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Palladium(II)-Catalyzed Directed Trifluoromethylthiolation of Unactivated C(sp^3)−H Bonds

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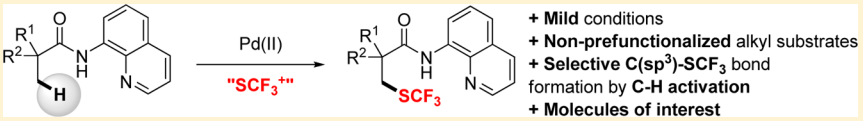
Supporting Information



ABSTRACT: The synthesis of trifluoromethylthiolated aliphatic acid derivatives by Pd-catalyzed C(sp^3)−H bond functionalization was developed. Using a bidentate directing group, the direct and selective introduction of a SCF_3 moiety was possible on a range of amides with remarkable selectivity for C(sp^3)-centers with an electrophilic SCF_3 source and pivalic acid as an additive. This work constitutes an example of the unactivated C(sp^3)−SCF_3 bond formation by C−H activation offering a new access to relevant molecules.

Over the past few years, organofluorine chemistry has experienced a resurgence of interest and consequently a very fast expansion.[1] Due to the unique features of the fluorine atom and fluorinated groups to modify the biological and physical properties of a molecule,[2] their presence is often crucial for the discovery and design of new pharmaceuticals and agrochemicals.[3] Quite recently, special attention has been paid to the trifluoromethylthiolated molecules, making the SCF_3 moiety an emerging fluorinated group. Indeed, due to its own features such as its high electron-withdrawing character[4] and its ability to enhance molecule lipophilicity (Hansch hydrophobic parameter: π = 1.44),[5] this very appealing fluorinated moiety has demonstrated a high potential for the elaboration of new agrochemicals, drugs, and materials. As a matter of consequence, it is worth mentioning that SCF_3-containing building blocks are of high interest. It is not surprising that the organic chemist community showed a strong interest in the quest for new SCF_3-containing reagents as well as novel, straightforward, and efficient synthetic transformations for its introduction.[6] Besides, among all the transition-metal catalyzed methods, C−H bond functionalization appeared as one of the most elegant and promising strategies to introduce functional groups directly in an atom- and step-economical way.[7] Despite the inert character of nonacidic C(sp^3)−H bonds, much progress has been made in the area of transition-metal catalyzed C(sp^3)−H bond transformations to construct new C−C, C−N, and C−O bonds.[8] In sharp contrast, the direct construction of C−S bonds by transition-metal mediated and catalyzed C−H bond activation remained underexplored and was often restricted to aryl derivatives.[9] Therefore, the development of catalytic systems allowing the formation of the difficult-to-access C(sp^3)−S bond by C−H activation represents a formidable synthetic challenge.[10] Moreover, no example of transition-metal catalyzed C(sp^3)−SCF_3 on nonactivated C(sp^3)−H bonds has been depicted since the direct formation of such a bond remains restricted to highly reactive benzylic derivatives.[11a,12] In 2012, Daugulis and co-workers pioneered the Cu-promoted *ortho*-directed trifluoromethylthiolation of benzamides using the volatile and toxic bis(trifluoromethyl)disulfide: $(CF_3S)_2$.[9j] Later, Shen and co-workers reported an elegant Pd(II)-catalyzed trifluoromethylthiolation of an aromatic C−H bond by using an electrophilic SCF_3 source,[9k] while Huang and co-workers used a nucleophilic SCF_3 source (i.e., $AgSCF_3$) for the Pd-catalyzed *ortho* trifluoromethylthiolation of 2-phenylpyridine derivatives.[9l] With regard to C(sp)−SCF_3 bond formation, Shen and co-workers reported, in 2013, the Cu-catalyzed trifluoromethylthiolation of terminal alkynes with a trifluoromethylsulfenate reagent.[11b] It is worth noting that the first example of transition-metal catalyzed direct introduction of the SCF_3 group on benzylic C(sp^3)−H bonds was recently developed by the group of Qing.[11a] This transformation involved an innate addition of $AgSCF_3$ on the benzylic C(sp^3)−H bond in the presence of a Cu-catalyst. Taking into account these considerations, the direct introduction of the SCF_3 moiety through a directed metal catalyzed C(sp^3)−H functionalization would be highly valuable and would offer new routes to access to C(sp^3)-trifluoromethylthiolated molecules. As part of our research program toward the development of new methods for the direct and selective introduction of fluorinated building blocks into molecules,[13] we herein report the first C(sp^3)−SCF_3 bond formation at the β-position of alkyl amides by means of Pd-catalyzed C(sp^3)−H bond functionalization, under mild conditions (Scheme 1).

At the outset of this study, we anticipated that one of the main synthetic issues to tackle would be the competing reductive elimination pathways over the desired C(sp^3)−SCF_3 bond formation. Inspired by several studies,[9k,14] we hypothe-

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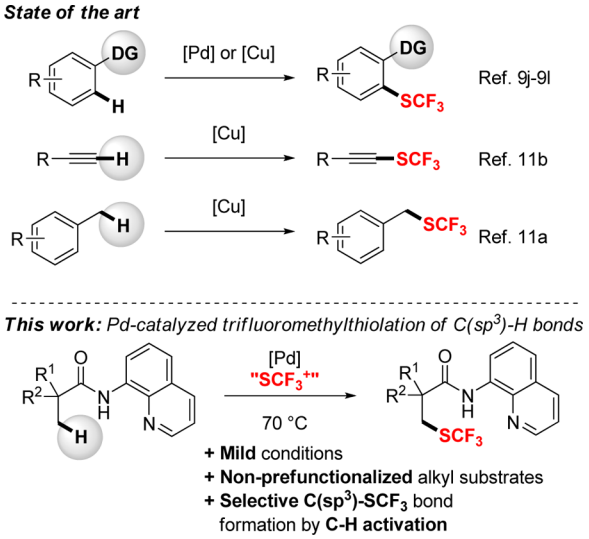
Scheme 1. Transition-Metal Promoted Trifluoromethylthiolation by C−H Functionalization

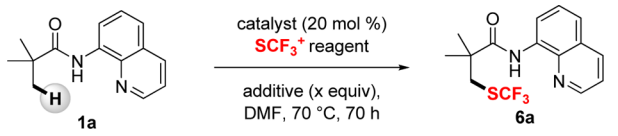


sized that the use of a readily available electrophilic SCF_3 reagent, which might act as both an oxidant and SCF_3 source, would allow the selective trifluoromethylthiolation event via a high Pd oxidation state. Our investigation started with the study of the Pd-catalyzed trifluoromethylthiolation of **1a** with the *N*-SCF_3-phthalimide **I** (Table 1). To our delight, in the presence of $Pd(OAc)_2$ as a catalyst, in DMF, the expected product **6a** was detected albeit in very low yield (entry 1). Several catalysts were then evaluated (entries 2−4), and gratifyingly Pd-$[CH_3CN]_2Cl_2$ afforded the expected trifluoromethylthiolated compound **6a** in 26% yield (entry 4).[15] Notably, the structure of **6a** was unambiguously confirmed by X-ray crystallographic analysis.[16] These promising results ascertained the regioselective C−H trifluoromethylthiolation of a primary C(sp^3)−H bond over the C(sp^2)−H bond of the directing group. After intensive investigations, the addition of a Brønsted acid as additive (entries 5−9) turned out to be highly beneficial for the success of such C−S coupling reactions, pivalic acid being the most efficient (entry 9, 31%). Remarkably, the trifluoromethylthiolation proceeded smoothly at 70 °C via a mild C−H activation process. Finally, the stoichiometry of the different reactants was further fine-tuned, offering the optimal conditions for the synthesis of **6a** in 53% yield (entry 11). Then, a screening of the electrophilic SCF_3 sources was performed (entries 11−16). No improvement was observed by using **II**, **III**, **IV**, or **VI** since poorer yields were obtained (up to 27%), while **V** gave **6a** in 44% yield. Notably, a control experiment performed in the absence of a Pd-catalyst revealed that no trifluoromethylthiolation reaction occurred (entry 17). Finally, the nature of the directing group was then investigated.

The transformation assisted by the 8-aminoquinoline bidentate chelating group **1a** proceeded smoothly, and against all expectations, other bicoordinating directing groups such as **2** and **3** as well as monocoordinating ones, **4** and **5**, were inefficient under our reaction conditions.

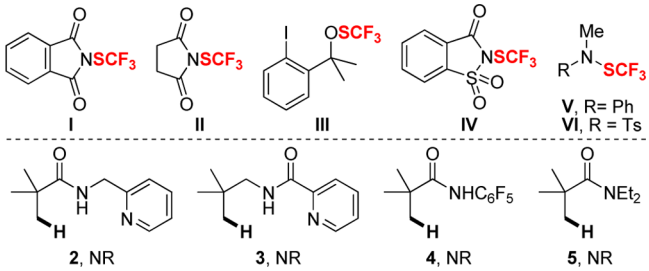
With these optimized reaction conditions in hand, we next sought to investigate the substrate scope (Scheme 2). A wide range of aliphatic amides having a primary β-C(sp^3)−H bond with different patterns were evaluated. At first, α,α-dialkyl substituted amides **1a** and **1b** were converted into the corresponding trifluoromethylated products **6a−6b** in good

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive (x equiv)	SCF_3^+ reagent	yield (%)
1[c,d]	$Pd(OAc)_2$	–	**I**	8[b]
2[c,d]	$Pd(TFA)_2$	–	**I**	4[b]
3[c,d]	$Pd[CH_3CN]_2BF_4$	–	**I**	1[b]
4[c,d]	$Pd[CH_3CN]_2Cl_2$	–	**I**	26[b]
5[e]	$Pd[CH_3CN]_2Cl_2$	AcOH (1)	**I**	40[b]
6[e]	$Pd[CH_3CN]_2Cl_2$	$PhCO_2H$ (1)	**I**	44[b]
7[e]	$Pd[CH_3CN]_2Cl_2$	$MesCO_2H$ (1)	**I**	41[b]
8[f]	$Pd[CH_3CN]_2Cl_2$	*p*-TSA (2)	**I**	31
9[f]	$Pd[CH_3CN]_2Cl_2$	PivOH (2)	**I**	53,[b] 31
10	$Pd[CH_3CN]_2Cl_2$	PivOH (5)	**I**	48
11	**$Pd[CH_3CN]_2Cl_2$**	**PivOH (10)**	**I**	**53**
12	$Pd[CH_3CN]_2Cl_2$	PivOH (10)	**II**	27[b]
13	$Pd[CH_3CN]_2Cl_2$	PivOH (10)	**III**	<2[b]
14	$Pd[CH_3CN]_2Cl_2$	PivOH (10)	**IV**	4[b]
15	$Pd[CH_3CN]_2Cl_2$	PivOH (10)	**V**	44
16	$Pd[CH_3CN]_2Cl_2$	PivOH (10)	**VI**	NR
17	–	PivOH (2)	**I**	NR

[a]Reaction conditions: **1a** (0.266 mmol), SCF_3^+ reagent (0.2 mmol), catalyst (20 mol %), additives (x equiv), DMF (2 mL), 70 °C, argon. [b]Determined by ^{19}F NMR on the crude reaction mixture using α,α,α-trifluoroacetophenone as an internal standard. [c]120 °C, 16 h. [d]catalyst (10 mol %). [e]80 °C, 16 h. [f]85 °C, 16 h. PivOH = pivalic acid, *p*-TSA = *p*-toluenesulfonamide. NR = no reaction.



and moderate yields, respectively. Then, a series of amides (**1c−o**) having an α-quaternary center were tested. When α,α-dimethylated hydrocinnamic acid derivatives (**1c−j**) were tested the transformation furnished the corresponding products in moderate to good yields. In those cases, the activation of the primary C(sp^3)−H bonds via a five-membered palladacycle intermediate was preferred over the activation of the intrinsically more reactive benzylic or aromatic C−H bonds. The reaction proceeded smoothly with aromatic rings bearing either an electron-donating (OMe, **6d**) or an electron-withdrawing group (halogens, CF_3 or CN; **6e−j**) showcasing the functional group tolerance of the process. Moreover, when the α-quaternary center was substituted by a homobenzylic substituent, no introduction of the SCF_3 group on the benzylic position was observed, and the desired product **6k** was obtained in 35% yield. The scope has been further extended to another class of substrates. Several amides prepared from phenylacetic acid derivatives were evaluated (**1l−o**), and the expected products (**6l−o**) were synthesized in 30−37% yields. Pleasingly, no trifluoromethylthiolation reaction has been observed on the aromatic ring. It is worth mentioning that this transformation was compatible with amides bearing α-C−

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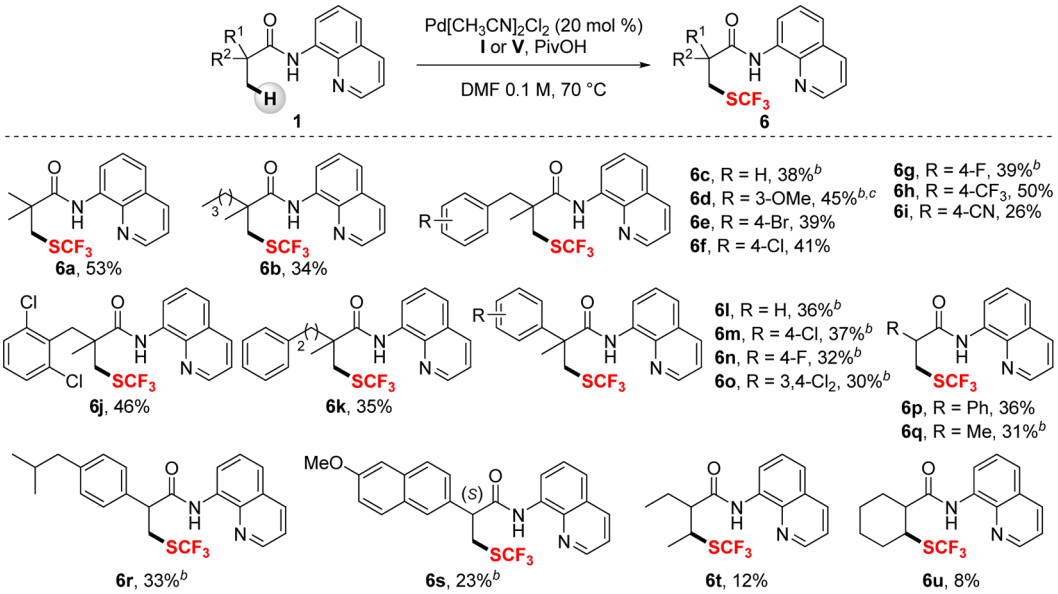
Scheme 2. Scope of Pd(II)-Catalyzed Trifluoromethylthiolation[a]



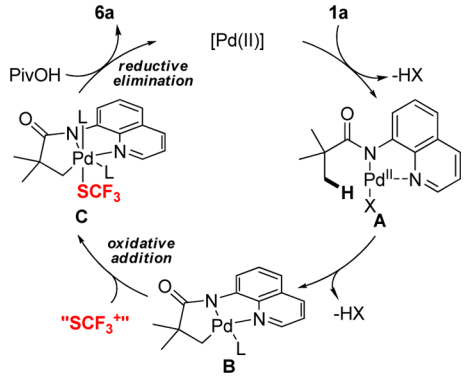
[a]Reaction conditions: **1** (0.266 mmol), **I** (0.2 mmol), $Pd[CH_3CN]_2Cl_2$ (20 mol %), PivOH (10 equiv), DMF (2 mL), 70 °C, argon. [b]**V** was used instead of **I** as an electrophilic SCF_3 reagent. [c]**6d** was contaminated with 10% of an inseparable impurity.

H bonds (**1p**−**1q**) giving **6p** and **6q** in 36% and 31% yields, respectively. Noteworthy, in some cases, the SCF_3 reagent **V** proved to be more efficient. The versatility of this method was then further illustrated through the synthesis of the SCF_3-containing analogues of bioactive molecules: Ibuprofen **1r** and Naproxen **1s**. The expected products **6r** and **6s** were obtained in moderate-to-low yields, 33% and 23%, respectively. These results appeared as a proof-of-concept for the potential application of our approach toward the late-stage functionalization of complex molecules and would open new valuable synthetic routes. Finally, under our reaction conditions, highly challenging secondary C(sp^3)−H bonds were functionalized even though the corresponding products (**6t** and **6u**) were obtained in low yields.

To gain insight into the mechanism, radical trapping experiments were performed.[16] The reaction was carried out in the presence of the commonly used radical quencher 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, 40 mol % and 1 equiv) and 3,5-di-*tert*-4-butylhydroxytoluene (BHT, 1 equiv). With TEMPO, the yield decreased in both cases; however, these observations might be easily explained by a side-reaction pathway between TEMPO and **I**.[16,17] Besides, in the presence of BHT, the reaction was slightly slower but no deleterious effect on the reaction yield was observed (42% vs 53%). Taking into consideration these observations, a plausible radical pathway might be thereby ruled out.

On the basis of the previous studies dealing with the C(sp^3)−H bond functionalization[18] and transition-metal catalyzed SCF_3 direct introduction on aromatic rings, a plausible mechanistic pathway has been proposed (Scheme 3).[19] First, the chelation of the Pd(II)-catalyst with the bidentate chelating group (intermediate **A**) is followed by the formation of the key palladacycle (intermediate **B**) after activation of the β-C(sp^3)−H bond according to a concerted metalation−deprotonation pathway. This latter undergoes an oxidative addition in the N−SCF_3 bond of the electrophilic reagent **I** leading to a putative Pd(IV) species **C**. Finally, a selective reductive elimination and a final protonation of the

Scheme 3. Proposed Mechanism



amide intermediate then affords the desired trifluoromethylthiolated derivative **6a** and regenerates the catalyst. At that stage, even though the exact role of PivOH in the catalytic process has not been elucidated so far, we suspected its assistance in the regeneration of the active catalyst as proposed by Sahoo and co-workers.[18b]

This novel strategy offers new possibilities to access other classes of products since these SCF_3-containing building blocks could easily undergo postfunctionalization. Indeed, the sulfide **6a** reacted in the presence of *m*-CPBA, giving the corresponding sulfoxide **7** in good yield (40%) taking into account the competitive oxidation of the quinoline residue and the possible overoxidation into sulfone.[11a] To highlight the synthetic value of our approach and the traceless character of the directing group, the removal of the 8-aminoquinoline group on **6a** was carried out.[20] The corresponding fluorinated carboxylic acid **8** was thus obtained in 89% yield (Scheme 4).

In summary, we have developed a method for the Pd-catalyzed trifluoromethylthiolation of the primary and secondary C(sp^3)−H bonds on aliphatic acid derivatives. The combination of an electrophilic SCF_3 reagent with a Brønsted acid (PivOH) using a bidentate directing group allowed the Pd-

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Scheme 4. Postfunctionalizations of Compound 6a

a) *m*-CPBA (2.5 equiv), CH_2Cl_2, 3 h, -10 to 5 °C, 40%. b) NaOH, EtOH, 90 °C, 89%. Q = quinolin-8-yl.

catalyzed direct introduction of a SCF_3 moiety on a $C(sp^3)$–H bond under mild conditions. Various amides were compatible, and a series of alkyl trifluoromethylated sulfides have been prepared. The products were obtained in a regiocontrolled fashion, and this transformation appeared as a synthetic milestone taking into account the associated synthetic issues (SCF_3 reagent decomposition, sulfur poisoning, and potential competing reductive eliminations). This approach offered synthetic disconnections for the preparation of tertiary and quaternary β-SCF_3-containing aliphatic acids. Moreover, this method was applied to the late-stage functionalization of relevant biomolecules such as Ibuprofen and Naproxen, opening avenues toward the synthesis of SCF_3-containing analogues.

EXPERIMENTAL SECTION

The trifluoromethylthiolation reactions were carried out in oven-dried glassware under an argon atmosphere with magnetic stirring bar. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Commercially available chemicals were used as received unless otherwise stated. Anhydrous DMF was degassed before using. Analytical TLC was performed on silica gel coated aluminum plates with F-254 indicator with visualization by UV irradiation (254 nm). Column chromatography was performed using 0.063–0.200 mm silica gel. NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts (δ) are quoted in ppm relative to TMS (^{1}H) and $CFCl_3$ (^{19}F). Coupling constants (J) are quoted in Hz. The following abbreviations were used to show the multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, m: multiplet. The residual solvent signals were used as references ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.00 ppm and $CFCl_3$: δ_F = 0.00 ppm). High-resolution mass spectrometry (HRMS) was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. The wave numbers (ν) of recorded IR-signals (ATR) are quoted in cm^{-1}.

The known amides **1** and trifluoromethylated reagents were prepared following the literature procedures: **1a**,[21] **1c**,[21] **1d**,[21] **1e**,[21] **1f**,[21,22] **1g**,[21,22] **1h**,[21,22] **1k**,[21,22] **1u**,[21] **I**,[9k] **II**,[9k] **III**,[23] **IV**,[24] and **V**.[24] No attempts were made to optimize yields for substrate synthesis.

General Procedure for Synthesis of 1. *General Procedure A.* To a solution of 8-aminoquinoline (1 equiv) and Et_3N (1.2 equiv) in CH_2Cl_2 (C = 0.25 mol·L^{-1}) was slowly added, at 0 °C, the acid chloride (1.2 equiv), and the reaction mixture was allowed to warm to room temperature and stirred overnight. Then, the reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous $NaHCO_3$. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography to afford the corresponding amide.

General Procedure B. To an oven-dried flask containing a carboxylic acid (1.2 equiv) was slowly added $SOCl_2$ (1.2 M). The reaction mixture was heated at 85 °C for 3 h and then evaporated under vacuum to provide the crude acid chloride, which was used immediately without further purification. CH_2Cl_2 was added to the acid chloride (0.4 M). Then, a solution of 8-aminoquinoline (1 equiv) and Et_3N (1.2 equiv) in CH_2Cl_2 (0.1M) was added dropwise at 0 °C to the solution of acid chloride. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Then, the reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous $NaHCO_3$. The aqueous layers were extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the corresponding amide.

General Procedure C. To a solution of diisopropylamine (DIPA) (1.25 equiv) in THF (0.4 M) at −78 °C was slowly added *n*-BuLi (1.6 M in hexane, 1.17 equiv), and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was then cooled down to −78 °C, and methyl isobutyrate (1 equiv) was added dropwise at the same temperature. The reaction mixture was stirred for 1 h at −78 °C. Then, a solution of the corresponding benzyl bromide (1.1 equiv) in THF (4.5 M) was added dropwise. After the addition, the mixture was slowly warmed to room temperature and stirred overnight. Then, the reaction mixture was quenched with water at 0 °C and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and then evaporated under vacuum to give the corresponding ester. To the obtained ester was added an aqueous solution of NaOH (2 M) and methanol, and the reaction mixture was stirred at 60 °C overnight. Once cooled to room temperature, methanol was removed under vacuum and the mixture was diluted with water and extracted with CH_2Cl_2 (3×). Then, the aqueous layer was acidified with 2 M HCl until pH = 2 and extracted with diethyl ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford the crude carboxylic acid, which was used directly for the next step without further purification. To an oven-dried round-bottom flask containing a carboxylic acid (1.2 equiv) was slowly added $SOCl_2$ (1.2 M). The reaction mixture was refluxed at 85 °C for 3 h and then evaporated under vacuum to provide the crude acid chloride, which was used immediately without further purification. Then, a solution of 8-aminoquinoline (1 equiv) and Et_3N (1.2 equiv) in CH_2Cl_2 (1.0 M) was added dropwise at 0 °C to a solution of acid chloride (1 equiv) in CH_2Cl_2 (0.3 M). After addition, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with water and saturated aqueous $NaHCO_3$. The aqueous layers were extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel to afford the corresponding amide.

General Procedure D. To a solution of benzyl cyanide (1 equiv), MeI (2.2 equiv) in DMSO (2 M) was added a 50 wt % aqueous solution of NaOH (2.1 equiv) via a syringe pump over 1 h at 45 °C. After the addition, the reaction mixture was stirred for 1 h. Once cooled down to room temperature, water was added to the solution and the aqueous layer was extracted with hexane/Et_2O (1:1, 3×). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under vacuum to afford the corresponding dialkylated product, which was used directly for the next step without further purification. To a 100 mL three-necked round-bottom flask with a reflux condenser were added dialkylated benzyl cyanide (1 equiv) and ethylene glycol/H_2O (4:1, 1 M). Solid KOH (3.2 equiv) was added portionwise to the mixture. The reaction mixture was stirred at 100 °C for 48 h. Once cooled to room temperature, the mixture was washed with $CHCl_3$ (3×). Then, the aqueous layer was acidified with 2 M HCl until pH = 2 and extracted with diethyl ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum to afford the corresponding carboxylic acid, which was used directly for the next step without further purification.[25] The acyl chloride was prepared according to the literature procedure[26] with oxalyl chloride and then engaged with 8-aminoquinoline according to procedure A.

Preparation and Characterization of Substrates 1. *2,2-Dimethyl-N-(quinolin-8-yl)hexanamide* ***1b.*** By following general procedure B, **1b** was obtained as a colorless oil (1.2 g, 78%) starting from 2,2-dimethylhexanoic acid. R_f (pentane/EtOAc 90:10): 0.42. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 10.16 (broad s, 1H), 8.75–8.67 (m,

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2H), 8.02 (dd, J = 8.1, 1.5 Hz, 1H), 7.47−7.27 (m, 3H), 1.66−1.55 (m, 2H), 1.30 (s, 6H), 1.27−1.18 (m, 4H), 0.78 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 176.6, 148.1, 138.7, 136.2, 134.6, 127.9, 127.4, 121.4, 121.1, 116.1, 43.7, 41.3, 27.1, 25.6, 23.2, 13.9. ATR-FTIR (cm^{-1}): 3367, 2960, 1680, 1523, 1484, 1387, 1325, 1253, 1147, 1009, 790, 680. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{17}H_{23}N_2O$ 271.1810; Found 271.1802.

3-(4-Cyanophenyl)-2,2-dimethyl-N-(quinolin-8-yl)propanamide ***1i.*** By following general procedure C, **1i** was obtained as a pale yellow vitrous solid (0.31 g, 13% overall yield) starting from 4-(bromomethyl)benzonitrile. R_f (pentane/EtOAc 90:10): 0.21. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.11 (broad s, 1H), 8.79 (dd, J = 6.9, 2.1 Hz, 1H), 8.73 (dd, J = 4.2, 1.5 Hz, 1H), 8.16 (dd, J = 8.4, 1.5 Hz, 1H), 7.59−7.51 (m, 2H), 7.49−7.41 (m, 3H), 7.30 (d, J = 8.1 Hz, 2H), 3.08 (s, 2H), 1.44 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.0, 148.2, 143.7, 138.6, 136.3, 134.1, 131.8, 130.9, 127.9, 127.3, 121.7, 121.6, 118.9, 116.3, 110.3, 46.9, 45.1, 25.4. ATR-FTIR (cm^{-1}): 3360, 2225, 1672, 1470, 1418, 1379, 1311, 917, 858, 798, 690. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}N_3O$ 330.1606; Found 330.1597.

3-(2,6-Dichlorophenyl)-2,2-dimethyl-N-(quinolin-8-yl)propanamide ***1j.*** By following general procedure C, **1j** was obtained as a white solid (1.6 g, 74% overall yield) starting from 2-(bromomethyl)-1,3-dichlorobenzene. R_f (pentane/EtOAc 90:10): 0.40. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.82 (dd, J = 7.5, 1.5 Hz, 1H), 8.72 (dd, J = 4.2, 1.5 Hz, 1H), 8.15 (dd, J = 8.4, 1.5 Hz, 1H), 7.59−7.47 (m, 2H), 7.42 (dd, J = 8.4, 4.2 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.23 (s, 1H), 7.05 (dd, J = 8.4, 7.5 Hz, 1H), 3.50 (s, 2H), 1.53 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.7, 148.0, 138.8, 137.1, 136.2, 134.8, 134.7, 128.4, 128.0, 127.8, 127.5, 121.4, 121.2, 116.3, 45.6, 40.0, 25.7. ATR-FTIR (cm^{-1}): 3360, 2947, 1671, 1528, 1485, 1142, 1053, 917, 825, 791, 678. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}Cl_2N_2O$ 373.0874; Found 373.0867.

2-Methyl-2-phenyl-N-(quinolin-8-yl)propanamide ***1l.*** By following general procedure D, **1l** was obtained as a white vitrous solid (1.2 g, 24% overall yield) starting from 2-phenylpropanenitrile. R_f (pentane/EtOAc 90:10): 0.33. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.89 (broad s, 1H), 8.74 (dd, J = 7.2, 1.5 Hz, 1H), 8.64 (dd, J = 4.2, 1.5 Hz, 1H), 8.10 (dd, J = 8.4, 1.5 Hz, 1H), 7.63−7.42 (m, 5H), 7.41−7.32 (m, 3H), 1.76 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.1, 148.2, 143.5, 138.6, 136.1, 134.5, 132.9, 128.8, 127.8, 127.3, 121.5, 121.4, 116.0, 48.0, 26.9. One carbon is overlapped. ATR-FTIR (cm^{-1}): 3340, 2973, 1676, 1524, 1488, 1388, 1324, 1104, 826, 681. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O$ 291.1497; Found 291.1487.

2-(4-Chlorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide ***1m.*** By following general procedure D, **1m** was obtained as a pale yellow vitrous solid (0.61 g, 23% overall yield) starting from (4-chlorophenyl)acetonitrile. R_f (pentane/EtOAc 90:10): 0.46. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.87 (broad s, 1H), 8.77 (d, J = 7.5 Hz, 1H), 8.60 (dd, J = 4.2, 1.5 Hz, 1H), 8.09 (dd, J = 8.1, 1.5 Hz, 1H), 7.57−7.32 (m, 7H), 1.79 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.8, 148.1, 144.8, 138.6, 136.1, 134.7, 128.7, 127.8, 127.3, 127.0, 126.3, 121.4, 121.2, 115.9, 48.4, 27.0. ATR-FTIR (cm^{-1}): 2929, 1666, 1520, 1387, 1090, 829, 656. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}ClN_2O$ 324.1029; Found 324.1035.

2-(4-Fluorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide ***1n.*** By following general procedure D, **1n** was obtained as a pale yellow vitrous solid (0.51 g, 15% overall yield) starting from 4-fluorophenylacetonitrile. R_f (pentane/EtOAc 90:10): 0.55. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.88 (broad s, 1H), 8.76 (dd, J = 7.5, 1.5 Hz, 1H), 8.62 (dd, J = 4.2, 1.5 Hz, 1H), 8.09 (dd, J = 8.1, 1.5 Hz, 1H), 7.55−7.43 (m, 4H), 7.37 (dd, J = 8.1, 4.2 Hz, 1H), 7.14−7.04 (m, 2H), 1.77 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.5, 161.8 (d, J = 246.1 Hz), 148.2, 140.7 (d, J = 3.0 Hz), 138.6, 136.1, 134.5, 128.1 (d, J = 7.6 Hz), 127.8, 127.2, 121.5, 121.3, 115.9, 115.5 (d, J = 21.1 Hz), 47.9, 27.1. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −116.5. ATR-FTIR (cm^{-1}): 3320, 2980, 1669, 1511, 1484, 1384, 1324, 1232, 1151, 1097, 821, 785. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}FN_2O$ 309.1403; Found 309.1412.

2-(3,4-Dichlorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide ***1o.*** By following general procedure D, **1o** was obtained as a pale yellow oil (0.71 g, 7% overall yield) starting from 3,4-dichlorophenylacetonitrile. R_f (pentane/EtOAc 82:8): 0.61. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.95 (broad s, 1H), 8.72 (d, J = 6.9 Hz, 1H), 8.68 (d, J = 4.2 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.46−7.45 (m, 3H), 7.44−7.33 (m, 2H), 1.76 (s, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 174.3, 148.3, 145.3, 138.6, 136.2, 134.3, 132.8, 131.1, 130.6, 128.5, 127.8, 127.3, 126.0, 121.6, 121.6, 116.1, 48.0, 26.8. ATR-FTIR (cm^{-1}): 2927, 1664, 1526, 1384, 1090, 829, 658. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}Cl_2N_2O$ 359.0718; Found 359.0713.

2-Phenyl-N-(quinolin-8-yl)propanamide ***1p.*** By following general procedure B, **1p** was obtained as a white vitrous solid (2.0 g, 72% overall yield) starting from 2-phenylpropionic acid. R_f (petroleum ether/EtOAc 90:10): 0.36. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.90 (broad s, 1H), 8.77 (dd, J = 7.2, 1.8 Hz, 1H), 8.71 (dd, J = 4.2, 1.8 Hz, 1H), 8.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.55−7.44 (m, 4H), 7.43−7.35 (m, 3H), 7.33−7.27 (m, 1H), 3.94 (q, J = 7.2 Hz, 1H), 1.70 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.5, 148.0, 141.0, 138.3, 136.0, 134.4, 128.8, 127.7, 127.6, 127.2, 121.3, 116.1, 65.7, 48.5, 18.5, 15.2. ATR-FTIR (cm^{-1}): 3340, 2803, 1741, 1688, 1523, 1482, 1228, 823. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O$ 277.1341; Found 277.1334.

N-(Quinolin-8-yl)isobutyramide ***1q.*** By following general procedure A, **1q** was obtained as a yellow oil (2.0 g, 92%) starting from isobutyryl chloride. R_f (petroleum ether/EtOAc 91:9): 0.47. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.90 (broad s, 1H), 8.84−8.76 (m, 2H), 8.15 (dd, J = 8.4, 1.5 Hz, 1H), 7.59−7.40 (m, 3H), 2.85−2.70 (m, 1H), 1.36 (d, J = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 175.7, 148.1, 138.5, 136.3, 134.6, 127.9, 127.4, 121.5, 121.3, 116.4, 37.1, 19.7. ATR-FTIR (cm^{-1}): 3353, 2968, 1684, 1520, 1483, 1422, 1383, 1322, 1155, 936, 825, 790, 673. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O$ 215.1184; Found 215.1181.

2-(4-Isobutylphenyl)-N-(quinolin-8-yl)propanamide ***1r.*** By following general procedure B, **1r** was obtained as a white vitrous solid (2.1 g, 63% overall yield) starting from 2-(4-isobutylphenyl)propanoic acid. R_f (pentane/EtOAc 90:10): 0.36. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.88 (broad s, 1H), 8.78 (dd, J = 7.2, 1.8 Hz, 1H), 8.66 (dd, J = 4.2, 1.8 Hz, 1H), 8.10 (dd, J = 8.1, 1.5 Hz, 1H), 7.54−7.43 (m, 2H), 7.41−7.35 (m, 3H), 7.17 (d, J = 8.1 Hz, 2H), 3.91 (q, J = 7.2 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 1.95−1.78 (m, 1H), 1.69 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.1, 148.0, 140.8, 138.5, 138.2, 136.2, 134.6, 129.7, 127.8, 127.5, 127.3, 121.4, 121.3, 116.2, 48.3, 45.0, 30.2, 22.4, 18.5. ATR-FTIR (cm^{-1}) 3347, 2953, 1683, 1521, 1484, 1423, 1323, 1161, 922, 825, 790, 755. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O$ 333.1967; Found 333.1980.

(S)-2-(6-Methoxynaphthalen-2-yl)-N-(quinolin-8-yl)propanamide ***1s.*** By following general procedure B, **1s** was obtained as a white solid (1.3 g, 73% overall yield) starting from (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid. R_f (petroleum ether/EtOAc 86:14): 0.27. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.96 (broad s, 1H), 8.79 (dd, J = 7.5, 1.5 Hz, 1H), 8.61 (dd, J = 4.2, 1.8 Hz, 1H), 8.09 (dd, J = 8.4, 1.8 Hz, 1H), 7.87 (s, 1H), 7.76 (dd, J = 8.4, 3.0 Hz, 2H), 7.57 (dd, J = 8.4, 1.8 Hz, 1H), 7.54−7.42 (m, 2H), 7.36 (dd, J = 8.4, 4.2 Hz, 1H), 7.18−7.10 (m, 2H), 4.07 (q, J = 6.9 Hz, 1H), 3.91 (s, 3H), 1.77 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.8, 157.6, 148.1, 138.4, 136.3, 136.1, 134.5, 133.8, 129.3, 129.1, 127.8, 127.5, 127.3, 126.3, 126.2, 121.4, 121.4, 119.0, 116.2 (s, CH), 105.6 (s, CH), 55.3 (s, CH_3), 48.6 (s, CH), 18.7 (s, CH_3). ATR-FTIR (cm^{-1}): 3351, 2980, 1687, 1524, 1483, 1384, 1229, 1172, 1026, 855, 791, 649. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_2O_2$ 357.1603; Found 357.1607.

2-Ethyl-N-(quinolin-8-yl)butanamide ***1t.*** By following general procedure A, **1t** was obtained as a colorless oil (2.1 g, 88%) starting from 2-ethylbutyryl chloride. R_f (petroleum ether/EtOAc 90:10): 0.47. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.75 (broad s, 1H), 8.81−8.64 (m, 2H), 7.99 (d, J = 8.1 Hz, 1H), 7.46−7.24 (m, 3H), 2.27−2.13 (m, 1H), 1.80−1.63 (m, 2H), 1.62−1.45 (m, 2H), 0.89 (t, J = 7.2 Hz, 6H).

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$^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 174.6, 148.0, 138.3, 136.1, 134.4, 127.8, 127.2, 121.4, 121.2, 116.3, 52.5, 25.7, 12.0. ATR-FTIR (cm^{-1}): 3359, 2958, 1677, 1593, 1523, 1484, 1324, 1191, 1175, 827, 794, 682. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O$ 243.1497; Found 243.1504.

General Procedure for the Pd(II)-Catalyzed Trifluoromethylthiolation of 1. *Procedure E.* An oven-dried 10 mL glassware equipped with a stir bar was charged with $Pd[CH_3CN]_2Cl_2$ (10.4 g, 0.04 mmol, 0.2 equiv), **I** (49.6 mg, 0.2 mmol, 1 equiv) or **V** (41.4 mg, 0.2 mmol, 1 equiv), PivOH (204.2 mg, 2 mmol, 10 equiv), and 2 mL of DMF under argon. Then, amide derivative **1** (0.266 mmol, 1.33 equiv) was added. The tube was flushed with argon, sealed, and then placed in an oil bath preheated to 70 °C and stirred rigorously (see time for each compound). The reaction mixture was cooled to room temperature and diluted with diethyl ether (20 mL) and water. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by flash chromatography on silica gel to give the desired product. Note that, in the case of solid amides, these are added in the tube before the solvent.

Preparation and Characterization of Products 6. *2,2-Dimethyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide* ***6a.*** Procedure E was followed, from **1a** and **I** (70 h). The product was purified by flash chromatography on silica gel (height 30 cm, width 2 cm, pentane/dichloromethane 60:40) as a pale yellow solid (34.6 mg, 53%), R_f (pentane/dichloromethane = 60:40): 0.35. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.30 (broad s, 1H), 8.83 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.79−8.69 (m, 1H), 8.17 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.58−7.50 (m, 2H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.22 (s, 2H), 1.58 (s, 6H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.3 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 174.0, 148.4, 138.7, 136.4, 134.0, 131.1 (q, *J* = 306.5 Hz), 127.9, 127.4, 121.8, 121.7, 116.6, 44.4, 39.2 (q, *J* = 2.3 Hz), 25.2, 25.2. ATR-FTIR (cm^{-1}): 3327, 2927, 1667, 1535, 1464, 1423, 1386 1328, 1293, 1136, 1096, 926, 822, 784, 693, 623. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}F_3N_2OS$ 329.0930; Found 329.0948.

2-Methyl-N-(quinolin-8-yl)-2-((trifluoromethylthio)methyl)-hexanamide ***6b.*** Procedure E was followed, from **1b** and **I** (60 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane 60:40) as a colorless oil (25.3 mg, 34%), R_f (pentane/dichloromethane = 60:40): 0.55. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.28 (broad s, 1H), 8.83 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.79−8.71 (m, 1H), 8.18 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.58−7.50 (m, 2H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.46 (d, *J* = 12.9 Hz, 1H), 3.04 (d, *J* = 12.9 Hz, 1H), 1.95−1.82 (m, 1H), 1.81−1.68 (m, 1H), 1.45−1.17 (m, 6H), 0.97−0.76 (m, 4H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.1 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.5, 148.4, 138.7, 136.4, 134.0, 131.1 (q, *J* = 306.5 Hz, C_{quat}), 127.9, 127.4, 121.8, 121.7, 116.5, 47.7, 39.3, 37.8 (q, *J* = 2.3 Hz), 26.6, 23.0, 21. 8, 13.8. ATR-FTIR (cm^{-1}): 3353, 2960, 2932, 1674, 1527, 1487, 1424, 1326, 1146, 1103, 825, 790. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{22}F_3N_2OS$ 371.1405; Found 371.1416.

2-Benzyl-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)-propanamide ***6c.*** Procedure E was followed, from **1c** and **V** (70 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane 60:40) as a white vitrous solid (30.8 mg, 38%), R_f (pentane/dichloromethane = 60:40): 0.43. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.80−8.70 (m, 2H), 8.16 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.59−7.50 (m, 2H), 7.44 (dd, *J* = 8.1, 4.2 Hz, 1H), 7.21−7.14 (m, 5H), 3.53 (d, *J* = 12.9 Hz, 1H), 3.26 (d, *J* = 13.5 Hz, 1H), 3.00 (d, *J* = 13.2 Hz, 2H), 1.59 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ − 42.0 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.7, 148.3, 138.6, 136.2, 135.9, 133.7, 131.0 (q, *J* = 306.5 Hz), 130.1, 128.3, 127.8, 127.3, 127.0, 121.9, 121.6, 116.5, 48.8, 45.5, 38.0 (q, *J* = 1.5 Hz), 21.0. ATR-FTIR (cm^{-1}): 3353, 2927, 2853, 1671, 1531, 1485, 1422, 1144, 788, 687. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{20}F_3N_2OS$ 405.1248; Found 405.1257.

2-(3-Methoxybenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6d.*** Procedure E was followed, from **1d** and **V** (61 h). The product was purified by flash chromatography on silica gel (height 31 cm, width 2 cm, pentane/dichloromethane 30:70) as a pale yellow oil (38.7 mg, 45%), R_f (pentane/dichloromethane = 30:70): 0.38. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.14 (broad s, 1H), 8.77 (dd, *J* = 6.0, 3.0 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.58−7.49 (m, 2H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.16−7.06 (m, 1H), 6.80−6.63 (m, 3H), 3.54 (d, *J* = 12.6 Hz, 1H), 3.53 (s, 3H), 3.23 (d, *J* = 13.5 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 1.60 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0. $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.7, 159.4, 148.3, 138.6, 137.4, 136.2, 133.7, 131.0 (q, *J* = 306.5 Hz), 129.1, 127.8, 127.3, 122.5, 121.9, 121.6, 116.5, 115.2, 112.9, 54.9, 48.9, 45.6, 38.1 (q, *J* = 1.5 Hz), 21.0. ATR-FTIR (cm^{-1}): 3350, 2934, 1671, 1527, 1487, 1262, 1106, 1043, 825, 789, 755, 695. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{22}F_3N_2O_2S$ 435.1349; Found 435.1352.

2-(4-Bromobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6e.*** Procedure E was followed, from **1e** and **I** (40 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 80:20 + 1% Et_3N) as a white vitrous solid (37.8 mg, 39%), R_f (pentane/dichloromethane = 60:40): 0.40. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.97 (broad s, 1H), 8.70−8.57 (m, 2H), 8.06 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.47−7.40 (m, 2H), 7.35 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.21−7.15 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.40 (d, *J* = 12.9 Hz, 1H), 3.12 (d, *J* = 13.2 Hz, 1H), 2.92 (d, *J* = 12.6 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 1.47 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.3, 148.4, 138.6, 136.3, 135.0, 133.6, 131.8, 131.4, 130.9 (q, *J* = 305.8 Hz), 127.9, 127.3, 122.1, 121.7, 121.1, 116.0, 48.1, 44.8, 38.2 (q, *J* = 2.3 Hz), 20.8. ATR-FTIR (cm^{-1}): 3348, 2924, 1671, 1528, 1487, 1425, 1385, 1326, 1261, 1103, 1012, 824, 790, 686. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{19}BrF_3N_2OS$ 483.0348; Found 483.0353.

2-(4-Chlorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6f.*** Procedure E was followed, from **1f** and **I** (40 h). The product was purified by flash chromatography on silica gel (height 35 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (36.1 mg, 41%), R_f (pentane/dichloromethane = 60:40): 0.50. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.08 (broad s, 1H), 7.79−7.68 (m, 2H), 8.16 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.59−7.51 (m, 2H), 7.45 (dd, *J* = 8.1, 4.2 Hz, 1H), 7.19−7.05 (m, 4H), 3.50 (d, *J* = 12.6 Hz, 1H), 3.24 (d, *J* = 13.5 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.92 (d, *J* = 13.5 Hz, 1H), 1.57 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.3, 148.4, 138.5, 136.3, 134.5, 133.6, 133.0, 131.4, 130.9 (q, *J* = 306.5 Hz), 128.5, 127.8, 127.3, 122.0, 121.7, 116.7, 48.8, 44.7, 38.2 (q, *J* = 1.5 Hz), 20.8. ATR-FTIR (cm^{-1}): 3347, 1670, 1527, 1487, 1425, 1384, 1325, 1260, 1103, 1016, 825, 790, 684. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{19}ClF_3N_2OS$ 439.0853; Found 439.0847.

2-(4-Fluorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6g.*** Procedure E was followed, from **1g** and **V** (86 h). The product was purified by flash chromatography on silica gel (height 34 cm, width 2 cm, toluene/pentane = 60:40 + 1% Et_3N) as a colorless oil (33.1 mg, 39%), R_f (pentane/dichloromethane = 60:40): 0.44. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.09 (broad s, 1H), 8.77−8.70 (m, 2H), 8.16 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.57−7.51 (m, 2H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.17−7.08 (m, 2H), 6.90−6.80 (m, 2H), 3.51 (d, *J* = 12.6 Hz, 1H), 3.24 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 12.6 Hz, 1H), 2.93 (d, *J* = 13.5 Hz, 1H), 1.58 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0 (s), −116.3 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.4, 162.0 (d, *J* = 246.1 Hz), 148.3, 138.6, 136.3, 133.6, 131.7 (d, *J* = 3.0 Hz), 131.6 (d, *J* = 7.6 Hz), 130.9 (q, *J* = 305.8 Hz), 127.8, 127.3, 122.0, 121.7, 116.5, 115.2 (d, *J* = 21.9 Hz), 48.9, 44.6, 38.1 (q, *J* = 1.5 Hz), 20.8. ATR-FTIR (cm^{-1}): 3348, 2927, 1673, 1528, 1510, 1487, 1224, 1102, 826, 790. HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{19}F_4N_2OS$ 423.1154; Found 423.1147.

2-Methyl-N-(quinolin-8-yl)-2-(4-(trifluoromethyl)benzyl)-3-(trifluoromethylthio)propanamide ***6h.*** Procedure E was followed, from **1h** and **I** (60 h). The product was purified by flash chromatography on silica gel (height 35 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (46.8 mg, 50%), R_f (pentane/dichloromethane = 60:40): 0.49. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.98 (broad s, 1H), 8.69−8.64 (m, 1H), 8.61 (dd, *J* = 4.2,

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1.5 Hz, 1H), 8.09 (dd, J = 8.4, 1.5 Hz, 1H), 7.50−7.45 (m, 2H), 7.39−7.30 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 3.45 (d, J = 12.9 Hz, 1H), 3.27 (d, J = 13.2 Hz, 1H), 2.99 (d, J = 12.9 Hz, 1H), 2.92 (d, J = 13.2 Hz, 1H), 1.51 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0 (s), −63.1 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.0, 148.4, 140.2, 138.5, 136.3, 133.5, 130.9 (q, J = 306.5 Hz), 130.4, 129.3 (q, J = 33.2 Hz), 127.8, 127.3, 125.2 (q, J = 3.8 Hz), 124.0 (q, J = 271.8 Hz), 122.1, 121.7, 116.6, 48.9, 45.1, 38.3 (q, J = 2.3 Hz), 20.8. ATR-FTIR (cm^{-1}): 3347, 2927, 2853, 1673, 1529, 1487, 1424, 1385, 1323, 1258, 1105, 1067, 906, 791, 687. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{22}H_{19}F_6N_2OS$ 473.1117; Found 473.1119.

2-(4-Cyanobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6i***. Procedure E was followed, from **1i** and **I** (39 h). The product was purified by flash chromatography on silica gel (height 35 cm, width 2 cm, dichloromethane) as a pale yellow oil (22.3 mg, 26%), R_f (dichloromethane): 0.48. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.96 (broad s, 1H), 8.68−8.59 (m, 2H), 8.09 (dd, J = 8.4, 1.5 Hz, 1H), 7.47 (d, J = 4.5 Hz, 2H), 7.41−7.33 (m, 3H), 7.20 (d, J = 7.2 Hz, 2H), 3.44 (d, J = 12.9 Hz, 1H), 3.28 (d, J = 13.2 Hz, 1H), 3.00 (d, J = 12.9 Hz, 1H), 2.88 (d, J = 13.2 Hz, 1H), 1.50 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −41.9 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 171.7, 148.4, 141.7, 138.5, 136.4, 133.3, 132.0, 130.8, 130.8 (q, J = 306.5 Hz), 127.8, 127.2, 122.3, 121.8, 118.6, 116.6, 111.0, 48.9, 45.3, 38.4 (q, J = 1.5 Hz), 20.6. ATR-FTIR (cm^{-1}): 3347, 2228, 1670, 1525, 1487, 1425, 1385, 1103, 826, 790. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{22}H_{19}F_3N_3OS$ 430.1195; Found 430.1195.

2-(2,6-Dichlorobenzyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6j***. Procedure E was followed, from **1j** and **I** (45 h). The product was purified by flash chromatography on silica gel (height 31 cm, width 2 cm, pentane/dichloromethane = 60:40) as a white solid (43.1 mg, 46%), R_f (pentane/dichloromethane = 60:40): 0.45. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 10.08 (broad s, 1H), 8.73 (dd, J = 6.6, 2.1 Hz, 1H), 8.65 (d, J = 4.2 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.58−7.48 (m, 2H), 7.41 (dd, J = 8.1, 4.2 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.04 (t, J = 7.8 Hz, 1H), 3.66 (t, J = 14.4 Hz, 2H), 3.46 (d, J = 14.1 Hz, 1H), 3.14 (d, J = 12.9 Hz, 1H), 1.71 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.3 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.3, 148.1, 138.5, 137.1, 136.2, 134.0, 133.0, 131.1 (q, J = 306.5 Hz), 128.6, 128.6, 127.7, 127.4, 121.7, 121.5, 116.6, 49.6, 39.5, 38.8 (q, J = 1.5 Hz), 21.3. ATR-FTIR (cm^{-1}): 3340, 1666, 1532, 1437, 1324, 1112, 781, 760. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{21}H_{18}Cl_2F_3N_2OS$ 473.0464; Found 473.0447.

2-Methyl-4-phenyl-N-(quinolin-8-yl)-2-((trifluoromethylthio)-methyl)butanamide ***6k***. Procedure E was followed, from **1k** and **I** (40 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 70:30 + 1% Et_3N) as a white vitrous solid (29.1 mg, 35%), R_f (pentane/dichloromethane = 60:40): 0.33. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 10.29 (broad s, 1H), 8.76 (dd, J = 4.2, 1.8 Hz, 1H), 8.73−8.65 (m, 1H), 8.12 (dd, J = 8.4, 1.5 Hz, 1H), 7.50−7.45 (m, 2H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 7.23−7.04 (m, 5H), 3.45 (d, J = 12.9 Hz, 1H), 3.05 (d, J = 12.9 Hz, 1H), 2.63 (dd, J = 9.6, 7.8 Hz, 2H), 2.22−2.06 (m, 1H), 2.05−1.91 (m, 1H), 1.59 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.0 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.0, 148.4, 141.1, 138.7, 136.4, 133.9, 131.0 (q, J = 306.5 Hz), 128.5, 128.3, 127.9, 127.4, 126.1, 121.9, 121.7, 116.6, 47.7, 41.5, 37.8 (q, J = 2.3 Hz), 31.0, 21.9. ATR-FTIR (cm^{-1}): 3353, 2933, 1673, 1527, 1486, 1469, 1424, 1384, 1326, 1253, 1105, 893, 825, 790, 697. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{22}H_{22}F_3N_2OS$ 419.1399; Found 419.1390.

2-Methyl-2-phenyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)-propanamide ***6l***. Procedure E was followed, from **1l** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 60:40 + 1% Et_3N) as a white vitrous solid (28.4 mg, 36%), R_f (pentane/dichloromethane = 60:40): 0.37. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.83 (broad s, 1H), 8.70 (dd, J = 6.6, 2.1 Hz, 1H), 8.63 (dd, J = 4.2, 1.5 Hz, 1H), 8.11 (dd, J = 8.4, 1.5 Hz, 1H), 7.55−7.48 (m, 2H), 7.47−7.36 (m, 6H), 3.66 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 2.00 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.5 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.8, 148.4, 139.4, 138.4, 136.2, 134.2, 133.9, 131.0 (q, J = 306.5 Hz), 129.3, 128.1, 127.8, 127.2, 122.0, 121.7, 116.3, 51.7, 39.5 (q, J = 1.5 Hz), 22.2. ATR-FTIR (cm^{-1}): 3327, 1664, 1522, 1486, 1327, 1141, 1106, 825, 760. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{20}H_{18}F_3N_2OS$ 391.1086; Found 391.1082.

2-(4-Chlorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6m***. Procedure E was followed, from **1m** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 31 cm, width 2 cm, toluene/pentane = 50:50 + 1% Et_3N) as a white amorphous solid (31.2 mg, 37%), R_f (toluene/pentane = 50:50 + 1% Et_3N): 0.30. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.83 (broad s, 1H), 8.73 (d, J = 7.2 Hz, 1H), 8.59 (d, J = 4.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.54−7.33 (m, 7H), 3.72 (d, J = 12.9 Hz, 1H), 3.38 (d, J = 12.9 Hz, 1H), 2.03 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ − 42.6 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.5, 148.2, 140.8, 138.5, 136.1, 134.1, 131.1 (q, J = 305.8 Hz), 129.1, 128.1, 127.8, 127.2, 126.6, 121.8, 121.6, 116.2, 52.1, 39.6 (q, J = 2.3 Hz), 22.2. ATR-FTIR (cm^{-1}): 3333, 1672, 1527, 1489, 1135, 1099, 1054, 824, 792. HRMS (ESI$^+$) m/z: $C_{20}H_{17}ClF_3N_2OS$ 425.0697; Found 425.0705.

2-(4-Fluorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6n***. Procedure E was followed, from **1n** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 50:50 + 1% Et_3N) as a white amorphous solid (26.2 mg, 32%), R_f (toluene/pentane = 50:50 + 1% Et_3N): 0.44. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.82 (broad s, 1H), 8.71 (dd, J = 6.9, 1.8 Hz, 1H), 8.62 (dd, J = 4.2, 1.2 Hz, 1H), 8.11 (dd, J = 8.1, 1.2 Hz, 1H), 7.55−7.45 (m, 4H), 7.39 (dd, J = 8.1, 4.2 Hz, 1H), 7.12 (t, J = 8.7 Hz, 2H), 3.67 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 13.2 Hz, 1H), 2.01 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.5 (s), −114.3 (m). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.2, 162.4 (d, J = 248.4 Hz), 148.3, 138.4, 136.6 (d, J = 3.8 Hz), 136.2, 133.9, 131.0 (q, J = 305.8 Hz), 128.6 (d, J = 27.9 Hz), 127.8, 127.2, 121.9, 121.6, 116.3 (d, J = 8.3 Hz), 115.9, 51.6, 39.7 (q, J = 1.5 Hz), 22.4. ATR-FTIR (cm^{-1}): 3327, 1668, 1527, 1488, 1141, 1100, 826, 790, 691. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{20}H_{17}F_4N_2OS$ 409.0992; Found 409.1012.

2-(3,4-Dichlorophenyl)-2-methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6o***. Procedure E was followed, from **1o** and **V** (86 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane = 60:40 + 1% Et_3N) as a colorless oil (27.3 mg, 30%), R_f (pentane/dichloromethane = 50:50): 0.68. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.69 (dd, J = 6.3, 2.7 Hz, 1H), 8.67 (dd, J = 4.8, 1.8 Hz, 1H), 8.13 (dd, J = 8.4, 1.8 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 7.55−7.45 (m, 3H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 7.34 (dd, J = 8.4, 2.1 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 3.33 (d, J = 13.2 Hz, 1H), 2.00 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −42.5 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.0, 148.5, 141.2, 138.4, 136.3, 133.7, 133.3, 132.5, 131.0, 130.8 (q, J = 306.5 Hz), 128.7, 127.8, 127.2, 126.2, 122.1, 121.7, 116.2, 51.7, 39.4 (q, J = 2.3 Hz), 22.1. ATR-FTIR (cm^{-1}): 3327, 1668, 1527, 1488, 1141, 1100, 825, 790, 691. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{20}H_{16}Cl_2F_3N_2OS$ 459.0312; Found 459.0305.

2-Phenyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6p***. Procedure E was followed, from **1p** and **I** (60 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, pentane/dichloromethane = 60:40) as a pale yellow oil (27 mg, 36%), R_f (pentane/dichloromethane = 60:40): 0.51. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 9.93 (broad s, 1H), 8.79−8.70 (m, 2H), 8.12 (dd, J = 8.4, 1.8 Hz, 1H), 7.54−7.45 (m, 4H), 7.44−7.32 (m, 4H), 4.13 (dd, J = 9.0, 6.0 Hz, 1H), 3.76 (dd, J = 14.1, 9.0 Hz, 1H), 3.30 (dd, J = 14.1, 6.0 Hz, 1H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −41.8. $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 169.4, 148.3, 138.2, 137.4, 136.2, 134.0, 131.2 (q, J = 306.5 Hz), 129.3, 128.3, 127.9, 127.8, 127.2, 121.9, 121.6, 116.5, 54.7, 32.6 (q, J = 2.3 Hz). ATR-FTIR (cm^{-1}): 3340, 2925, 2855, 1688, 1527, 1486, 1462, 1385, 1324, 1276, 1111, 825, 791, 698. HRMS (ESI$^+$) m/z: [M + H]$^+$ Calcd for $C_{19}H_{16}F_3N_2OS$ 377.0930; Found 377.0935.

2-Methyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide ***6q***. Procedure E was followed, from **1q** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 32 cm,

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width 2 cm, toluene + Et_3N 1%) as pale yellow oil (19.6 mg, 31%), R_f (toluene + Et_3N 1%): 0.28. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.97 (broad s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.80−8.73 (m, 1H), 8.17 (dd, J = 8.1, 1.5 Hz, 1H), 7.58−7.51 (m, 2H), 7.47 (dd, J = 8.1, 4.2 Hz, 1H), 3.39−3.26 (m, 1H), 3.11−2.95 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −41.7 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 172.3, 148.3, 138.3, 136.4, 134.0, 131.1 (q, J = 305.8 Hz), 127.9, 127.3, 121.9, 121.7, 116.7, 43.0, 32.8 (q, J = 2.3 Hz), 18.0. ATR-FTIR (cm^{-1}): 3347, 2927, 1688, 1526, 1486, 1457, 1426, 1379, 1323, 1258, 1105, 942, 826, 791, 671. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2OS$ 315.0773; Found 315.0784.

2-(4-Isobutylphenyl)-N-(quinolin-8-yl)-3-(trifluoromethylthio)-propanamide **6r**. Procedure E was followed, from **1r** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane 80:20 + 1% Et_3N) as a pale yellow oil (28.2 mg, 33%), R_f (toluene/pentane 80:20 + 1% Et_3N): 0.48. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.91 (broad s, 1H), 8.76 (dd, J = 6.9, 2.1 Hz, 1H), 8.70 (dd, J = 4.2, 1.5 Hz, 1H), 8.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.54−7.46 (m, 2H), 7.41 (dd, J = 8.4, 4.5 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 4.10 (dd, J = 9.0, 6.0 Hz, 1H), 3.76 (dd, J = 13.8, 9.0 Hz, 1H), 3.29 (dd, J = 13.8, 6.0 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.91−1.78 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ − 41.8 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 169.7, 148.2, 141.9, 138.3, 136.2, 134.6, 134.1, 131.3 (q, J = 306.5 Hz), 130.0, 127.8, 127.6, 127.2, 121.9, 121.6, 54.3, 45.1, 32.6 (q, J = 2.3 Hz), 30.2, 22.3, 22.3. ATR-FTIR (cm^{-1}): 3340, 2953, 2920, 1683, 1525, 1486, 1148, 1104, 825, 790. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}F_3N_2OS$ 433.1556; Found 433.1548.

(S)-2-(6-Methoxynaphthalen-2-yl)-N-(quinolin-8-yl)-3-(trifluoromethylthio)propanamide **6s**. Procedure E was followed, from **1s** and **V** (143 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane 90:10 + 1% Et_3N) as a yellow oil (21.2 mg, 23%), R_f (toluene/pentane 80:20 + 1% Et_3N): 0.26. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.98 (broad s, 1H), 8.78 (dd, J = 7.2, 1.8 Hz, 1H), 8.67 (dd, J = 4.2, 1.8 Hz, 1H), 8.10 (d, dd, J = 8.4, 1.8 Hz, 1H), 7.87 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.58−7.46 (m, 3H), 7.38 (dd, J = 8.4, 4.2 Hz, 1H), 7.17 (dd, J = 9.0, 2.4 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H) 4.26 (dd, J = 9.0, 6.0 Hz, 1H), 3.91 (s, 3H), 3.83 (dd, J = 13.8, 9.0 Hz, 1H), 3.37 (dd, J = 13.8, 6.0 Hz, 1H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −41.7 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 169.6, 158.0, 148.2, 138.2, 136.2, 134.3, 134.0, 132.4, 131.3 (q, J = 306.5 Hz), 129.4, 129.0, 128.0, 127.8, 127.2, 127.0, 125.7, 121.9, 121.6, 119.4, 116.5, 105.6, 55.3, 54.6, 32.6 (q, J = 2.3 Hz). ATR-FTIR (cm^{-1}): 3333, 2923, 1680, 1633, 1525, 1484, 1262, 1099, 1028, 789. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}F_3N_2O_2S$ 457.1192; Found 457.1208.

2-Ethyl-N-(quinolin-8-yl)-3-(trifluoromethylthio)butanamide **6t**. Procedure E was followed, from **1t** and **I** (60 h). The product was purified by flash chromatography on silica gel (height 31 cm, width 1.5 cm, pentane/dichloromethane = 40:60) as a colorless oil (8.3 mg, 12%), R_f (pentane/dichloromethane = 40:60): 0.42. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.92 (broad s, 1H), 8.86−8.74 (m, 2H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.54 (d, J = 4.5 Hz, 2H), 7.48 (dd, J = 8.4, 4.2 Hz, 1H), 3.63−3.49 (m, 1H), 2.74−2.62 (m, 1H), 2.07−1.94 (m, 1H), 1.92−1.79 (m, 1H), 1.57 (d, J = 6.3 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −41.3 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 171.5, 148.3, 138.4, 136.4, 133.9, 127.9, 127.4, 121.9, 121.7, 116.8, 55.4, 42.3 (q, J = 306.5 Hz), 23.9, 21.6, 12.0. The CF_3-carbon was not detectable. ATR-FTIR (cm^{-1}): 3347, 2966, 1682, 1524, 1487, 1425, 1324, 1110, 826, 791, 679. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}F_3N_2OS$ 343.1086; Found 343.1086.

N-(Quinolin-8-yl)-2-(trifluoromethylthio)cyclohexane-1-carboxamide **6u**. Procedure E was followed, from **1u** and **I** (60 h). The product was purified by flash chromatography on silica gel (height 32 cm, width 2 cm, toluene/pentane 94:6 + Et_3N 1%) as a colorless oil (5.6 mg, 8%), R_f (pentane/dichloromethane = 40:60): 0.26. ^1H NMR (300.13 MHz, $CDCl_3$): δ 9.87 (broad s, 1H), 8.84−8.76 (m, 2H), 8.17 (dd, J = 8.1, 1.5 Hz, 1H), 7.59−7.50 (m, 2H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 3.66−3.47 (m, 1H), 2.69−2.53 (m, 1H), 2.46−2.32 (m, 1H), 2.25−2.11 (m, 1H), 1.93−1.69 (m, 4H), 1.55−1.34 (m, 2H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −38.1 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 171.5, 148.2, 138.4, 136.4, 134.2, 127.9, 127.4, 121.8, 121.6, 116.8, 52.1, 45.5, 34.5, 31.3, 26.0, 24.5. The CF_3-carbon was not detectable. ATR-FTIR (cm^{-1}): 3347, 2933, 2860, 1683, 1524, 1486, 1325,1099, 790. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}F_3N_2OS$ 355.1086; Found 355.1091.

Further Transformations of the Product 6. *Procedure for the Oxidation of Compound* **6a**:[27] An oven-dried 10 mL flask equipped with a stir bar was charged with **6a** (32.8 mg, 0.1 mmol, 1 equiv) and distilled CH_2Cl_2 (1.5 mL), and the reaction mixture was cooled down to −10 °C. Then, *m*-CPBA (61.6 mg, 0.25 mmol, 2.5 equiv, assay ca.70%) was added portionwise while keeping the temperature at −10 °C. The reaction mixture was allowed to warm up to 5 °C and was stirred for 3 h until complete disappearence of the starting material. Then, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was washed with sodium sulfite solution (5 mL), aqueous $NaHCO_3$ solution (5 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (petroleum ether/dichloromethane, 40:60) to afford the desired product **7** as a pale yellow vitrous solid in 40% yield (13.9 mg). *2,2-Dimethyl-N-(quinolin-8-yl)-3-(trifluoromethylsulfinyl)propanamide* **7**. R_f (pentane/dichloromethane = 30:70): 0.15. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.41 (broad s, 1H), 8.83 (dd, J = 4.2, 1.5 Hz, 1H), 8.77−8.69 (m, 1H), 8.19 (dd, J = 8.1, 1.5 Hz, 1H), 7.58−7.52 (m, 2H), 7.49 (dd, J = 8.1, 4.2 Hz, 1H), 3.58 (d, J = 13.5 Hz, 1H), 3.09 (d, J = 13.5 Hz, 1H), 1.78 (s, 3H), 1.67 (s, 3H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −74.5 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 173.4, 148.5, 138.6, 136.4, 133.7, 127.9, 127.3, 125.6 (q, J = 334.5 Hz), 122.2, 121.8, 116.7, 59.6 (q, J = 3.0 Hz), 42.9, 27.5, 25.2. ATR-FTIR (cm^{-1}): 3333, 2958, 1670, 1531, 1489, 1328, 1173, 1137, 1064, 791, 695. HRMS (ESI^+) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}F_3N_2O_2S$ 345.0885; Found 345.0887.

Procedure for the Removal of the Directing Group on Compound **6a**:[20] An oven-dried 10 mL flask equipped with a stir bar was charged with **6a** (65.6 mg, 0.2 mmol, 1 equiv), NaOH (120 mg, 3 mmol, 15 equiv), and EtOH (1 mL). The resulting mixture was stirred at 90 °C for 4 days. After completion, the reaction mixture was cooled to room temperature, water (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The pH of the aqueous layer was adjusted to 2 with HCl (1 M), and the resulting aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated under vacuum to afford pure product **8** (34.6 mg, 89%) as a yellow oil. *2,2-Dimethyl-3-(trifluoromethylthio)propanoic acid* **8**. ^1H NMR (300.13 MHz, $CDCl_3$): δ 10.21 (broad s, 1H), 3.08 (s, 2H), 1.35 (s, 6H). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ−42.2 (s). $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 182.4, 130.8 (q, J = 305.8 Hz), 42.9, 38.2 (q, J = 2.3 Hz), 24.3. ATR-FTIR (cm^{-1}): 2983, 2940, 1702, 1477, 1151, 1099. HRMS (ESI^-) m/z: $[M - H]^+$ Calcd for $C_6H_8F_3O_2S$ 201.0197; Found 201.0193.

■ ASSOCIATED CONTENT

Supporting Information

Radical trapping experiments, spectral data, crystallographic information (CCDC 1050504 (**6j**)) and 1050505 (**6a**)). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Selected reviews: (a) For a special issue on fluorine chemistry, see: *Chem. Rev.* **2015**, *115*, 563−1306. (b) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (e) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem.—Eur. J.* **2014**, *20*, 16830. (f) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941. (g) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (h) Catalán, S.; Munoz, S. B.; Fustero, S. *Chimia* **2014**, *68*, 382. (i) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135.

(2) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem.* **2004**, *5*, 637.

(3) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832.

(4) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(5) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

(6) For selected examples, see: (a) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, 2415 and references therein. (b) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731 and references therein. (c) Alazet, S.; Zimmer, L.; Billard, T. *Chem.—Eur. J.* **2014**, *20*, 8589. (d) Huang, Y.; He, X.; Lin, X.; Rong, M.; Weng, Z. *Org. Lett.* **2014**, *16*, 3284. (e) Hu, M.; Rong, J.; Miao, W.; Ni, C.; Han, Y.; Hu, J. *Org. Lett.* **2014**, *16*, 2030. (f) Zhu, L.; Wang, G.; Guo, Q.; Xu, Z.; Zhang, D.; Wang, R. *Org. Lett.* **2014**, *16*, 5390. (g) Liu, J.-B.; Xu, X.-H.; Chen, Z.-H.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 897. (h) Yang, T.; Lu, L.; Shen, Q. *Chem. Commun.* **2015**, *51*, 5479. (i) Dai, X.; Cahard, D. *Synlett* **2015**, *26*, 40. (j) Ye, K.-Y.; Zhang, X.; Dai, L.-X.; You, S.-L. *J. Org. Chem.* **2014**, *79*, 12106. (k) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, *17*, 1063. (l) Danoun, G.; Bayarmagnai, B.; Gruenberg, M. F.; Goossen, L. J. *Chem. Sci.* **2014**, *5*, 1312. (m) Zhang, K.; Liu, J.-B.; Qing, F.-L. *Chem. Commun.* **2014**, *50*, 14157.

(7) For selected reviews of C−H activation, see: (a) Shi, G.; Zhang, Y. *Adv. Synth. Catal.* **2014**, *356*, 1419. (b) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751. (c) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (f) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf. *Chem. Rev.* **2012**, *112*, 5879. (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (j) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(8) For selected reviews, see: (a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (b) Zhang, Q.; Chen, K.; Shi, B.-F. *Synlett* **2014**, *25*, 1941. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (f) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (g) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191.

(9) For selected examples of C−S bond formation, see: (a) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2014**, *44*, 291. (b) Yan, S.-Y.; Liu, Y.-J.; Liu, B.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 4069. (c) Yang, K.; Wang, Y.; Chen, X.; Kadi, A. A.; Fun, H.-K.; Sun, H.; Zhang, Y.; Lu, H. *Chem. Commun.* **2015**, *51*, 3582. (d) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644. (e) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (f) Iwasaki, M.; Iyanaga, M.; Tsuchiya, Y.; Nishimura, Y.; Li, W.; Li, Z.; Nishihara, Y. *Chem.—Eur. J.* **2014**, *20*, 2459. (g) Yang, Y.; Hou, W.; Qin, L.; Du, J.; Feng, H.; Zhou, B.; Li, Y. *Chem.—Eur. J.* **2014**, *20*, 416. (h) Li, X.; Xu, Y.; Wu, W.; Jiang, C.; Qi, C.; Jiang, H. *Chem.—Eur. J.* **2014**, *20*, 7911. (i) Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 5644. For selected examples of C−SCF_3 bond formation, see: (j) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (k) Xu, C.; Shen, Q. *Org. Lett.* **2014**, *16*, 2046. (l) Yin, W.; Wang, Z.; Huang, Y. *Adv. Synth. Catal.* **2014**, *356*, 2998.

(10) During the manuscript preparation, a nickel-catalyzed direct thioetherification of β-C(sp^3)−H bonds of aliphatic amides was reported: Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340.

(11) (a) Chen, C.; Xu, X.-H.; Yang, B.; Qing, F.-L. *Org. Lett.* **2014**, *16*, 3372. (b) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457.

(12) During the preparation of the manuscript, trifluoromethylthiolation of unactivated aliphatic C−H bonds via a radical process was reported: (a) Guo, S.; Zhang, X.; Tang, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 4065. (b) Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4070.

(13) (a) Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 413. (b) Belhomme, M.-C.; Dru, D.; Xiong, H.-Y.; Cahard, D.; Besset, T.; Poisson, T.; Pannecoucke, X. *Synthesis* **2014**, 1859. (c) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 3428. (d) Besset, T.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2014**, 7220.

(14) For selected references, see: (a) Racowski, J. M.; Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18022. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094.

(15) Other catalysts such as Cu- or Ni-based ones were inefficient in our hands.

(16) See Supporting Information for details.

(17) When a reaction was performed under standard conditions in the presence of 1 equiv of TEMPO and **I** without addition of **1a**, the degradation of **I** into new fluorinated species was observed.

(18) For selected examples, see: (a) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (b) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258. (c) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790.

(19) At this stage, other mechanism pathways such as electrophilic substitution cannot be ruled out.

(20) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.

(21) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(22) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496.

(23) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457.

(24) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316.

(25) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

(26) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167.

(27) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1650.

DOI: 10.1021/acs.joc.5b00505
J. Org. Chem. 2015, 80, 4204−4212