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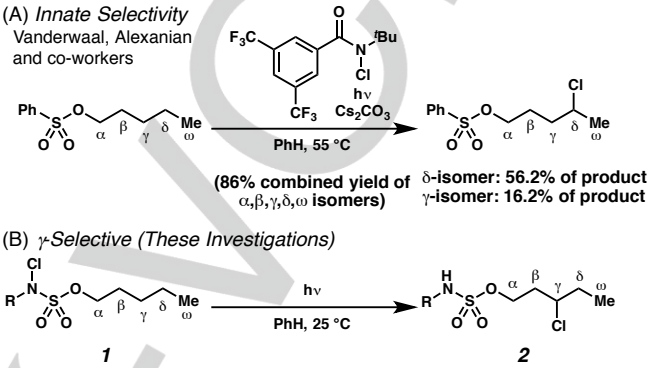
Sulfamate Esters Guide Selective Radical-Mediated Chlorination of Aliphatic C–H Bonds

Melanie A. Short,[a],[+] J. Miles Blackburn,[a],[+] and Jennifer L. Roizen*[a]

Abstract: Masked alcohols are particularly appealing as directing groups because of the ubiquity of hydroxyl groups in organic small molecules. Herein, we disclose a general strategy for aliphatic γ-C(sp^3)–H functionalization guided by a masked alcohol. Specifically, we determine that sulfamate ester-derived nitrogen-centered radicals mediate 1,6-hydrogen-atom transfer (HAT) processes to guide γ-C(sp^3)–H chlorination. This reaction proceeds through a light-initiated radical chain-propagation process and is capable of installing chlorine atoms at primary, secondary, and tertiary centers.

Late-stage alkyl C–H functionalization[1] facilitates investigations into pharmaceutical small molecule leads.[2] Unfortunately, position-selective reactivity is difficult to achieve at unactivated C(sp^3)–H centers, which have high bond dissociation energies (90–105 kcal/mol), are not acidic ($pK_a \geq 50$), and do not integrate more polarizable and electronically accessible π-orbitals. Consequently, in most efficient atom-transfer processes, site-selective activation originates at an electron-rich, sterically accessible bond (Scheme 1A),[1b,d,3] or is controlled kinetically by a directing group (Scheme 1B). A hydroxyl group is attractive as a directing moiety because alcohols are common within readily available small molecules. To our knowledge, there are no general strategies for aliphatic γ-C–H functionalization guided by a masked alcohol.[4,5] Herein described are the first experiments to demonstrate that sulfamate esters[6,7] can mediate 1,6-hydrogen-atom transfer (HAT) processes to guide the light-promoted chlorination of unactivated γ-C(sp^3)–H centers.

Our strategy for γ-functionalization is inspired by the modern resurgence of interest[8,9] in the Hofmann-Löffler-Freytag (HLF)[10–12] reaction. In traditional HLF processes, position selectivity arises based on formation of an intermediate nitrogen-centered radical that engages in a 1,5-HAT process[13] through a kinetically favored, six-membered transition state. [14] By contrast, we anticipate sulfamate esters may be capable of mediating 1,6-HAT processes, which are rare[15] as they are expected to proceed through seven-membered transition states, which are often kinetically disfavored.[16] We hypothesize that sulfamate esters enable 1,6-HAT because their elongated O–S and S–N bonds (~1.58 Å) and compressed O–S–N bond angles (~103°)[17] geometrically favor a seven-membered ring transition state for C–H abstraction. The site-selectivity available through these reactions complements that achieved using traditional HLF chlorination transformations,[18] alternative guided chlorination methods,[19] or site-selective intermolecular[20] chlorination processes.



Scheme 1. C(sp^3)–H chlorination reactions

This approach is demonstrated in the course of site-selective chlorine-transfer to convert *N*-chlorinated sulfamate esters **1** to alkyl chlorides **2** (Scheme 1B). Predictable control has proven more challenging in C(sp^3)–H chlorination[21] than bromination reactions,[12d,22,23] owing to the promiscuity of chlorine radical promoted hydrogen-atom abstraction. Nevertheless, alkyl chlorides are useful synthetic intermediates, and components of bioactive small molecules, with >2000 known chlorine-containing natural products.[24] Consequently, new technologies for selective aliphatic C–H chlorination have potential to streamline syntheses of bioactive small molecules.[25]

To minimize mechanistic uncertainty, we chose to generate nitrogen-centered radicals by using light to homolyze nitrogen–chlorine bonds of *N*-chlorosulfamate esters **1**. *N*-chlorosulfamate esters **1** are readily available from sulfamate esters **3**[26] upon treatment with trichloroisocyanuric acid or *tert*-butyl hypochlorite (see supporting information for details). As anticipated, photolysis of pentyl methylchlorosulfamate ester **1a** results in selective γ-chlorination at a methylene center (Table 1, entry 1, C–H bond dissociation energy (BDE) ~ 98 kcal mol^{-1}).[27] This reaction does not occur in the absence of light, indicating that photolysis initiates the reaction.

Chlorine-transfer proceeds from *N*-methyl-, *N*-*tert*-butyl-, *N*-trifluoroethyl- and *N*-2-(pyridin-2-yl)isopropylchlorosulfamate esters **1a**–**d** (Table 1, entries 1–7). The corresponding series of sulfamate esters **3** are predicted to differ in terms of N–H bond acidity[28] by more than three pK_a units, indicating that the reaction tolerates broad electronic variations across *N*-alkyl substituents. In all of these cases, the remaining mass balance can be accounted for principally by reduced **3**. Notably, in the reaction of substrate **1b**, <2% yield of δ-chlorinated product **4b** (not depicted) can be detected in the crude reaction mixture along with desired γ-chlorinated **2b**. While *N*-alkylsulfamate esters facilitate chlorination, some *N*-arylsulfamate esters may

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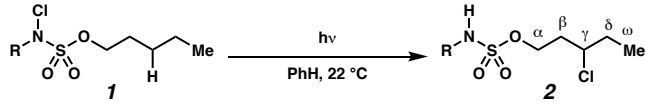
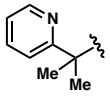
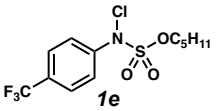
not engage in productive guided chlorine-transfer processes, as photochemical irradiation of arylated **1e** generates a complex mixture of products.

Table 1. Chlorine-transfer robust to *N*-substitution



1 *2*

entry[a]	R	predicted[b] pK_a for *3*	substrate for chlorine-transfer (*1*)	reaction time (min)	product (*2*)	yield (%)[c]
1	**Me**	12.65	***1a***	45	***2a***	85
2[d]	**^{t}Bu**	12.74	***1b***	15	***2b***	98
3[e]	**^{t}Bu**		***1b***	60	***2b***	83
4	**CH_2CF_3**	9.18	***1c***	15	***2c***	96
5[e]	**CH_2CF_3**		***1c***	60	***2c***	86
6[f]	**CH_2CF_3**		***1c***	90	***2c***	70
7		11.05	***1d***	45	***2d***	66
generates complex mixture of products						



1e

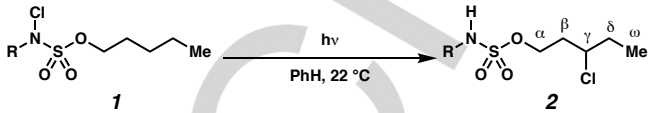
[a] General reaction conditions: 1.0 equiv *N*-chlorosulfamate ester **1**, PhH, 22 °C, irradiated with a blue Kessil lamp. [b] Aqueous ionization pK_a values have been predicted using SPARC.[28] [c] Isolated yield. [d] Trace amount of δ-chlorinated product **4b** (not depicted) detected in crude ^{1}H NMR. See Supporting Information for details. [e] Reaction run in $PhCF_3$. [f] Reaction run in PhCl.

In these chlorine-transfer processes, site-selectivity is orthogonal to that available through most atom-transfer processes reliant on innate selectivity. In the productive transformations of *N*-chlorinated **1a**–**d**, chlorinated alkanes **2a**–**d** are formed with exquisite γ-selectivity, despite the fact that δ-functionalization is expected to be favored under conditions that rely on inherent selectivity (Table 1; Scheme 1A).

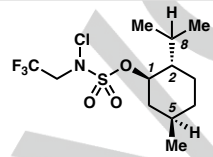
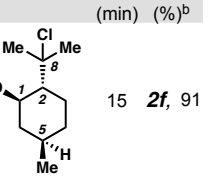
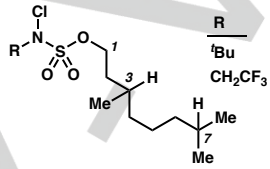
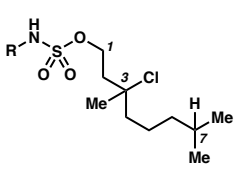
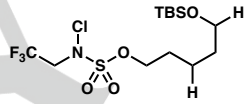
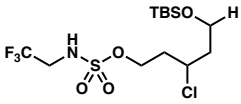
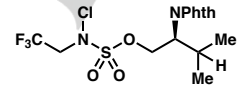
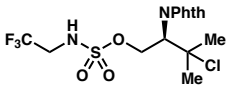
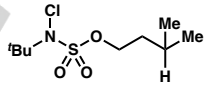
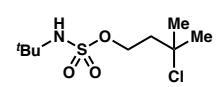
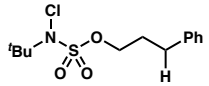
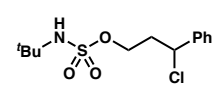
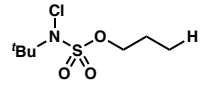
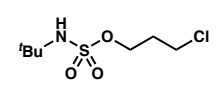
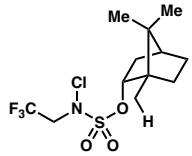
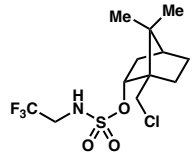
Guided selectivity is preserved across a range of *O*-alkyl sulfamate esters (Table 2). For menthol-derived **1f**, C(5)–H and C(8)–H bonds are expected to have very similar electron densities.[29] Nevertheless, unguided tertiary-selective intermolecular oxidation[29] and amination[30] processes result in selective functionalization of analogues at C(5), presumably because the C(8)–H bond is sterically encumbered.[29] By contrast, under the described conditions, chlorination occurs exclusively at C(8)–H, which is poised to interact with the sulfamate ester nitrogen-centered radical (entry 1) via a seven-membered transition state. This position-selectivity is analogous to that displayed in iron- and manganese-nitrene-mediated intramolecular amination reactions of sulfamate esters.[31,32]

Furthermore, the directed chlorination reaction overcomes the innate site-selectivity that arises from inductive deactivation in unguided oxidation processes. In unguided C–H functionalization reactions, proximity to inductively electron-withdrawing groups deactivates C–H bonds to oxidation. This phenomenon is evident when 3,7-dimethyloctanol is masked with an electron withdrawing group, and engages in undirected fluorination,[33] oxygenation,[34] amination,[35] azidation,[36] or trifluoromethylthiolation[37] processes that functionalize C(7) in preference to C(3). By contrast, the sulfamate ester-guided chlorination installs chlorine at the electronically deactivated C(3) position (entries 2–3).

Table 2. Chlorine-transfer robust to *O*-alkyl substitution



1 *2*

entry[a]	substrate	product	time (min)	yield (%)[b]
1			15	***2f,*** 91
2			15	***2g,*** 85
3			15	***2h,*** 96
4			15	***2i,*** 54
5			240	***2j,*** 82
6			30	***2k,*** 87
7			90	***2l,*** 92
8			120	***2m,*** 19
9			15	***2n,*** 36

[a] General reaction conditions: 1.0 equiv *N*-chlorosulfamate ester **1**, PhH, 22 °C, irradiated with a blue Kessil lamp. [b] Isolated yield.

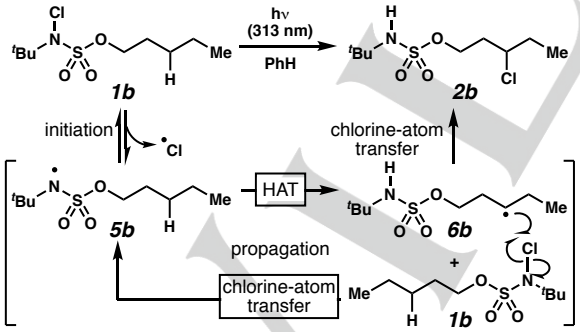
Moreover, this guided functionalization process overcomes selectivity that typically arises from differences in bond strength. Pendant silyl ether **1i** undergoes efficient and selective γ-chlorination, without oxidation of the weak etherial C–H bonds (BDE ~ 85 kcal mol^{-1}, entry 4).[27]

In addition to differentially masked diols, the reaction conditions are compatible with a variety of functional groups. Sulfamate esters derived from *N*-protected amino alcohols engage in selective atom-transfer, as phthalimidyl **1j** provides chlorinated **2j** in 82% isolated yield (entry 5). As noted

previously, the reaction also allows pendant heteroaromatic moieties (Table 1, entry 7) and fluorides (Table 1, entries 4–6; Table 2, entries 1, 3–5, 9).

This method transforms C(sp^3)–H bonds at secondary, tertiary (BDE ~ 96 kcal mol^{-1}),[27] and benzylic centers (BDE ~ 90 kcal mol^{-1})[27] in synthetically useful yields (entries 1–8). Generally, chlorination of γ-C(sp^3)–H centers occurs in preference to β-C–H centers, even when the γ-C–H bond is primary and significantly stronger (BDE ~ 101 kcal mol^{-1})[27] than a secondary β-C–H bond. For example, chlorination of propyl *tert*-butylsulfamate ester **1m** and (–)-borneol derivative **1n** occur at the stronger primary C–H bonds, albeit with diminished efficiency (entries 8–9). While each of these substrates displays a geometrically accessible β-methylene center, chlorination at these positions is not detected. Instead, dehalogenated sulfamate esters **3m** and **3n** are the primary byproducts of these transformations. An analogous reactivity trend has been documented with White's manganese-catalyzed intramolecular amination with sulfamate esters.[32]

In principle, this chlorination reaction could proceed through a closed cycle and/or a radical chain propagation mechanism (Scheme 2). In either pathway, initiation would occur by light-promoted N–Cl bond homolysis, thereby converting *N*-chlorosulfamate ester **1b** to chlorine radical and sulfamyl radical **5b.** The resulting nitrogen-centered radical **5b** mediates an intramolecular 1,6-HAT to generate a carbon-centered radical **6b** with exquisite position selectivity. Subsequent divergence in carbon–chlorine bond forming events then distinguishes between the proposed pathways. In the closed radical cycle mechanism, intermediate carbon-centered radical **6b** recombines with the chlorine radical to terminate the reaction and provide **2b** (not depicted). Alternatively, carbon-centered radical **6b** could engage in chlorine-atom abstraction with another equivalent of *N*-chlorosulfamate ester **1b** (Scheme 2). This sequence would release desired halogenated **2b**, along with another equivalent of radicalloid **5b**, which could propagate this chain reaction.



Scheme 2. Chlorination proceeds through light-initiated chain-propagation

These mechanistic hypotheses differ in terms of the number of product equivalents that can be generated per absorbed photon, a relationship that defines quantum yield (Φ). While a closed radical cycle could furnish a maximum of one product molecule per absorbed photon ($\Phi \leq 1$), a radical chain propagation mechanism could provide multiple equivalents of the product per absorbed photon ($\Phi > 1$).

Quantum yield measurements have been performed to provide insight into the operative reaction mechanism,[38] and provide evidence that the reaction proceeds through a light-initiated chain propagation mechanism. Briefly, standard chemical actinometry using potassium ferrioxalate allowed us to determine the photon flux of a fluorimeter at 313 nm.[38,39] After 15 minutes of irradiation of *N*-chlorinated **1b** in benzene at 313 nm in the calibrated fluorimeter, 68% conversion to chloroalkane **2b** is observed. This yield corresponds to 77 equivalents of product formed per absorbed photon (Φ = 77), indicating that this reaction proceeds through a chain propagation mechanism.

This sulfamate ester-guided HLF reaction is expected to provide a powerful and general platform to complement current HLF technologies. This research is among the first to establish that sulfamate esters can mediate 1,6-HAT such that the generated carbon-centered radicals can be trapped efficiently in guided intermolecular reactions. Furthermore, the method provides efficient access to secondary and tertiary alkyl chlorides, a valuable class of synthetic intermediates, with novel and predictable site-selectivity.

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Keywords: radical reactions • hydrogen transfer • halogenation • directing group • chlorination

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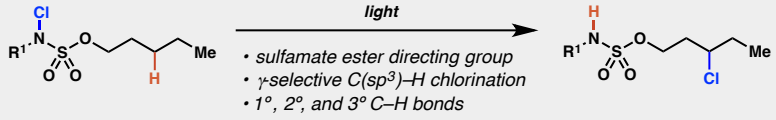

Guided Chlorination: Aliphatic γ-C(sp^3)–H chlorination is directed by a sulfamate-ester masked alcohol. This reaction involves a light-initiated N–Cl bond homolysis, followed by an unusual radical-mediated 1,6-hydrogen-atom abstraction with subsequent chlorination enabled by a chain-propagation process. Through this process, chlorine atoms can be selectively installed at primary, secondary, and tertiary centers with predictable selectivity.

*Melanie A. Short, J. Miles Blackburn, Jennifer L. Roizen**

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