</sup>	electrophile	product	<b>13</b> [%] <sup>b</sup>	yield [%] <sup>c</sup>
1		<b>15a</b>	22	74
2		<b>15b</b>	7	72
3		<b>15c</b>	38	58
4		<b>15d</b>	9	66
5		<b>16a</b>	nd <sup>d</sup>	58
6		<b>16b</b>	Me Ph	80
7 <sup>f</sup>		<b>16c</b>	Me NBoc <sub>2</sub>	nd <sup>d</sup> 89
8 <sup>f</sup>		<b>16d</b>		21 78
9		<b>16e</b>		11 87
10		<b>15e</b>	Ph	47 50
11		<b>15f</b>	Me	24 72
12		<b>15g</b>	H	58 43
13		<b>15h</b>	NMe <sub>2</sub>	4 66
14		<b>15i</b>	NHMe	4 55
15		<b>15j</b>		52 44
16		<b>16f</b>		nd <sup>d</sup> ≥98 >20:1 dr

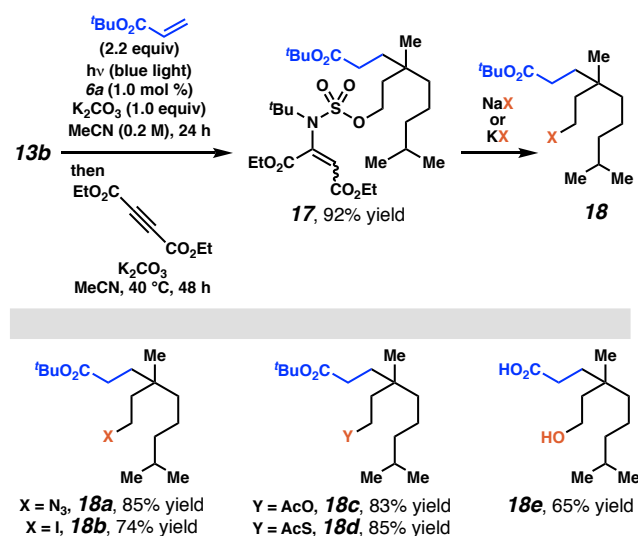
<sup>a</sup> General reaction conditions: 1.0 equiv sulfamate ester, 2.2 equiv electrophile, two 34 W blue Kessil lamps, photocatalyst (1.0 mol %), 1.0 equiv K<sub>2</sub>CO<sub>3</sub>, MeCN (0.2 M), 900 mot/min stirring, 21–28 °C. <sup>b</sup> Recovered **13b** or **13f** Isolated yields. <sup>d</sup> Not detected in crude <sup>1</sup>H NMR of the crude reaction. <sup>e</sup> Not isolated. <sup>f</sup> 1.2 equiv electrophile.

Radical conjugate addition reactions benefit from a rich library of enantioenriched electrophiles, designed to induce asymmetry in the course of radical addition reactions, even with acyclic nucleophilic free radicals.<sup>32</sup> In principle, this rich array of enantioenriched

electrophiles could be used to intercept this radical translocation protocol and induce asymmetry in the course of these transformations. Gratifyingly, sulfamate ester **13f** reacts with a known enantioenriched methyleneoxazolidinone electrophile<sup>33,34</sup> to furnish amino acid derivative **16f** in quantitative yield with complete diastereocontrol (>20:1 d.r., entry 16). In principle, this approach could provide access to a broad array of enantioenriched non-natural alkylated amino acids.

Ultimately, to maximize the utility of this process, it is necessary to cleave or displace the sulfamate ester template for this alkylation process. To make sulfamate esters more liable to displacement, typically they are *N*-acylated.<sup>10a</sup> To our disappointment, the *N*-*tert*-butyl sulfamate ester products are not efficiently carbamoylated under standard conditions. Fortunately, *N*-vinylation of *N*-*tert*-butyl sulfamate esters can be achieved with diethyl acetylene dicarboxylate (Scheme 5). This renders vinyllated **17** susceptible to displacement to furnish azide,<sup>15</sup> iodide,<sup>15</sup> acetate,<sup>10a</sup> thioacetate,<sup>10a</sup> or free alcohol<sup>10a</sup> analogues.

### Scheme 5. Strategies for sulfamate ester displacement



### CONCLUSION

This sulfamate ester-guided photoredox-mediated reaction provides a powerful and general platform for directed C–H functionalization. This is the first research to establish that sulfamate ester anions can be photochemically oxidized. Moreover, the resultant nitrogen-centered radicals guide 1,6-HAT to furnish tertiary or secondary carbon-centered radicals, which can be trapped to generate racemic and diastereoselective products. Thereby, this process affords complementary position-selectivity to that achieved using known photoredox-mediated carbon–carbon bond-forming reactions. Finally, a new tactic for sulfamate ester vinylation and displacement introduces further diversity to the array of accessed small molecules.

### ASSOCIATED CONTENT

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