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

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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(sp³)-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(sp³)-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.

Graphical abstract

Guided Chlorination: Aliphatic γ -C(sp³)-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.

Keywords

radical reactions; hydrogen transfer; halogenation; directing group; chlorination

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(sp³)-H centers, which have high bond dissociation energies (90–105 kcal/mol), are not acidic (pK_a > 50), and do not integrate more polarizable and electronically accessible π -orbitals. Consequently, in most efficient atom-transfer processes, site-selective

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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(sp³)–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 ($\sim 103^\circ$)^[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.

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(sp³)–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 not engage in productive guided chlorine-transfer processes, as photochemical irradiation of arylated **1e** generates a complex mixture of products.

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).

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 $\sim$ 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(sp³)–H bonds at secondary, tertiary (BDE $\sim$ 96 kcal mol^{–1}),^[27] and benzylic centers (BDE $\sim$ 90 kcal mol^{–1})^[27] in synthetically useful yields (entries 1–8). Generally, chlorination of γ -C(sp³)–H centers occurs in preference to β -C–H centers, even when the γ -C–H bond is primary and significantly stronger (BDE $\sim$ 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 by products 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 radicaloid **5b**, which could propagate this chain reaction.

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 ($\Phi = 1$), 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 ($\Phi = 77$), 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(A) *Innate Selectivity*
Vanderwaal, Alexanian
and co-workers

(B) γ -Selective (These Investigations)

Scheme 1. C(sp³)-H chlorination reactions

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

Table 1

Chlorine-transfer robust to *N*-substitution

entry ^a	R	Substrate for chlorine-transfer (1)		Reaction time (min)	Product (2)	Yield (%) ^c
1	Me	12.65		45	2a	85
2 ^d	^t Bu	12.74		15	2b	98
3 ^e	^t Bu	9.18		60	2b	83
4	CH ₂ CF ₃			15	2c	96
5 ^e	CH ₂ CF ₃			60	2c	86
6 ^f	CH ₂ CF ₃			90	2c	70

entry^a R Substrate for chlorine-transfer (*1*) Reaction time (min) Product (*2*) Yield (%)^c

7

11.05

1d

45

2d

66

generates complex mixture of products

entry^a   R   Substrate for chlorine-transfer (*I*)   Reaction time (min)   Product (*2*)   Yield (%)^c

^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 ¹H NMR. See Supporting Information for details.

Reaction run in PhCF_3 .
 f_j Reaction run in PhCl .

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

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

^aGeneral reaction conditions: 1.0 equiv *N*-chlorosulfamate ester **1**, PhH, 22 °C, irradiated with a blue Kessil lamp.

^bIsolated yield.