University of Groningen

Identifying Amidyl Radicals for Intermolecular C-H Functionalizations

Tierney, Matthew M.; Crespi, Stefano; Ravelli, Davide; Alexanian, Erik J.

Published in:
Journal of Organic Chemistry

DOI:
[10.1021/acs.joc.9b01774](https://doi.org/10.1021/acs.joc.9b01774)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Tierney, M. M., Crespi, S., Ravelli, D., & Alexanian, E. J. (2019). Identifying Amidyl Radicals for Intermolecular C-H Functionalizations. *Journal of Organic Chemistry*, 84(20), 12983-12991. <https://doi.org/10.1021/acs.joc.9b01774>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Identifying Amidyl Radicals for Intermolecular C–H Functionalizations

Matthew M. Tierney,[†] Stefano Crespi,^{‡,§,lb} Davide Ravelli,^{‡,lb} and Erik J. Alexanian^{*,†,lb}[†]Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States[‡]PhotoGreen Lab, Department of Chemistry, University of Pavia, viale Taramelli 12, 27100 Pavia, Italy

S Supporting Information

ABSTRACT: Recent studies have demonstrated the capabilities of amidyl radicals to facilitate a range of intermolecular functionalizations of unactivated, aliphatic C–H bonds. Relatively little information is known regarding the important structural and electronic features of amidyl and related radicals that impart efficient reactivity. Herein, we evaluate a diverse range of nitrogen-centered radicals in unactivated, aliphatic C–H chlorinations. These studies establish the salient features of nitrogen-centered radicals critical to these reactions in order to expedite the future development of new site-selective, intermolecular C–H functionalizations.

INTRODUCTION

The functionalization of aliphatic C–H bonds using a variety of strategies has become a valuable tool in chemical synthesis.^{1–3} For example, C–H functionalization provides facile access to molecular analogues of drugs with modified physicochemical and biological properties.⁴ A classical approach to C–H functionalization involves the use of heteroatom-centered radicals in intramolecular hydrogen-atom transfer (HAT) processes^{5–8} (Figure 1). Recent efforts by Suarez,⁹ Du Bois,^{10,11} Nagib,¹² and others^{13–23} have utilized this intramolecular HAT strategy to unlock practical C–H functionalizations of diverse substrates.

Pioneering work by Minisci,²⁴ Greene,²⁵ and Deno²⁶ demonstrated the potential for intermolecular aliphatic C–H functionalizations using nitrogen-centered radicals. The development of practical synthetic reactions of this type, however, involves several difficult challenges that must be addressed. For example, these processes do not benefit from

the kinetic advantages of intramolecular HAT. Furthermore, the highly reactive nature of heteroatom-centered radicals could lead to poor reaction site- and chemoselectivity.

We have recently demonstrated the ability of *N*-functionalized amides to achieve site-selective, intermolecular radical-mediated C–H functionalizations.^{27–30} Both *N*-halo and *N*-xanthylamides are useful precursors of amidyl radicals, which using either photochemical or radical initiation undergo HAT with a diverse array of organic substrates (Figure 1). These aliphatic C–H functionalizations facilitate the introduction of a range of molecular functionality in concise fashion. Our initial efforts have used reagents derived from bulky *N*-*t*Bu amides, which combined with the electrophilicity of the amidyl radical favor functionalization at sterically accessible, electron-rich C–H sites.

The modularity of the amide scaffold is amenable to the development of alternative reagents in this class. Indeed, we have begun work in this area via the modification of the aromatic substituent to increase the sterically dictated selectivity of our system.³⁰ There is little known concerning the requirements and limitations of the *N*-functionalized amide (or related) reagents in promoting efficient intermolecular C–H functionalization, however (Figure 2). Herein, we report a detailed analysis of amidyl radical reactivity for intermolecular HAT, focusing on aliphatic C–H chlorination. These experimental and computational studies outline several key components of the amide scaffold important in developing intermolecular HAT processes and identify several possible side reactions that are problematic with unsuccessful reactions of nitrogen-centered radicals.

Intramolecular C–H functionalization via 1,5-HAT: a remarkably useful manifold

Intermolecular C–H functionalization via hydrogen atom transfer from functionalized amides: emerging general approach

Figure 1. Intra- and intermolecular aliphatic C–H functionalization using nitrogen-centered radicals.

Special Issue: C–H Bond Functionalization

Received: July 1, 2019

Published: August 23, 2019

Figure 2. Elements of nitrogen-centered radicals addressed in these studies.

RESULTS AND DISCUSSION

We commenced our studies by evaluating the C–H chlorination of (+)-sclareolide as a test substrate with a range of *N*-chloroamides containing varied *N*-alkyl substitution (Table 1). Our previously reported chlorination of this

Table 1. C–H Chlorination of (+)-Sclareolide Varying Chloroamide *N*-Alkyl Substitution*

entry	<i>N</i> -alkyl chloroamide	yield (%) ^a
1	R = <i>t</i> Bu (2a)	75
2	<i>i</i> Pr (2b)	8
3	Et (2c)	<2
4	Me (2d)	8
5	<i>n</i> Pr (2e)	<2 ^b
6	<i>t</i> Bu (2f)	<2 ^b
7	Ar–C(=O)–N(CH ₂ CF ₃) ₂ (2g)	5
8	Ar–C(=O)–N(Me)CO ₂ Me (2h)	65
9	Ar–C(=O)–N(Me)CO ₂ Me (2i)	<2

*Reactions were performed with [1]₀ = 0.5 M. ^aYields determined by ¹H NMR spectroscopy of the crude reaction mixture using an internal standard. ^bMinor chlorination of the *N*-alkyl group was observed by ¹H NMR.

substrate using *N*-*t*Bu amide **2a** proceeded in good yield (entry 1, 75%) with excellent site selectivity and served as our baseline result. Surprisingly, only a slight variation in the chloroamide structure—using *N*-*i*Pr amide **2b**—led to a far inferior reaction providing only 8% of the chlorination product **3** (entry 2). Similar primary, branched, and nonbranched *N*-alkyl chloroamides also displayed poor reactivity (entries 3–6). The *N*-trifluoroethyl amide **2g**—which we previously reported was capable of functionalizing cyclohexane²⁷—also provided very little product (entry 7). Attempts using an ester derivative containing a fully substituted α -carbon similar to reagent **2a** provided **3** in good yield (entry 8). However, once again removing full alkyl substitution from the α -substituent completely shut down reactivity (entry 9). We note that *N*-

aryl amides were not investigated owing to the low N–H bond strength, preventing an energetically favorable C–H abstraction.³¹

We next studied the effect of electronic modification of the aryl substituent of *N*-*t*Bu chloroamide **2a** on the C–H chlorination (Table 2). A range of aryl substituents were

Table 2. C–H Chlorination of (+)-Sclareolide Varying *N*-*t*Bu-chloroamide Electronics*

entry	<i>N</i> - <i>t</i> Bu chloroamide	yield (%) ^a
1	2a	75
2	2j	75
3	X = NO ₂ (2k)	66
4	F (2l)	67
5	H (2m)	68
6	OMe (2n)	21 ^b
7	<i>t</i> Bu (2o)	58
8	2p	39

*Reactions were performed with [1]₀ = 0.5 M. ^aIsolated yields.

^bChlorination on the methoxy substituent observed by ¹H NMR.

permitted, with the exception of *p*-OMe amide (**2n**) likely owing to the abstractable C–H bonds of the methoxy group. There is no clear electronic preference for the aryl substituent, as the electron-poor aryl-substituted **2k** and **2l** (66% and 67% yield, respectively) performed similarly to unsubstituted reagent **2m** (68% yield, entry 5). Furthermore, the aryl group is not required, as a reagent containing a perfluoroalkyl group (**2p**) also provided **3** in moderate yield (39% yield, entry 8). We note that PhCF₃ is the solvent of choice, as nonaromatic solvents with abstractable C–H bonds are not tolerated (see Table S1). For example, the use of common organic solvents such as 1,2-dichloroethane revealed significant amounts of 1,1,2-trichloroethane, confirming C–H chlorination of the solvent.

Lastly, we investigated the efficiency of C–H chlorination using several other classes of *N*-chloro reagents (Figure 3). In addition to *N*-chloroamide **2a**, *N*-chlorosulfonamide **2q**

Figure 3. Intermolecular C–H chlorination using alternative electron-poor nitrogen-centered radicals. (a) Incomplete conversion of the reagent observed; see the [Supporting Information](#) for more details.

provided product **3** in moderate yield (53%). Reactions involving the *N*-chlorophosphoramidate **2r** and *N*-chlorocarbamate **2s** also delivered product, although both reactions proceeded with incomplete conversion. The use of common chlorinating agent *N*-chlorophthalimide provided no product. These results are consistent with the requirement of strong parent N–H bonds (i.e., > 100 kcal/mol) for the C–H chlorination reagents. Our calculated N–H BDE for the parent amide of **2a** is 110.7 kcal/mol, and those for reagents **2r** and **2s** are estimated to be within a ~3 kcal/mol range of this value.³² According to our calculations, the N–H BDE of the parent sulfonamide for **2q** is 7.2 kcal/mol weaker than that of **2a** but still relatively strong (103.5 kcal/mol). The N–H BDE of phthalimide is only ~89 kcal/mol making C–H abstraction significantly endergonic.³³

We next examined the structures of the *N*-*t*Bu and *N*-*i*Pr amidyl radicals computationally to glean any insights into the remarkable difference in reaction efficiency—75% yield versus 8% yield, respectively—involving these species ([Figure 4](#)). While the C–O and C–N bond lengths of the amidyl radicals are almost identical (<0.01 Å difference), the bulkier *t*Bu group induces a more pronounced “twisting” effect of the *N*-*t*Bu amidyl. The nitrogen substituent is markedly displaced out of the plane of the carbonyl group, with a -49° OC₇NC₁₀ dihedral in the case of the *N*-*t*Bu amidyl radical. On the other hand, two different conformers of the *N*-*i*Pr amidyl radical (α and β ; see [Figure S4](#) for the complete potential energy surface scan) had an almost identical energy. Both conformers show a less pronounced twisting (-32° and -49° OC₇NC₁₀ dihedral angle, for α and β , respectively). This disparity affects the distribution of spin density of the radicals, with a larger share of radical character localized on the nitrogen atom in the *N*-*t*Bu amidyl radical, with more spin density located on oxygen in the *N*-*i*Pr analogue.³⁴

In order to study the electronics of the two amidyl radicals in further detail, we performed a dedicated NBO (natural bond order) analysis.³⁵ This approach determines the contribution of the second-order perturbation stabilization terms ($E^{(2)}$) and the orbitals involved in them, shedding light on specific stereoelectronic interactions. It has recently been demonstrated to provide reliable estimates in predicting the reactivity of species with diradical transition-state character.³⁶ As depicted in [Figure 5](#), the *N*-*i*Pr amidyl radical achieves more

Figure 4. Spin density plots for (a) *N*-*t*Bu and (b) α and β conformers of *N*-*i*Pr amidyl radicals, along with some relevant geometric parameters. Spin densities for O, C₇, and N have been reported in red. These data have been obtained from calculations at the UwB97XD/def2svp level in the gas phase.

$E^{(2)}$ kcal mol ⁻¹			N radical character	
			π (%)	σ (%)
R = <i>i</i> Pr- α	42.05	14.57	94.75	5.15
R = <i>i</i> Pr- β	36.21	10.84	91.80	8.10
R = <i>t</i> Bu	33.43	7.76	88.81	11.10

Figure 5. Stabilization energies and orbital analysis obtained from the interactions of the *N*-*i*Pr (the analysis of both conformers has been reported) and *N*-*t*Bu amidyl radicals with π and π^* orbitals of the neighboring C=O calculated with the NBO6 software at the ω B97X-D/def2-SVP level of theory.

stabilization via both $n \rightarrow \pi^*$ and $\pi \rightarrow n$ interactions with the C=O group than the *N*-*t*Bu amidyl radical. This behavior can also be appreciated by comparing the percentage of σ character of the orbital of the N radical.

Given the overall structural and electronic similarities of the *N*-*t*Bu and *N*-*i*Pr amidyl radicals, combined with the similar parent amide N–H bond strengths,³¹ we considered other possibilities to explain the much greater efficiency of the *N*-*t*Bu reagents in C–H functionalization. It is clear from [Table 1](#) that the presence of α -C–H bonds on the *N*-alkyl group leads to a dramatic decrease in reaction yield. A hypothesis that is consistent with this trend is undesired C–H abstraction on the *N*-alkyl group occurring in preference to reaction with the substrate ([Scheme 1](#)). This side product pathway would consume *N*-chloroamide while providing no C–H chlorination product. The α -C–H abstraction of amines is well-documented,³⁷ while that of amides is much less known. The reported α -C–H BDE of *N*-*i*Pr acetamide is ~93 kcal/mol, making the HAT from the radicals studied herein exergonic.²⁸

The requirement for fully substituted α -positions on the *N*-alkyl side chain of functionalized amides reduces the possibility of diversifying these reagents for C–H functionalization. In order to address this issue, we examined the use of a more hindered aromatic scaffold. We have recently reported the enhanced steric selectivity of C–H functionalizations using 2,6-bis-trifluoromethyl *N*-*t*Bu amides.³⁰ We hypothesized that the significantly increased steric profile of this derivative could mitigate undesired side reactions (i.e., α -C–H abstraction). The reaction of 2,6-bis-trifluoromethyl *N*-*i*Pr chloroamide **2u** with (+)-sclareolide did provide product **3** in 34% yield (Figure 9), with up to a 75% yield using excess substrate (**3**

Figure 9. C–H chlorination of (+)-sclareolide with an *N*-*i*Pr chloroamide containing sterically demanding aryl substitution.

equiv). For comparison, the reaction with *N*-*i*Pr reagent **2b** under the same conditions produced only 8% of product. These results suggest that tuning the steric profile of the amidyl radical can permit the use of *N*-substituents which otherwise would have little chance of success.

In conclusion, these studies provide a set of guidelines for the design of reagents for intermolecular C–H functionalization using *N*-functionalized amides and derivatives. Highly effective N–H BDEs (>100 kcal/mol) are necessary to promote HAT of unactivated C–H bonds, and amides are desirable in this regard. Most importantly, reagents containing α -C–H bonds in the *N*-substituent can lead to sharply decreased efficiencies of intermolecular C–H functionalization. Increasing the steric profile of the aryl substituents can overcome this issue and permit further reagent diversification. We expect this work will support further reagent development in intermolecular radical-mediated aliphatic C–H functionalization in the future.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification unless otherwise noted. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker AVANCE III 600 CryoProbe (^1H NMR at 400 or 600 MHz and ^{13}C NMR at 100 or 151 MHz) spectrometer with solvent resonance as the internal standard (^1H NMR: CDCl_3 at 7.26 ppm; ^{13}C NMR: CDCl_3 at 77.16 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, tdd = triplet of doublet of doublets, qd = quartet of doublets, m = multiplet, br s = broad singlet, app = apparent), coupling constants (Hz), and integration. Mass spectra were obtained using a ThermoScientific Q Exactive HF-X Hybrid Quadrupole-Orbitrap with electrospray introduction and external calibration. Thin-layer chromatography (TLC) was performed on SiliaPlate 250 μm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), iodine, aqueous basic potassium permanganate solution, or aqueous acidic ceric ammonium molybdate solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40–63 μm) purchased from Silicycle.

Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use.

General Procedure for C–H Chlorination of (+)-Sclareolide Using *N*-Chloro Reagents **2a–u.** A flame-dried 1 dram vial was charged with a stir bar and brought into the glove where substrate (0.15 mmol, 1 equiv), BPO (0.015 mmol, 10 mol %), cesium carbonate (0.075 mmol, 0.5 equiv), PhCF_3 (0.3 mL, 0.5 M), and *N*-chloro reagent (0.15 mmol, 1.0 equiv) were added. The reaction was capped with a PTFE-lined screw cap, sealed with Teflon tape, taken out of the glovebox, and stirred at 65 °C on a heating mantle with a pie block for 7 h. After being cooled to room temperature, the reaction was brought back into the glovebox where BPO (0.015 mmol, 10 mol %) was added. The reaction was capped and resealed with Teflon tape, taken out of the glovebox, heated to 65 °C on the pie block, and stirred for an additional 17 h. Upon completion, the reaction mixture was then filtered through a silica plug, concentrated in vacuo, and analyzed by NMR using 10.0 μL of hexamethyldisiloxane as an internal standard.

General Procedure A for Amide Synthesis. Prepared similarly to previous reports from our laboratory.²⁴ To a solution of benzoic acid (10 mmol, 1 equiv) in CH_2Cl_2 and a few drops of DMF at 0 °C was added oxalyl chloride (20 mmol, 2 equiv) dropwise, and the resulting solution was allowed to warm to rt overnight. The mixture was concentrated in vacuo, resuspended in THF, and chilled to 0 °C. Amine (20 mmol, 2 equiv) was added, and the mixture was warmed to room temperature and stirred overnight. The mixture was concentrated in vacuo and the residue suspended in Et_2O , washed with 3 M NaOH, 1 M HCl, and brine, dried with MgSO_4 , and concentrated to afford the corresponding amide which was used without purification.

***N*-tert-Butyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. Spectral data matched literature values.²⁴

***N*-Isopropyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. Spectral data matched literature values.³⁹

***N*-Ethyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. ^1H NMR (600 MHz, chloroform-*d*): δ 8.24 (d, J = 1.5 Hz, 2H), 8.01 (s, 1H), 6.45 (s, 1H), 3.61–3.51 (m, 2H), 1.32 (td, J = 7.3, 1.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 164.5, 132.2 (q, J = 33.3, 32.9 Hz), 127.3, 125.4–123.8 (m), 122.0, 35.4, 14.8. HRMS (ESI+): exact mass calcd for $\text{C}_{11}\text{H}_{10}\text{N}_1\text{O}_1\text{F}_6$ [$M + \text{H}$]⁺ 286.0661, found 286.0658.

***N*-Methyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. ^1H NMR (600 MHz, chloroform-*d*): δ 8.07 (s, 2H), 8.01 (s, 1H), 3.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 169.5, 135.5, 131.9 (q, J = 34.1 Hz), 128.4 (d, J = 4.1 Hz), 124.6, 122.8 (d, J = 272.9 Hz), 42.5. HRMS (ESI+): exact mass calcd for $\text{C}_{10}\text{H}_8\text{N}_1\text{O}_1\text{F}_6$ [$M + \text{H}$]⁺ 272.0504, found 272.0507.

***N*-Propyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. ^1H NMR (600 MHz, chloroform-*d*): δ 8.23 (s, 2H), 8.02 (s, 1H), 6.37 (s, 1H), 3.49 (dt, J = 7.4, 5.9 Hz, 2H), 1.71 (m, J = 7.3 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 164.7, 136.8, 132.1 (q, J = 34.0 Hz), 127.3 (q, J = 3.7 Hz), 125.4–124.3 (m), 126.3–115.5 (m), 42.2, 22.8, 11.4. HRMS (ESI+): exact mass calcd for $\text{C}_{12}\text{H}_{12}\text{N}_1\text{O}_1\text{F}_6$ [$M + \text{H}$]⁺ 300.0817, found 300.0819.

***N*-Isobutyl-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. ^1H NMR (500 MHz, chloroform-*d*): δ 8.01 (s, 2H), 8.00–7.99 (s, 1H), 3.63 (d, J = 7.3 Hz, 2H), 2.30 (dp, J = 13.7, 6.9 Hz, 1H), 1.00 (d, J = 6.7 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, chloroform-*d*): δ 164.7, 136.9, 132.4 (t, J = 33.9 Hz), 127.2, 125.4–123.0 (m), 121.6, 47.8, 28.6, 20.2. HRMS (ESI+): exact mass calcd for $\text{C}_{13}\text{H}_{14}\text{N}_1\text{O}_1\text{F}_6$ [$M + \text{H}$]⁺ 314.0974, found 314.0976.

***N*-(2,2,2-Trifluoroethyl)-3,5-bis(trifluoromethyl)benzamide.** Obtained as a white powder according to general procedure A. Spectral data matched the reported literature values.²⁷

Methyl 2-(3,5-Bis(trifluoromethyl)benzamido)-2-methylpropanoate. Obtained as a white powder according to [general procedure A](#). ^1H NMR (500 MHz, chloroform-*d*): δ 8.25 (s, 1H), 8.04 (s, 1H), 6.95 (s, 1H), 3.84 (s, 3H), 1.75 (s, 6H). HRMS (ESI⁺): exact mass calcd for $\text{C}_{14}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_3$ 358.0872, found 358.0865.

Methyl (3,5-Bis(trifluoromethyl)benzoyl)alaninate. Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴⁰

***N*-tert-Butyl-2,3,4,5,6-pentafluorobenzamide.** Obtained as a white powder according to [general procedure A](#). ^1H NMR (600 MHz, chloroform-*d*): δ 5.70 (s, 1H), 1.49 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 156.3, 145.9–140.6 (m), 139.3–134.4 (m), 112.7 (t, J = 20.4 Hz), 53.2, 28.9. ^{19}F NMR (564 MHz, chloroform-*d*): δ -139.1 to -143.2 (m), -151.8 (d, J = 20.4 Hz), -158.0 to -161.5 (m). HRMS (ESI⁺): exact mass calcd for $\text{C}_{11}\text{H}_{11}\text{N}_1\text{O}_1\text{F}_5$ $[\text{M} + \text{H}]^+$ 268.0755, found 268.0755.

***N*-tert-Butyl-4-nitrobenzamide.** Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴¹

***N*-tert-Butyl-4-fluorobenzamide.** Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴¹

***N*-tert-Butylbenzamide.** Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴²

***N*-tert-Butyl-4-methoxybenzamide.** Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴¹

***N*,4-Di-*tert*-butylbenzamide.** Obtained as a white powder according to [general procedure A](#). Spectral data matched the reported literature values.⁴¹

***N*-Isopropyl-2,6-bis(trifluoromethyl)benzamide.** Obtained as colorless crystals according to [general procedure A](#). ^1H NMR (600 MHz, chloroform-*d*): δ 7.93 (d, J = 8.0 Hz, 2H), 7.68 (t, J = 8.0 Hz, 1H), 5.58 (s, 1H), 4.37 (m, J = 6.6 Hz, 1H), 1.28 (d, J = 6.6, 1.7 Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 163.1, 134.5 (d, J = 1.8 Hz), 129.9 (q, J = 4.9 Hz), 129.6, 129.2 (q, J = 32.0 Hz), 123.1 (q, J = 274.6 Hz), 42.4, 22.2. HRMS (ESI⁺): exact mass calcd for $\text{C}_{12}\text{H}_{12}\text{N}_1\text{O}_1\text{F}_6$ $[\text{M} + \text{H}]^+$ 300.0817, found 300.0815.

Procedure for Synthesis of Diphenyl *tert*-Butylphosphoramidate. Prepared similarly to previous reports in the literature. A solution of diphenyl chlorophosphate (10 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was cooled in an ice bath. *tert*-Butylamine (25 mmol, 2.5 equiv) was added dropwise, and the mixture was warmed to rt and stirred overnight. The mixture was washed with satd NaHCO_3 and 1 M HCl, brine, dried with MgSO_4 , and concentrated to afford the corresponding phosphoramidate as a white solid (3.0 g, 98% yield), which was used without purification. ^1H NMR (600 MHz, chloroform-*d*): δ 7.35 (t, J = 7.4 Hz, 4H), 7.30–7.24 (m, 6H), 7.17 (t, J = 7.3 Hz, 4H), 3.01 (s, 1H), 1.38 (d, J = 1.9 Hz, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 151.1 (d, J = 7.1 Hz), 129.6, 124.7, 120.2 (d, J = 5.1 Hz), 51.8, 31.3 (d, J = 4.9 Hz). HRMS (ESI⁺): exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{N}_1\text{O}_3\text{P}_1$ $[\text{M} + \text{H}]^+$ 306.1254, found 306.1247.

Procedure for Synthesis of *N*-tert-Butyl-3,5-bis(trifluoromethyl)benzenesulfonamide. Prepared similarly to previous reports in the literature. A solution of 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (15 mmol, 1 equiv) in CH_2Cl_2 was cooled in an ice bath. *tert*-Butylamine (38 mmol, 2.5 equiv) was added dropwise, and the mixture was warmed to rt and stirred overnight. The mixture was washed with satd NaHCO_3 , 1 M HCl, and brine, dried with MgSO_4 , and concentrated to afford the corresponding sulfonamide as a white solid (5.0 g, 95% yield) which was used without purification. ^1H NMR (600 MHz, chloroform-*d*): δ 8.36 (s, 2H), 8.07 (s, 1H), 4.81 (s, 1H), 1.30 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 146.1, 132.8 (q, J = 34.3 Hz), 127.2 (d, J = 3.9 Hz), 122.5 (q, J = 273.3 Hz), 55.8, 30.2. HRMS (ESI⁻): exact mass calcd for $\text{C}_{12}\text{H}_{12}\text{F}_6\text{N}_1\text{O}_2\text{S}$ $[\text{M} - \text{H}]^-$ 348.0487, found 348.0487.

Procedure for Synthesis of 2,2,2-Trichloroethyl *tert*-Butylcarbamate. Prepared similarly to previous reports in the

literature. A solution of 2,2,2-trichloroethyl chloroformate (10 mmol, 1 equiv) in CH_2Cl_2 was cooled in an ice bath. *tert*-Butylamine (25 mmol, 2.5 equiv) was added dropwise, and the mixture was warmed to rt and stirred overnight. The mixture was washed with satd NaHCO_3 , 1 M HCl, and brine, dried with MgSO_4 , and concentrated to afford the corresponding carbamate as a colorless amorphous solid (2.2 g, 89% yield), which was used without purification. ^1H NMR (600 MHz, chloroform-*d*): δ 4.94 (s, 1H), 4.69 (s, 2H), 1.38 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 152.6, 95.9, 73.9, 50.9, 28.7. HRMS (ESI⁺): exact mass calcd for $\text{C}_7\text{H}_{12}\text{Cl}_3\text{N}_1\text{O}_1$ $[\text{M} + \text{H}]^+$ 248.0006, found 248.0007.

Procedure for Synthesis of *N*-tert-Butyl-2,2,3,3,3-pentafluoropropanamide. A solution of 2,2,3,3,3-pentafluoropropionic anhydride (11 mmol, 1.1 equiv) in CH_2Cl_2 (75 mL) was cooled in an ice bath. *tert*-Butylamine (10 mmol, 1 equiv) and triethylamine (12 mmol, 1.2 equiv) were carefully added dropwise [caution: reaction is very exothermic]. The mixture was then warmed to rt and stirred overnight. The mixture was washed with water, satd NH_4Cl , and brine, dried with MgSO_4 , and concentrated to afford the corresponding amide as a yellow liquid (1.9 g, 89% yield), which was used without purification. ^1H NMR (600 MHz, chloroform-*d*): δ 6.18 (s, 1H), 1.44 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 156.6 (t, J = 24.6 Hz), 121.4–115.2 (m), 105.6 (dd, J = 266.7, 38.5 Hz), 53.0, 28.2. ^{19}F NMR (564 MHz, chloroform-*d*): δ -82.9, -122.7. HRMS (ESI⁻): exact mass calcd for $\text{C}_7\text{H}_9\text{F}_5\text{N}_1\text{O}_1$ $[\text{M}]$, 218.0610, found 218.0603.

General Procedure B for Synthesis of *N*-Chloro Reagents. Synthesized according to the literature procedure.²⁸ To a foil-wrapped flask under N_2 was added amide (5 mmol, 1 equiv) and the mixture dissolved in a mixture of ethyl acetate (10 mL) and *tert*-butyl alcohol (5 mmol, 1 equiv). Ten equivalents of a sodium hypochlorite solution was then added (~1.5 M in H_2O Sigma-Aldrich), followed by acetic acid (50 mmol, 10 equiv). The reaction was stirred at room temperature for 3–4 h. When the reaction was complete as judged by TLC analysis (3 h usually sufficient), the reaction was diluted with Et_2O and washed three times with saturated sodium bicarbonate solution, once with water, and once with brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude material usually contains traces of chlorinated ethyl acetate. The crude product was purified via column chromatography (EtOAc /hexane) to give the desired product. *General storage: N-Chloro reagents were stored in foil-wrapped vials in the freezer when not in use. The reagents can be weighed out on the benchtop without risk of decomposition.*

General Procedure C for Synthesis of *N*-Chloro Reagents. To a foil wrapped flask under N_2 was added amide (5 mmol, 1 equiv) and the mixture dissolved in a mixture of ethyl acetate (10 mL) and *tert*-butyl alcohol (5 mmol, 1 equiv). One equivalent of a sodium hypochlorite solution was then added (~1.5 M in H_2O Sigma-Aldrich), followed by acetic acid (10 mmol, 2 equiv). The reaction was monitored by TLC until all starting material was consumed. When the reaction was complete, the solution was diluted with Et_2O and washed three times with saturated sodium bicarbonate solution, once with water, and once with brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude material usually contains traces of chlorinated ethyl acetate. The crude product was purified via column chromatography (EtOAc /Hexane) to give the desired product.

***N*-tert-Butyl-*N*-chloro-3,5-bis(trifluoromethyl)benzamide (2a).** Obtained as a pale yellow oil (0.75 g, 86% yield) according to [general procedure B](#) (2.5 mmol). Purified using 1:20 EtOAc /hexanes. Spectral data are in accordance with the literature.²⁸

***N*-Chloro-*N*-isopropyl-3,5-bis(trifluoromethyl)benzamide (2b).** Obtained as a pale yellow oil (1.5 g, 90% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc /hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 8.07–7.96 (m, 3H), 4.77 (m, 1H), 1.36 (d, J = 8.7, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 168.8, 136.8, 132.8–131.0 (m), 128.0, 124.3, 122.8 (q, J = 273.1 Hz), 52.7, 19.7. HRMS (ES⁻): exact mass calcd for $\text{C}_{12}\text{H}_{11}\text{Cl}_1\text{F}_6\text{N}_1\text{O}_1$ $[\text{M} + \text{H}]^+$ 334.0439, found 334.0430.

N-Chloro-N-ethyl-3,5-bis(trifluoromethyl)benzamide (2c). Obtained as a pale yellow oil (0.60 g, 75% yield) according to [general procedure B](#) (2.5 mmol). Purified using 1:10 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 8.05 (s, 2H), 8.01 (s, 1H), 3.86 (q, *J* = 1.4 Hz, 2H), 1.39 (t, *J* = 1.4 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 168.8, 136.0, 132.0 (q, *J* = 34.2 Hz), 128.2, 125.51, 124.1 (d, *J* = 118.1 Hz), 121.9, 49.5, 12.5. HRMS (ES[−]): exact mass calcd for $\text{C}_{11}\text{H}_9\text{ClF}_6\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 320.0282, found 320.0270.

N-Chloro-N-methyl-3,5-bis(trifluoromethyl)benzamide (2d). Obtained as an off-white solid (0.78 g, 51% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:10 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 8.07 (s, 2H), 8.01 (s, 1H), 3.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 169.5, 135.5, 131.9 (q, *J* = 34.1 Hz), 128.4 (d, *J* = 4.1 Hz), 124.6, 122.8 (q, *J* = 272.9), 42.5. HRMS (ES[−]): exact mass calcd for $\text{C}_{10}\text{H}_7\text{ClF}_6\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 306.0126, found 306.0116.

N-Chloro-N-propyl-3,5-bis(trifluoromethyl)benzamide (2e). Obtained as a pale yellow oil (1.68 g, 98% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (500 MHz, chloroform-*d*): δ 8.02 (s, 2H), 8.00 (s, 1H), 3.81–3.72 (m, 2H), 1.85 (h, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 169.0, 136.3, 131.9 (q, *J* = 33.9 Hz), 128.1 (t, *J* = 3.8 Hz), 126.1–117.0 (m), 60.6, 26.7, 19.4. HRMS (ES[−]): exact mass calcd for $\text{C}_{12}\text{H}_{11}\text{ClF}_6\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 334.0439, found 334.0429.

N-Chloro-N-isobutyl-3,5-bis(trifluoromethyl)benzamide (2f). Obtained as a pale yellow oil (0.70 g, 40% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (500 MHz, chloroform-*d*): δ 8.01 (s, 2H), 8.00–7.99 (s, 1H), 3.63 (d, *J* = 7.3 Hz, 2H), 2.30 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 169.0, 136.3, 131.9 (q, *J* = 33.9 Hz), 128.1 (t, *J* = 3.8 Hz), 126.1–117.0 (m), 60.6, 26.7, 19.4. HRMS (ES[−]): exact mass calcd for $\text{C}_{13}\text{H}_{13}\text{ClF}_6\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 348.0584, found 348.0588.

N-Chloro-N-(2,2,2-trifluoroethyl)-3,5-bis(trifluoromethyl)benzamide (2g). Obtained as an off-white solid (1.7 g, 91% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*) δ 8.11 (s, 2H), 8.09 (s, 1H), 4.49 (q, *J* = 8.1 Hz, 2H). ^{13}C NMR $\{^1\text{H}\}$ (151 MHz, chloroform-*d*) δ 169.3, 133.9, 132.1 (q, *J* = 34.3 Hz), 128.5 (q, *J* = 3.8 Hz), 126.1–118.9 (m), 52.8 (q, *J* = 35.6 Hz). ^{19}F NMR (564 MHz, chloroform-*d*): δ −63.1, −69.7. HRMS (ES[−]): exact mass calcd for $\text{C}_{11}\text{H}_6\text{ClF}_9\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 373.9999, found 373.9989.

Methyl 2-(N-Chloro-3,5-bis(trifluoromethyl)benzamido)-2-methylpropanoate (2h). Obtained as an off-white solid (0.31 g, 63% yield) according to [general procedure B](#) (1.25 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 8.13 (s, 2H), 8.05–7.98 (s, 1H), 3.79 (s, 3H), 1.69 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 172.0, 170.9, 135.9, 131.8 (d, *J* = 34.2 Hz), 127.1–119.2 (m), 66.5, 53.0, 23.4. Exact mass calcd for $\text{C}_{14}\text{H}_{13}\text{ClF}_6\text{N}_2\text{O}_3$ [*M* + *H*]⁺ 392.0493, found 392.0482.

Methyl N-(3,5-Bis(trifluoromethyl)benzoyl)-N-chloroalaninate (2i). Obtained as an off-white solid (0.95 g, 50% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (500 MHz, chloroform-*d*): δ 8.09 (d, *J* = 1.7 Hz, 2H), 8.03 (s, 1H), 5.27 (br s, 1H), 3.85 (s, 3H), 1.68 (d, *J* = 7.0 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 169.9, 169.5, 135.5, 132.0 (q, *J* = 34.1 Hz), 128.3 (q, *J* = 3.5 Hz), 125.3–124.6 (m), 122.8 (d, *J* = 273.0 Hz), 57.9, 53.0, 14.7. HRMS (ES[−]): exact mass calcd for $\text{C}_{13}\text{H}_{11}\text{ClF}_6\text{N}_2\text{O}_3$ [*M* + *H*]⁺ 378.0337, found 378.0326.

N-tert-Butyl-N-chloro-2,3,4,5,6-pentafluorobenzamide (2j). Obtained as a white solid (1.0 g, 66% yield) according to [general procedure B](#) (5.0 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 1.64 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 156.3, 145.9–140.6 (m), 139.3–134.4 (m), 112.7 (t, *J* = 20.4 Hz), 53.2, 28.9. ^{19}F NMR (564 MHz, chloroform-*d*) δ −141.7 (d, *J* = 21.8 Hz), −152.5 (t, *J* = 20.9 Hz), −158.8 to −161.8 (m). HRMS (ES[−]): exact mass calcd for $\text{C}_{11}\text{H}_{10}\text{ClF}_5\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 302.0376, found 302.0365.

N-tert-Butyl-N-chloro-4-nitrobenzamide (2k). Obtained as a white solid (0.31 g, 61% yield) according to [general procedure B](#). Purified using 1:20 EtOAc/hexanes (2.0 mmol). ^1H NMR (600 MHz, chloroform-*d*): δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 1.62 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 129.1, 123.4, 64.6, 28.0. HRMS (ES⁺): exact mass calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_2\text{O}_3$ [*M* + *H*]⁺ 257.0698, found 257.0694.

N-tert-Butyl-N-chloro-4-fluorobenzamide (2l). Obtained as a white solid (0.50 g, 48% yield) without purification according to [general procedure B](#) (5.0 mmol). ^1H NMR (600 MHz, chloroform-*d*): δ 7.73–7.65 (m, 2H), 7.13–7.06 (m, 2H), 1.58 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 174.6, 165.1, 147.8 (d, *J* = 472.1 Hz), 131.0 (d, *J* = 8.8 Hz), 115.0 (d, *J* = 21.8 Hz), 78.7–74.5 (m), 63.8, 27.9. ^{19}F NMR (564 MHz, chloroform-*d*): δ −108.4 (d, *J* = 10.0 Hz). HRMS (ES⁺): exact mass calcd for $\text{C}_{11}\text{H}_{14}\text{FClN}_2\text{O}_1$ [*M* + *H*]⁺ 230.0742, found 230.0740.

N-tert-Butyl-N-chlorobenzamide (2m). Obtained as a white solid (0.55 g, 52% yield) according to [general procedure C](#). Purified using 1:10 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 7.68–7.64 (m, 2H), 7.50–7.46 (m, 1H), 7.42 (dd, *J* = 8.2, 6.7 Hz, 2H), 1.60 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 175.6, 136.3, 130.9, 128.42, 128.0, 78.3–75.4 (m), 63.7, 28.0. HRMS (ES⁺): exact mass calcd for $\text{C}_{11}\text{H}_{13}\text{ClN}_2\text{O}_1$ [*M* + *H*]⁺ 212.0837, found 212.0834.

N-tert-Butyl-N-chloro-4-methoxybenzamide (2n). Obtained as a white solid (0.40 g, 34% yield) according to [general procedure C](#). Purified using 1:10 EtOAc/hexanes. ^1H NMR (500 MHz, chloroform-*d*): δ 7.69 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 1.57 (s, 9H). HRMS (ES⁺): exact mass calcd for $\text{C}_{12}\text{H}_{17}\text{ClN}_2\text{O}_2$ [*M* + *H*]⁺ 244.0904, found 244.0921.

N,4-Di-tert-butyl-N-chlorobenzamide (2o). Obtained as a white solid (0.39 g, 24% yield) according to [general procedure C](#). Purified using 1:10 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 1.58 (s, 9H), 1.35 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 175.7, 154.5, 133.2, 128.5, 124.9, 63.5, 34.9, 31.2, 28.0. HRMS (ES⁺): exact mass calcd for $\text{C}_{15}\text{H}_{23}\text{ClN}_2\text{O}_1$ [*M* + *H*]⁺ 268.1474, found 268.1459.

N-tert-Butyl-N-chloro-2,2,3,3,3-pentafluoropropanamide (2p). Obtained as a yellow oil (70 mg, 15%) according to [general procedure B](#) (2.5 mmol). Purified using 1:10 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 1.56 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 159.9, 118.1 (qt, *J* = 286.6, 34.1 Hz), 107.7 (tq, *J* = 274.4, 36.4 Hz), 67.2, 27.7. ^{19}F NMR (564 MHz, chloroform-*d*): δ −81.5, −112.1 to −118.0 (m). HRMS (ES[−]): exact mass calcd for $\text{C}_7\text{H}_{10}\text{ClF}_5\text{N}_2\text{O}_1$ [*M* + *H*]⁺ 254.0365, found 254.0370.

N-tert-Butyl-N-chloro-3,5-bis(trifluoromethyl)benzenesulfonamide (2q). Obtained as a colorless solid (0.82 g, 85% yield) without purification according to [general procedure B](#) (2.5 mmol). ^1H NMR (600 MHz, chloroform-*d*) δ 8.46 (s, 2H), 8.14 (s, 1H), 1.60 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 141.1, 132.8 (q, *J* = 34.8 Hz), 129.1 (q, *J* = 3.8 Hz), 127.1 (p, *J* = 3.6 Hz), 122.4 (q, *J* = 273.5 Hz), 69.5, 29.3. HRMS (ES⁺): exact mass calcd for $\text{C}_{12}\text{H}_{13}\text{ClF}_6\text{N}_2\text{O}_2\text{S}_1$ [*M* + *H*]⁺ 384.0247, found 384.0254.

Diphenyl tert-Butylchlorophosphoramidate (2r). Obtained as a pale yellow oil (1.7 g, 98% yield) without purification according to [general procedure C](#) (5.0 mmol). ^1H NMR (600 MHz, chloroform-*d*): δ 7.42–7.32 (m, 8H), 7.22 (t, *J* = 8.2 Hz, 2H), 1.45 (s, *J* = 1.0 Hz, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 150.6, 129.7, 125.3, 120.4, 63.4, 29.3. ^{31}P NMR (243 MHz, chloroform-*d*): δ −4.97. HRMS (ES⁺): exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{ClP}_1\text{N}_2\text{O}_3$ [*M* + *H*]⁺ 340.0864, found 340.0862.

2,2,2-Trichloroethyl tert-Butylchlorocarbamate (2s). Obtained as a colorless oil (0.46 g, 65% yield) according to [general procedure B](#) (2.5 mmol). Purified using 1:20 EtOAc/hexanes. ^1H NMR (600 MHz, chloroform-*d*): δ 4.79 (s, 2H), 1.55 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 154.5, 94.9, 76.0, 64.5, 28.7. HRMS (ES[−]): exact mass calcd for $\text{C}_7\text{H}_{12}\text{Cl}_3\text{N}_1\text{O}_2$ [*M* + *H*]⁺ 281.9628, found 281.9611.

N-Chloro-N-isopropyl-2,6-bis(trifluoromethyl)benzamide (2u). Obtained as a white solid (0.30 g, 45% yield) according to [general procedure B](#) (2.5 mmol). Purified using 1:10 EtOAc/hexanes. ^1H

NMR (600 MHz, chloroform-*d*): δ 7.94 (d, J = 8.0 Hz, 2H), 7.74–7.67 (m, 1H), 5.21 (p, J = 6.5 Hz, 1H), 1.30 (d, J = 6.5 Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, chloroform-*d*): δ 166.2, 132.8–132.1 (m), 130.5–129.5 (m), 128.3 (q, J = 32.5 Hz), 123.0 (q, J = 274.7 Hz), 49.9, 19.0. HRMS (ES[−]): exact mass calcd for $\text{C}_{12}\text{H}_{11}\text{Cl}_1\text{F}_6\text{N}_1\text{O}_1$ [$\text{M} + \text{H}$]⁺ 334.0439, found 334.0426.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01774.

Computational data and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ej@email.unc.edu.

ORCID

Stefano Crespi: 0000-0002-0279-4903

Davide Ravelli: 0000-0003-2201-4828

Erik J. Alexanian: 0000-0002-0256-2133

Present Address

[§](S.C.) Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Award No. R01 GM 120163 from the National Institute of General Medical Sciences. M.M.T. thanks the NSF for a Graduate Research Fellowship. We thank Christina Na for performing N–H BDE calculations. Amide radical and structure calculations were carried out at the CINECA Supercomputer Center (Italy), with computer time granted by ISCRA projects (code: HP10C30YAJ).

■ REFERENCES

- (1) White, M. C. Adding Aliphatic C–H Bonds to Synthesis. *Science* **2012**, *335*, 807–809.
- (2) Newhouse, T.; Baran, P. S. If C–H Bonds Could Talk: Selective C–H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.
- (3) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960–9009.
- (4) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576.
- (5) Hofmann, A. W. Zur Kenntniss des Piperidins und Pyridins. *Ber. Dtsch. Chem. Ges.* **1879**, *12*, 984–990.
- (6) Zard, S. Z. Recent Progress in the Generation and Use of Nitrogen-Centered Radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603–1618.
- (7) Stateman, L. M.; Nakafuku, K. M.; Nagib, D. Remote C–H Functionalization via Selective Hydrogen Atom Transfer. *Synthesis* **2018**, *50*, 1569–1586.
- (8) Majetich, G.; Wheless, K. Remote Intramolecular Free Radical Functionalizations: An Update. *Tetrahedron* **1995**, *51*, 7095–7129.
- (9) Hernández, R.; Rivera, A.; Salazar, J. A.; Suárez, E. Nitroamine Radicals as Intermediates in the Functionalization of Non-activated Carbon Atoms. *J. Chem. Soc., Chem. Commun.* **1980**, 958–959.
- (10) Zalatan, D. N.; Du Bois, J. Oxidative Cyclization of Sulfamate Esters Using NaOCl – A Metal-Mediated Hoffman–Löffler–Freitag Reaction. *Synlett* **2009**, 143–146.
- (11) Du Bois, J. Rhodium-Catalyzed C–H Amination. An Enabling Method for Chemical Synthesis. *Org. Process Res. Dev.* **2011**, *15*, 758–762.
- (12) Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. Triiodide-Mediated Amination of Secondary C–H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 9974–9978.
- (13) Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459*, 824–828.
- (14) Petterson, R. C.; Wambsgans, A. Photochemical Rearrangement of *N*-Chloroimides to 4-Chloroimides. A New Synthesis of α -Lactones. *J. Am. Chem. Soc.* **1964**, *86*, 1648–1649.
- (15) Kerwin, J. F.; Wolff, M. E.; Owings, F. F.; Lewis, B. B.; Blank, B.; Magnani, A.; Karash, C.; Georgian, V. The Synthesis of C-18 Functionalized Steroid Hormone Analogs. II. Preparation and Some Reactions of 18-Chloro Steroids. *J. Org. Chem.* **1962**, *27*, 3628–3639.
- (16) Chow, Y. L.; Joseph, T. C. Selectivity of Intramolecular Hydrogen Transfer in the Free Amido-Radical. *J. Chem. Soc. D* **1969**, *9*, 490–491.
- (17) Groendyke, B. J.; AbuSalim, D. I.; Cook, S. P. Iron-Catalyzed, Fluoroamide-Directed C–H Fluorination. *J. Am. Chem. Soc.* **2016**, *138*, 12771–12774.
- (18) Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. Efficient Method for Selective Introduction of Substituents as C(5) of Isoleucine and Other α -Amino Acids. *Org. Lett.* **2006**, *8*, 2819–2821.
- (19) Liu, T.; Mei, T.-S.; Yu, J.-Q. γ - δ , ϵ -C(sp³)-H Functionalization through Directed Radical H-Abstraction. *J. Am. Chem. Soc.* **2015**, *137*, 5871–5874.
- (20) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C–H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539*, 268–271.
- (21) Chu, J. C. K.; Rovis, T. Amide-Directed Photoredox-Catalyzed C–C Bond Formation at Unactivated sp³ C–H Bonds. *Nature* **2016**, *539*, 272–275.
- (22) Chen, D.-F.; Chu, J. C. K.; Rovis, T. Directed γ -C(sp³)-H Alkylation of Carboxylic Acid Derivatives through Visible Light Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 14897–14900.
- (23) Tang, N.; Wu, X.; Zhu, C. Practical, Metal-free Remote Heteroarylation of Amides via Unactivated C(sp³)-H Bond Functionalization. *Chem. Sci.* **2019**, *10*, 6915–6919.
- (24) Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. J. Selective Aromatic Chlorination and Bromination with *N*-Halogenoamines in Acidic Solution. *J. Chem. Soc., Perkin Trans. 2* **1989**, *2*, 123–126.
- (25) Johnson, R. A.; Greene, F. D. Chlorination with *N*-Chloro Amides. II. Selectivity of Hydrogen Abstraction by Amidyl Radicals. *J. Org. Chem.* **1975**, *40*, 2192–2196.
- (26) Deno, N. C.; Fishbein, R.; Wyckoff, J. C. Cation Radicals. III. Sterically Hindered Chlorinating Agents. *J. Am. Chem. Soc.* **1971**, *93*, 2065–2066.
- (27) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. Site-Selective Aliphatic C–H Bromination Using *N*-Bromoamides and Visible Light. *J. Am. Chem. Soc.* **2014**, *136*, 14389–14392.
- (28) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. Site-Selective Aliphatic C–H Chlorination Using *N*-Chloroamides Enables a Synthesis of Chlorolissoclimide. *J. Am. Chem. Soc.* **2016**, *138*, 696–702.
- (29) Czaplyski, W. L.; Na, C. G.; Alexanian, E. J. C–H Xanthylation: A Synthetic Platform for Alkane Functionalization. *J. Am. Chem. Soc.* **2016**, *138*, 13854–13857.
- (30) Carestia, A. M.; Ravelli, D.; Alexanian, E. J. Reagent-Dictated Site Selectivity in Intermolecular Aliphatic C–H Functionalizations Using Nitrogen-Centered Radicals. *Chem. Sci.* **2018**, *9*, 5360–5365.
- (31) Hioe, J.; Sakic, D.; Vrcek, V.; Zipse, H. The Stability of Nitrogen-Centered Radicals. *Org. Biomol. Chem.* **2015**, *13*, 157–169.
- (32) Šakić, D.; Zipse, H. Radical Stability as a Guideline in C–H Amination Reactions. *Adv. Synth. Catal.* **2016**, *358*, 3983–3991.
- (33) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press, 2003; ISBN 0-8493-1589-1.

- (34) Sutcliffe, R.; Griller, D.; Lessard, J.; Ingold, K. U. The Structure of Amidyl Radicals. Evidence for the π -Electronic Ground State and for Twist about the Acyl-Nitrogen Bond by Electron Paramagnetic Resonance Spectroscopy. *J. Am. Chem. Soc.* **1981**, *103*, 624–628.
- (35) Glendening, E. D.; Landis, C. R.; Weinhold, F. Natural Bond Orbital Methods. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2012**, *2*, 1–42.
- (36) Crespi, S.; Simeth, N. A.; Bellisario, A.; Fagnoni, M.; König, B. Unraveling the Thermal Isomerization Mechanisms of Heteroaryl Azoswitches: Phenylazaindoles as Case Study. *J. Phys. Chem. A* **2019**, *123*, 1814–1823.
- (37) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. The Chemistry of Amine Radical Cations Produced by Visible Light Photoredox Catalysis. *Beilstein J. Org. Chem.* **2013**, *9*, 1977–2001.
- (38) Finn, M.; Friedline, R.; Suleman, N. K.; Wohl, C. J.; Tanko, J. M. Chemistry of the t-Butoxyl Radical: Evidence that Most Hydrogen Abstractions from Carbon are Entropy-Controlled. *J. Am. Chem. Soc.* **2004**, *126*, 7578–7584.
- (39) Prosser, A. R.; Banning, J. E.; Rubina, M.; Rubin, M. Formal Nucleophilic Substitution of Bromocyclopropanes with Amides en route to Conformationally Constrained β -Amino Acid Derivatives. *Org. Lett.* **2010**, *12*, 3968–3971.
- (40) Frébault, F.; Luparia, M.; Oliveira, M. T.; Goddard, R.; Maulide, N. A Versatile and Stereoselective Synthesis of Functionalized Cyclobutenes. *Angew. Chem., Int. Ed.* **2010**, *49*, 5672–5676.
- (41) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. Synthesis of Amides via Palladium-Catalyzed Amidation of Aryl Halides. *Org. Lett.* **2011**, *13*, 1028–1031.
- (42) Yoo, W.-J.; Li, C.-J. Highly Efficient Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065.