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One-Pot Cascade Trifluoromethylation/Cyclization of Imides: Synthesis of α-Trifluoromethylated Amine Derivatives

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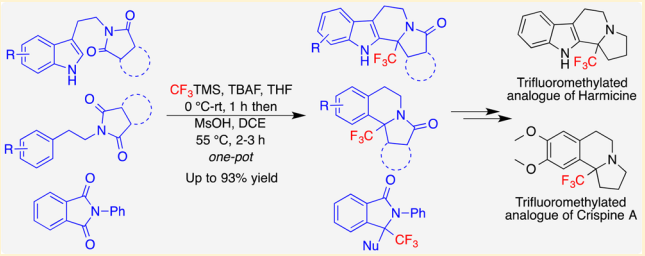
Supporting Information

ABSTRACT: Tryptamine- and phenethylamine-derived imides were selectively monotrifluoromethylated using CF_3TMS. Subsequent methanesulfonic acid mediated cyclization of the intermediate hemiaminals afforded the α-trifluoromethylated amine derivatives via the formation of trifluoromethylated acyliminium ions, in one pot. The strategy was applicable to the both inter- and intramolecular versions. Furthermore, the utility of the present method was demonstrated through the synthesis of trifluoromethylated analogues of harmicine and crispine A.



Many synthetic bioactive molecules, both in pharmaceuticals and agrochemicals, contain fluorine in the form of either fluoro, trifluoromethyl (CF_3), or thiotrifluoromethyl (SCF_3) groups.[1] The presence of fluorine in the important structural backbone can profoundly alter the biological and physicochemical properties of compounds through concurrent changes in steric, electronic, lipophilic, and metabolic characteristics.[2] Consequently, over the last few decades, fluorinated compounds have attracted significant attention in various fields, such as organic synthesis, medicinal chemistry, and materials.[3] Among them, trifluoromethylated compounds are of great interest since the trifluoromethyl group is an excellent bioisostere of the methyl group, which is stable under metabolic oxidative conditions. Although trifluoromethylated compounds and/or building blocks can be synthesized employing both nucleophilic trifluoromethylating reagents[4] and electrophilic trifluoromethylating reagents[5] with appropriate substrates, the well-practiced strategies utilize a nucleophilic trifluoromethylating reagent, like (trifluoromethyl)trimethylsilane (CF_3SiMe_3) and trifluoromethylated hemiaminals.[6]

Trifluoromethylated hemiaminals possess unique reactivity under different conditions. Thus, under basic conditions, trifluoromethylated hemiaminals produce nucleophilic "CF_3^-"; in contrast, the trifluoromethylated iminium ions, efficient trifluoromethylated synthons, are generated under acidic conditions. The latter phenomenon was utilized in the synthesis of various *N*-based trifluoromethylated building blocks.[7] However, the generation of related trifluoromethylated acyliminium ions[8] from hemiaminals derived from imides and their application to the synthesis of trifluoromethylated heterocycles and building blocks, which are precursors for the synthesis of trifluoromethylated natural product analogues of therapeutic importance, are yet to be studied (Scheme 1).

Among the currently marketed drugs, ∼40% are of natural product origin or inspired.[9] The tetrahydro-β-carboline and the tetrahydroisoquinoline families of alkaloids are classes of ubiquitous natural products associated with diverse biological functions, particularly, in the brain as neurotoxins and neuroprotectants.[10] Introduction of trifluoromethyl groups in these therapeutically important natural product motifs at a specific site may improve their biological profile[11] and are highly desirable. Inspired by the reactivity of trifluoromethylated hemiaminals and the unique properties of trifluoromethylated compounds in biological systems, we herein disclose a new cascade trifluoromethylation/cyclization of imides for the synthesis of trifluoromethylated heterocycles and nitrogen-based building blocks.

For the present study, the phthalimide derivative **1a** derived from tryptamine was chosen as a suitable starting material. Next, selective monotrifluoromethylation of imide **1a** with CF_3SiMe_3 was examined.[12] After optimization, the monotrifluoromethylated product, hemiaminal **2**, was isolated from the reaction of imide **1a** and CF_3SiMe_3 with a catalytic amount of tetrabutylammonium fluoride (TBAF) in 81% yield (Scheme 2).

After synthesizing the hemiaminal **2**, acid-mediated cyclization of **2** to the trifluoromethylated heterocycle **3a** through formation of the trifluoromethylated acyliminium ion **2′** was investigated (Table 1 and Scheme 3).[8] Reaction of hemiaminal **2** with Lewis acids, such as $BF_3{\cdot}OEt_2$ and $TiCl_4$, known to generate iminium ions from hemiaminals,[7] in chlorinated solvents at room temperature did not afford the expected cyclized product **3a**; instead, decomposition of the starting material was observed (Table 1, entries 1 and 2). Similar results were obtained with Brønsted acids, such as trifluoroacetic acid (TFA) or triflic acid (TfOH) (Table 1, entries 3 and 4). To our delight, treatment of hemiaminal **2** with methanesulfonic acid (MsOH) in dichloromethane (DCM) at room temperature

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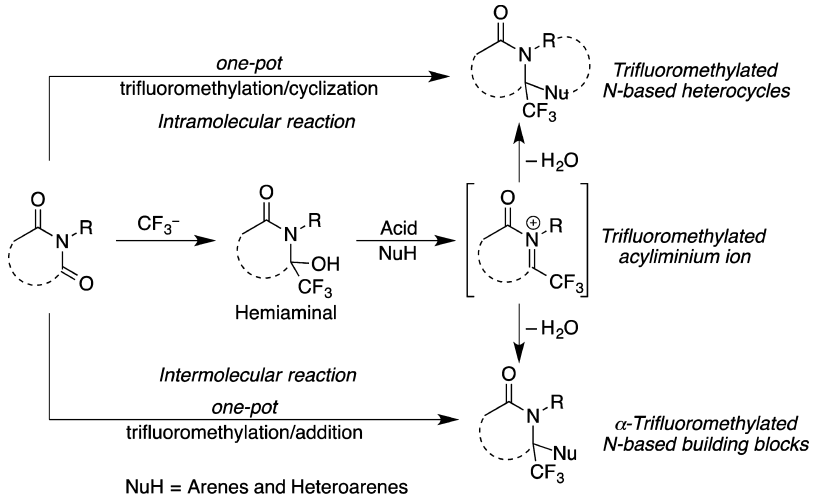
Scheme 1. Generation and Functionalization of Trifluoromethylated Acyliminium Ion from Imides



Scheme 2. Synthesis of Trifluoromethylated Hemiaminal 2 from Imide 1a

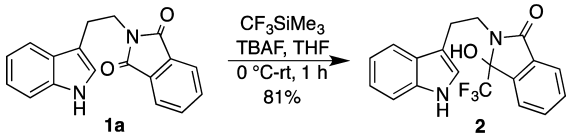
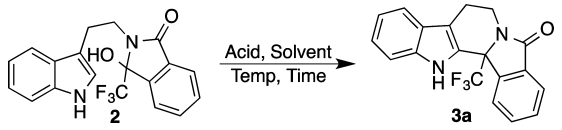


Table 1. Optimization of Acid-Mediated Cyclization of 2[a]



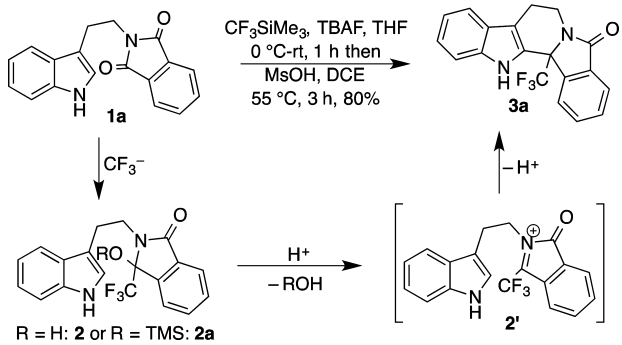
entry	acid (X equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$BF_3{\cdot}OEt_2$ (1.5)	DCM	rt	20	0[c]
2	$TiCl_4$ (2)	DCE	rt	24	0[d]
3	TFA (2)	DCM	rt	24	0
4	TfOH (1.5)	DCM	rt	24	0
5	MsOH (2)	DCM	rt	12	23
6	MsOH (5)	DCM	rt	12	35
7	MsOH (5)	DCE	rt	24	34
8	MsOH (2)	DCE	55	12	42
9	MsOH (2)	DCE	70	10	55
10	MsOH (5)	DCE	55	12	84 (80)[e]

[a]Reaction conditions: **2** (0.13 mmol), acid (X equiv), solvent (1 mL), temp, time. [b]Isolated yield. [c]Starting material decomposed. [d]Starting material was recovered. [e]3 h.

afforded the cyclized product **3a** in 23% yield (Table 1, entry 5).

Subsequently, increasing the equivalents of MsOH to 5 equiv showed only a slight improvement in the yield (Table 1, entry 6). However, increasing the temperature to 55 °C in 1,2-dichloroethane (DCE) gave the product in 42% yield (Table 1, entry 8). A further increase in the temperature did not show a profound effect on the outcome of the reaction (Table 1, entry 9). Next, keeping the temperature at 55 °C, followed by increasing the equivalents of acid (5 equiv), furnished the cyclized product in 84% yield. Interestingly, an 80% yield of product **3a** was obtained after 3 h under the same reaction conditions (Table 1, entry 10). After identifying the suitable conditions for the synthesis of hemiaminal **2** from imide **1a** and its subsequent cyclization, we envisaged a one-pot synthesis of trifluoromethylated cyclized product **3a** from imide **1a** (Scheme 3).

Scheme 3. One-Pot Cascade Trifluoromethylation/Cyclization of Imide 1a



The reaction of imide **1a** and CF_3SiMe_3 with a catalytic amount of TBAF in THF for 1 h at 0 °C to rt afforded the mixture of hemiaminal **2** and its TMS ether. Evaporation of the THF and treatment of the residue with MsOH in DCE for 3 h at 55 °C afforded the expected cyclized product **3a** in 80% yield, through the formation of trifluoromethylated acyliminium ion **2′** (Scheme 3). The formation of product was further confirmed by X-ray analysis (see the Supporting Information).[13]

After obtaining the optimized conditions for one-pot trifluoromethylation/cyclization, the scope and limitations of the substituted tryptamines and imides were investigated.[14] As shown in Scheme 4, various substituted tryptamine derivatives were tolerated under the optimized conditions. The halogenated tryptamine derivatives, which are amenable for the subsequent functionalization, also underwent smooth reaction to furnish the corresponding cyclized products **3b−3d** in excellent yield. Interestingly, the electron-withdrawing trifluoromethyl substituted tryptamine derivative also gave the cyclized product **3e**. Reaction of a mixture of 4- and 6-methyl tryptamine derivatives in a ∼1:1 ratio under the optimized conditions afforded the trifluoromethylated heterocycles **3f/f′** in good yield in the ratio of ∼1:2, due to the possible steric effect present in the 4-methyltryptamine derivative. Changing the phthalimide to succinimide also gave the corresponding

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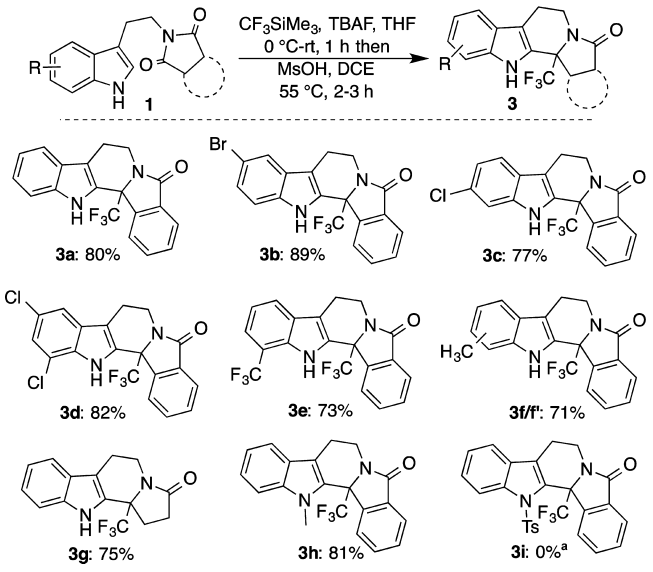
Scheme 4. One-Pot Cascade Trifluoromethylation/Cyclization of Imides 1 Derived from Tryptamine Derivatives[a]



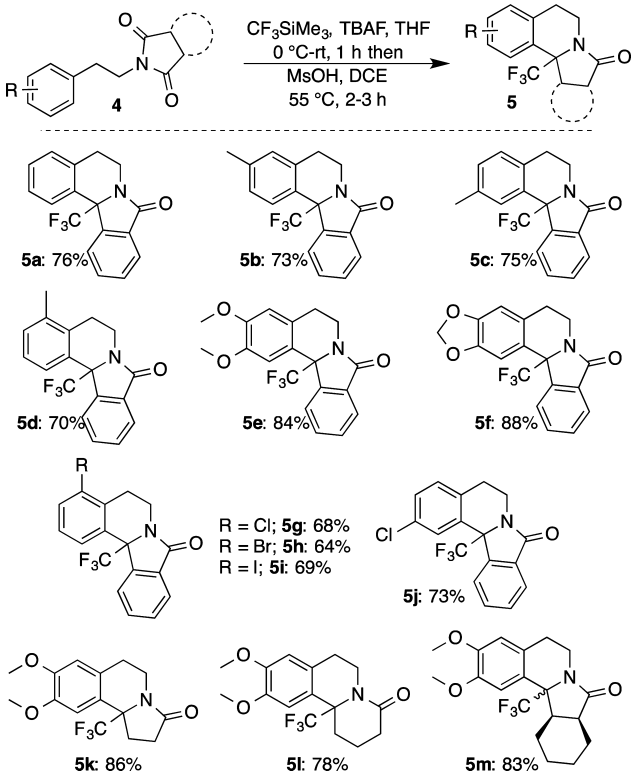
[a]84% of corresponding detosylated compound **3a** was isolated.

product **3g** in 75% yield. Next, substitution on the nitrogen was also examined. A *N*-methyltryptamine derivative gave the product **3h** in good yield, but *N*-tosyltryptamine derivative did not afford the expected cyclized product **3i**; instead, the detosylated product **3a** was observed in 84% yield.

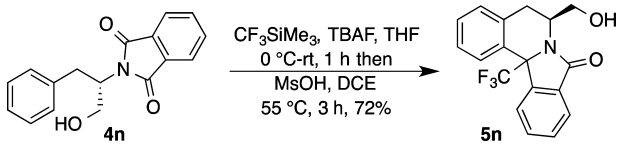
Next, the synthesis of various trifluoromethylated tetrahydroisoquinolines was envisioned by replacing the indole with a simple aromatic system. After synthesizing the suitable starting material **4a** derived from phenethylamine and phthalic anhydride,[15] the one-pot trifluoromethylation/cyclization was investigated employing the optimized conditions used for the synthesis of **3**. Delightfully, the one-pot trifluoromethylation/cyclization of **4a** under the optimized conditions furnished the expected trifluoromethylated tetrahydroisoquinoline **5a** in 76% yield (Scheme 5). Substitution at *ortho*, *meta*, and *para* positions are tolerated and afforded the cyclized products **5b**−**5d** in good yield. 3,4-Dimethoxy- and 3,4-methylenedioxy substituted trifluoromethylated tetrahydroisoquinolines (**5e** and **5f**, respectively) were also achieved employing the optimized conditions. Halogenated phenethylamines were tolerated under the trifluoromethylation/cyclization conditions and furnished the cyclized products **5g**−**5j** in good yields. Subsequently, replacement of phthalimide with other imides was also studied. Treatment of the succinimide derivative with CF_3SiMe_3, followed by MsOH, afforded the cyclized product **5k**, a potential precursor for the synthesis of the trifluoromethylated analogue of crispine A, in 86% yield. Similarly, the imides derived from glutaric acid and cyclohexyl-1,2-dicarboxylic acid also underwent smooth reaction and afforded the cyclized products **5l** and **5m** in 78% and 83% yield, respectively; the latter gave a mixture of diastereomers in a 1.6:1 ratio.

Next, phthalimide derivative **4n** derived from (*S*)-phenylalaninol was synthesized and subjected to the present conditions. Trifluoromethylation/cyclization of imide **4n** with CF_3SiMe_3 and MsOH afforded the cyclized product **5n** in 72% yield (Scheme 6). Although the absolute configuration of the newly formed stereocenter was not determined, the ^{1}H NMR spectra showed the presence of a single diastereomer.

Scheme 5. One-Pot Cascade Trifluoromethylation/Cyclization of Imides 4 Derived from Arylethylamines



Scheme 6. One-Pot Cascade Trifluoromethylation/Cyclization of Imide 4n



After exploring the intramolecular version of the trifluoromethylative functionalization, intermolecular versions were also investigated. *N*-Phenylphthalimide **6** was chosen as the substrate for the intermolecular reaction. Reaction of **6** with CF_3SiMe_3 gave **7** in 93% yield (Scheme 7). Methanesulfonic acid mediated generation of the acyliminium ion from the hemiaminal **7**, followed by trapping with *N*-methylindole **8**, furnished the product **9** in 62% yield. Similarly, trapping with 1,3-dimethoxybenzene **10** afforded the product **11** in 92% yield. This demonstrates that the present methodology can also be applied to the synthesis of a wide range of α-trifluoromethylated nitrogen-based building blocks and heterocycles.

After the successful demonstration of a one-pot trifluoromethylation/cyclization of an imide, the utility of the synthesized trifluoromethylated heterocycles was also revealed by the synthesis of trifluoromethylated natural products and analogues such as harmicine[16] and crispine A,[8a] therapeutically important tetrahydro-β-carboline and tetrahydroisoquinoline natural products, respectively. Reduction of lactam **3g** with lithium aluminum hydride ($LiAlH_4$) in THF furnished the trifluoromethylated harmicine **12** in excellent yield (Scheme 8). Similarly, synthesis of the trifluoromethylated analogue of crispine A **13** was also achieved from the lactam **5k** in 80% yield. Furthermore, reduction of lactam **5e** gave the

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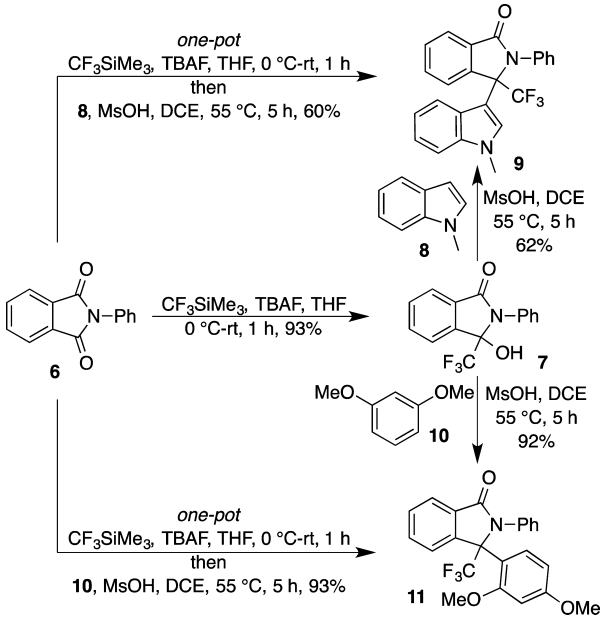
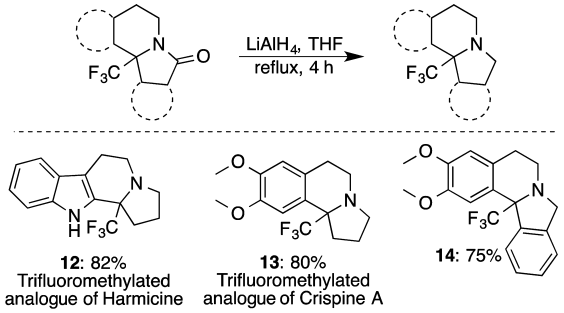
Scheme 7. Intermolecular Functionalization of a Trifluoromethylated Acyliminium Ion



Scheme 8. Synthesis of Trifluoromethylated Analogues of Natural Product and Related Compounds



trifluoromethylated tetrahydroisoquinoline natural product analogue **14** in good yield.

In conclusion, we developed the new one-pot cascade trifluoromethylation/cyclization strategy for the synthesis of α-trifluoromethylated amine derivatives. Efficacy of the trifluoromethylated hemiaminal to form an acyliminium ion and its application is the key feature of the present strategy. Interestingly, the developed strategy is applicable to both intra- and intermolecular transformations, where a number of indole and arene derivatives were employed as trapping agents to lead to the synthesis of trifluoromethylated heterocycles and building blocks. Furthermore, the synthesis of trifluoromethylated analogues of harmicine and crispine A was described to demonstrate the utility of the present method.

EXPERIMENTAL SECTION

Synthesis of Trifluoromethylated Hemiaminal 2 from Imide 1a. Phthalimide derived from tryptamine (**1a**)[14] (0.5 g, 1.7 mmol) was dissolved in dry THF (10 mL) in a reaction tube under a N_2 atmosphere and cooled to 0 °C. (Trifluoromethyl)trimethyl silane (CF_3TMS, 0.3 g, 2.6 mmol) was added, followed by a 1 M solution of TBAF in THF (1–2 mol %, 20–34 μL), and the reaction mixture was warmed to room temperature and stirred for 1 h. The THF was evaporated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate:hexane (1:3) as eluent to afford hemiaminal **2** (0.5 g, 81% yield) as a pale yellow solid. mp: 174–176 °C; IR (KBr): 3417, 3257, 2933, 1695, 1401, 1181 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.88 (brs, 1H), 8.35 (brs, 1H) 7.82 (d, 1H, J = 7.2 Hz), 7.77 (d, 2H, J = 4.2 Hz), 7.74–7.69 (m, 1H), 7.64 (d, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 8.0 Hz), 7.25 (d, 1H, J = 2.1 Hz), 7.10 (td, 1H, J = 7.0, 1.0 Hz), 7.30 (td, 1H, J = 7.9, 1.0 Hz), 3.74 (td, 1H, J = 13.7, 5.3 Hz), 3.63 (td, 1H, J = 12.7, 4.9 Hz), 3.17 (td, 1H, J = 13.4, 4.9 Hz), 2.98 (td, 1H, J = 12.1, 5.2 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 167.1, 140.8, 136.3, 133.0, 131.4, 131.3, 127.0, 123.9, 123.6 (q, J = 286.1 Hz), 122.9, 122.8, 121.0, 118.4, 118.0, 111.5, 111.0, 87.1 (q, J = 31.0 Hz), 40.2, 24.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −78.76 (s, 3F); HRMS: calcd. for $C_{19}H_{15}N_2F_3O_2$ + Na: 383.0983; found: 383.0992.

Acid-Mediated Cyclization of Hemiaminal 2. Hemiaminal **2** (0.17 mmol) was dissolved in 1 mL of solvent (see Table 1 and the Supporting Information); then the acid was added (equivalents as specified in Table 1 and the Supporting Information) under a N_2 atmosphere. The reaction tube was sealed with a stopper and stirred at the temperature mentioned in Table 1 and the Supporting Information. After completion, the reaction mixture was cooled to room temperature, quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 2 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate:hexane (1:4) as eluent to afford the trifluoromethylated heterocycle **3**.

General Procedure for One-Pot Cascade Trifluoromethylation/Cyclization of Imides 1. Tryptamine-derived phthalimide **1** (0.17–0.20 mmol) was dissolved in dry THF (2 mL) in a reaction tube under a N_2 atmosphere and cooled to 0 °C. CF_3SiMe_3 (0.26–0.3 mmol) was added, followed by a 1 M solution of TBAF in THF (1–2 mol %, ∼34 μL), and the reaction mixture was warmed to rt and stirred for 1 h. After 1 h, the THF was evaporated under reduced pressure and DCE (1 mL) and methanesulfonic acid (0.85–1.0 mmol) were added. The reaction tube was sealed with a stopper and kept at 55 °C using a preheated oil bath. After completion of the reaction, it was cooled to rt, quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 4 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford trifluoromethylated heterocycles **3**.

3a: 47 mg, 80% yield; pale yellow solid; mp: 258–260 °C; IR (KBr): 3410, 2927, 1693, 1561, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (brs, 1H), 7.92 (d, 2H, J = 6.5 Hz), 7.66 (t, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.41 (d, 1H, J = 8.0 Hz), 7.29–7.21 (m, 1H), 7.13 (t, 1H, J = 7.4 Hz), 4.94–4.82 (m, 1H), 3.70–3.54 (m, 1H), 3.02–2.87 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 168.0, 139.9, 136.8, 133.2, 130.8, 125.1, 124.5 (q, J = 286.5 Hz), 124.0, 123.8, 123.0, 119.3, 118.9, 111.7, 110.9, 64.8 (q, J = 30.9 Hz), 36.8, 20.5; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −77.06 (s, 3F); HRMS: calcd. for $C_{19}H_{13}N_2F_3O$ + Na: 365.0878; found: 365.0865.

3b: 64 mg, 89% yield; white solid; mp: 208–210 °C; IR (KBr): 3410, 2972, 1697, 1561, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (brs, 1H), 7.92 (t, 2H, J = 7.7 Hz), 7.69 (td, 1H, J = 7.6, 1.2 Hz), 7.64 (d, 1H, J = 1.8 Hz), 7.61 (td, 1H, J = 7.5, 1.0 Hz), 7.33 (dd, 1H, J = 8.6, 1.7 Hz), 7.28 (d, 1H, J = 8.6 Hz), 4.93–4.82 (m, 1H), 3.67–3.54 (m, 1H), 2.95–2.82 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 140.2, 135.5, 133.0, 131.9, 130.7, 127.8, 126.8, 126.0, 125.0, 124.7 (q, J = 288.0 Hz), 123.0, 122.0, 113.6, 113.0, 112.7, 65.4 (q, J = 31.6 Hz), 37.3, 21.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.94 (s, 3F); HRMS: calcd. for $C_{19}H_{12}N_2F_3OBr$ + H: 421.0163; found: 421.0145.

3c: 49 mg, 77% yield; white solid; mp: 268–270 °C; IR (KBr): 3350, 2920, 1693, 1459, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (brs, 1H), 7.92 (d, 2H, J = 7.8 Hz), 7.68 (t, 1H, J = 7.7 Hz), 7.60 (t, 1H, J = 7.7 Hz), 7.44–7.38 (m, 2H), 7.10 (dd, 1H, J = 8.4, 1.7 Hz), 4.93–4.82 (m, 1H), 3.68–3.53 (m, 1H), 2.97–2.85 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.3, 140.2, 137.2, 133.0, 132.0, 130.7, 129.7, 125.4, 125.0, 124.8, 124.7 (q, J = 286.0 Hz), 123.0, 121.3, 120.2, 113.3, 111.6, 65.3 (q, J = 31.1 Hz), 37.3, 21.1; ^{19}F NMR (470 MHz,

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$CDCl_3/C_6F_6$): δ −77.01 (s, 3F); HRMS: calcd. for $C_{19}H_{12}N_2F_3OCl$ + H: 377.0669; found: 377.0685.

3d: 57 mg, 82% yield; white solid; mp: 282−284 °C; IR (KBr): 3420, 2972, 1700, 1609, 1470, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (brs, 1H), 7.98 (d, 1H, J = 7.7 Hz), 7.94 (d, 1H, J = 7.7 Hz), 7.72 (t, 1H, J = 7.5 Hz), 7.62 (t, 1H, J = 7.5 Hz), 7.39 (s, 1H), 7.23 (s, 1H), 4.88 (dd, 1H, J = 14.0, 5.5 Hz), 3.68−3.51 (m, 1H), 2.99−2.78 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.1, 139.8, 133.2, 132.7, 131.9, 130.8, 127.9, 127,0, 126.4, 125.1, 124.6 (q, J = 285.0 Hz), 123.4, 123.1, 117.7, 117.4, 114.0, 65.1, 37.1, 21.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.93 (s, 3F); HRMS: calcd. for $C_{19}H_{11}N_2F_3OCl_2$ + H: 411.0279; found: 411.0299.

3e: 51 mg, 73% yield; brown solid; mp: 166−168 °C; IR (KBr): 3413, 2924, 1693, 1620, 1466, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.58 (br s, 1H), 7.94 (d, 1H, J = 7.5 Hz), 7.88 (d, 1H, J = 7.5 Hz), 7.78−7.66 (m, 2H), 7.62 (t, 1H, J = 7.5 Hz), 7.51 (d, 1H, J = 7.5 Hz), 7.22 (t, 1H, J = 7.5 Hz), 4.90 (d, 1H, J = 13.6 Hz), 3.71−3.54 (m, 1H), 3.04−2.86 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.1, 140.0, 133.2, 132.4, 131.9, 130.8, 127.7, 126.2, 125.1, 124.9 (q, J = 273 Hz), 124.7 (q, J = 289 Hz), 123.4, 122.8, 121.4 (q, J = 4.4 Hz), 120.1, 114.0 (t, J = 33.3 Hz), 113.6, 65.3 (q, J = 31.1 Hz), 37.2, 21.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −63.31 (s, 3F), −77.01 (s, 3F); HRMS: calcd. for $C_{20}H_{13}N_2F_6O$ + H: 411.0932; found: 411.0944.

3g: 38 mg, 75% yield; white solid; mp: 198−200 °C; IR (KBr): 3413, 2969, 1686, 1620, 1564, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (brs, 1H), 7.51 (d, 1H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.24 (t, 1H, J = 7.7 Hz), 7.14 (t, 1H, J = 7.7 Hz), 4.64−4.52 (m, 1H), 3.37−3.24 (m, 1H), 2.91−2.81 (m, 2H), 2.80−2.69 (m, 2H), 2.55−2.41 (m, 1H), 2.28−2.13 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.1, 136.8, 127.4, 126.3 (q, J = 287 Hz), 126.2, 123.6, 120.4, 119.1, 111.7, 111.5, 63.7 (q, J = 28.7), 36.6, 30.4, 28.0, 20.7; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −79.52 (s, 3F); HRMS: calcd. for $C_{15}H_{13}N_2OF_3$ + H: 295.1058; found: 295.1067.

3h: 49 mg, 81% yield; yellow solid; mp: 128−130 °C; IR (KBr): 2924, 1717, 1620, 1466, 1368, 1260, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 7.6 Hz), 7.95 (d, 1H, J = 7.6 Hz), 7.68 (t, 1H, J = 7.8 Hz), 7.61 (t, 1H, J = 7.8 Hz), 7.25 (d, 1H, J = 7.8 Hz), 7.37−7.26 (m, 2H), 7.14 (t, 1H, J = 7.5 Hz), 4.89 (dd, 1H, J = 13.4, 6.5 Hz), 4.11 (s, 3H), 3.62 (dt, 1H, J = 12.5, 5.0 Hz), 3.17−3.02 (m, 1H), 2.98 (dd, 1H, J = 15.8, 5.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 139.7, 138.6, 132.8, 132.3, 130.5, 126.7, 125.6, 125.2, 125.0, 124.8 (q, J = 285 Hz), 123.8, 120.1, 119.2, 114.3, 109.7, 68.1, 36.5, 33.0, 21.5; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −77.61 (s, 3F); HRMS: calcd. for $C_{20}H_{15}N_2F_3O$ + Na: 379.1034; found: 379.1016.

General Procedure for One-Pot Cascade Trifluoromethylation/Cyclization of Imides 4. Phenethylamine-derived phthalimide **4** (0.17−0.20 mmol) was dissolved in dry THF (2 mL) in a reaction tube under a N_2 atmosphere and cooled to 0 °C. CF_3SiMe_3 (0.26−0.3 mmol) was added, followed by a 1 M solution of TBAF in THF (1−2 mol %, ∼34 μL), and the reaction mixture was warmed to rt and stirred for 1 h. After 1 h, the THF was evaporated under reduced pressure and DCE (1 mL) and methanesulfonic acid (0.85−1.0 mmol) were added. The reaction tube was sealed with a stopper and kept at 55 °C using an oil bath. After completion of the reaction, it was cooled to rt, quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 4 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate/hexane as eluent to afford trifluoromethylated heterocycles **5**.

5a: 46 mg, 76% yield; white solid; mp: 110−112 °C; IR (KBr): 2927, 2848, 1711, 1385, 1253, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 1H, J = 7.7 Hz), 7.97 (d, 1H, J = 6.0 Hz), 7.89 (d, 1H, J = 7.7 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.36−7.27 (m, 2H), 7.24−7.17 (m, 1H), 4.73 (dd, 1H, J = 13.6, 7.0 Hz), 3.59 (dt, 1H, J = 4.6, 13.0 Hz), 3.13−3.01 (m, 1H), 2.89 (dd, 1H, J = 16.6, 4.6 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.5, 141.9, 135.6, 132.7, 132.2, 130.3, 130.2, 129.4, 129.1, 127.5, 126.9, 125.0 (q, J = 286.7 Hz), 124.4, 124.3, 66.8, 36.1, 28.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.13 (s, 3F); HRMS: calcd. for $C_{17}H_{12}NOF_3$ + H: 304.0949; found: 304.0936.

5b: 47 mg, 73% yield; orange liquid; IR (Neat): 2928, 1706, 1614, 1466, 1382, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 1H, J = 7.7 Hz), 7.91−7.81 (m, 2H), 7.65 (td, 1H, J = 7.6, 1.0 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.13 (d, 1H, J = 7.9 Hz), 7.01 (s, 1H), 4.72 (dd, 1H, J = 13.5, 6.8 Hz), 3.56 (td, 1H, J = 12.6, 4.6 Hz), 3.09−2.97 (m, 1H), 2.84 (dd, 1H, J = 16.6, 4.4 Hz), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.5, 142.2, 139.1, 135.3, 132.6, 132.1, 130.7, 130.1, 127.8, 127.3, 126.4, 125.1 (q, J = 287.0 Hz), 124.3, 124.2, 66.7 (q, J = 30.0 Hz), 36.1, 28.9, 21.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.29 (s, 3F); HRMS: calcd. for $C_{18}H_{14}NOF_3$ + H: 318.1106; found: 318.1097.

5c: 48 mg, 75% yield; white solid; mp: 134−136 °C; IR (KBr): 2963, 1713, 1643,1254, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 7.7 Hz), 7.88 (d, 1H, J = 7.7 Hz), 7.75 (s, 1H), 7.67 (td, 1H, J = 7.6, 1.0 Hz), 7.57 (td, 1H, J = 7.6, 1.0 Hz), 7.13 (dd, 1H, J = 7.8, 1.0 Hz), 7.08 (d, 1H, J = 7.8 Hz), 4.71 (dd, 1H, J = 13.6, 6.8 Hz), 3.56 (td, 1H, J = 12.5, 4.6 Hz), 3.06−2.96 (m, 1H), 2.84 (dd, 1H, J = 16.4, 4.4 Hz), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.5, 142.0, 136.5, 132.6, 132.4, 132.2, 130.1, 130.0, 129.1, 127.8, 125.1 (q, J = 286.5 Hz), 124.4, 124.3, 66.8 (q, J = 29.5 Hz), 36.2, 28.5, 20.4; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.05 (s, 3F); HRMS: calcd. for $C_{18}H_{14}NOF_3$ + Na: 340.0925; found: 340.0937.

5d: 44 mg, 70% yield; white solid; mp: 146−148 °C; IR (KBr): 2924, 2861, 1717, 1508, 1263, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 1H, J = 7.7 Hz), 7.90−7.83 (m, 2H), 7.64 (td, 1H, J = 7.6, 1.0 Hz), 7.56 (td, 1H, J = 7.6, 1.0 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.20 (t, 1H, J = 7.1 Hz), 4.86−4.74 (m, 1H), 3.65−3.51 (m, 1H), 2.93−2.78 (m, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.3, 142.1, 137.7, 134.0, 132.6, 132.2, 130.6, 130.1, 129.3, 126.3, 125.2, 125.1 (q, J = 288.0 Hz), 124.4, 124.3, 66.8 (q, J = 30.0 Hz), 35.5, 26.2, 20.1; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.02 (s, 3F); HRMS: calcd. for $C_{18}H_{14}NOF_3$ + H: 318.1106; found: 318.1093.

5e: 61 mg, 84% yield; white solid; IR (Neat): 2930, 1710, 1518, 1260, 1168, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H, J = 7.8 Hz), 7.88 (d, 1H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.6 Hz), 7.57 (t, 1H, J = 7.6 Hz), 7.39 (s, 1H), 6.63 (s, 1H), 4.73 (dd, 1H, J = 13.6, 7.0 Hz), 3.95 (s, 3H), 3.84 (s, 3H), 3.54 (dt, 1H, J = 12.7, 4.6 Hz), 3.06−2.94 (m, 1H), 2.78 (dd, 1H, J = 16.3, 4.6 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.5, 149.7, 147.9, 142.2, 132.6, 132.2, 130.1, 128.5, 125.1 (q, J = 287 Hz), 124.5, 123.8, 120.8, 112.1, 110.4, 66.3 (q, J = 28.9 Hz), 56.3, 55.9, 36.2, 28.5; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.19 (s, 3F); HRMS: calcd. for $C_{19}H_{16}NO_3F_3$ + H: 364.1161; found: 364.1149.

5f: 62 mg, 88% yield; pale yellow semisolid; IR (Neat): 2924, 2854, 1792, 1710, 1487, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 1H, J = 7.7 Hz), 7.88 (d, 1H, J = 7.7 Hz), 7.65 (td, 1H, J = 7.7, 1.0 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.40 (brs, 1H), 6.61 (s, 1H), 5.98 (d, 1H, J = 1.2 Hz), 5.93 (d, 1H, J = 1.2 Hz), 4.68 (dd, 1H, J = 13.5, 6.7 Hz), 3.52 (dt, 1H, J = 13.0, 4.5 Hz), 3.04−2.91 (m, 1H), 2.76 (dd, 1H, J = 16.2, 4.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.5, 148.3, 146.9, 142.0, 132.7, 132.1, 130.2, 129.7, 125.0 (q, J = 286.7 Hz), 124.4, 124.1, 121.9, 109.5, 107.3, 101.6, 66.8 (q, J = 30.1 Hz), 36.0, 29.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.23 (s, 3F); HRMS: calcd. for $C_{18}H_{12}NO_3F_3$ + Na: 370.0667; found: 370.0677.

5h: 43 mg, 64% yield; colorless solid; mp: 124−126 °C; IR (KBr): 2962, 1714, 1603, 1473, 1295, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03−7.94 (m, 2H), 7.91−7.86 (m, 1H), 7.66 (td, 1H, J = 7.6, 1.2 Hz), 7.63−7.56 (m, 2H), 7.20 (t, 1H, J = 8.0 Hz), 4.78 (dd, 1H, J = 13.9, 7.4 Hz), 3.61−3.52 (m, 1H), 3.09 (dd, 1H, J = 17.5, 4.7 Hz), 2.96−2.85 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.1, 141.5, 135.3, 133.5, 132.8, 132.1, 131.8, 130.4, 127.8, 126.7, 126.4, 124.9 (q, J = 285.7 Hz), 124.5, 124.3, 66.5, 35.4, 29.9; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −75.75 (s, 3F); HRMS: calcd. for $C_{17}H_{11}NOBrF_3$ + H: 382.0054; found: 382.0065.

5g: 52 mg, 68% yield; colorless solid; mp: 146−148 °C; IR (KBr): 2942, 1716, 1519, 1263, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, 1H, J = 7.7 Hz), 7.95−7.86 (m, 2H), 7.66 (td, 1H, J = 7.6, 1.0 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.41 (d, 1H, J = 7.8 Hz), 7.28 (t, 1H, J =

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7.8 Hz), 4.79 (dd, 1H, J = 13.8, 7.4 Hz), 3.56 (td, 1H, J = 12.9, 5.0 Hz), 3.12 (dd, 1H, J = 17.3, 4.8 Hz), 2.9−2.84 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.4, 141.8, 135.9, 134.2, 133.1, 132.4, 131.9, 130.7, 130.4, 127.7, 126.3, 125.2 (q, J = 285.6 Hz), 124.8, 124.6, 66.8 (q, J = 29.8 Hz), 35.5, 27.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.29 (s, 3F); HRMS: calcd. for $C_{17}H_{11}NOClF_3$ + H: 338.0560; found: 338.0560.

5j: 63 mg, 73% yield; colorless solid; mp: 158−160 °C; IR (KBr): 2924, 2861, 1717, 1633, 1508, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 7.7 Hz), 7.93 (s, 1H), 7.90 (d, 1H, J = 7.8 Hz), 7.70 (td, 1H, J = 7.6, 1.0 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.29 (dd, 1H, J = 8.2, 2.0 Hz), 7.14 (d, 1H, J = 8.2 Hz), 4.73 (dd, 1H, J = 13.5, 6.7 Hz), 3.55 (td, 1H, J = 13.1, 4.4 Hz), 3.07−2.93 (m, 1H), 2.87 (dd, 1H, J = 16.3, 4.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.3, 141.3, 134.0, 132.9, 132.6, 132.1, 131.4, 131.0, 130.4, 129.4, 127.5, 124.8 (q, J = 286.5 Hz), 124.5, 124.1, 66.5, 35.8, 28.3; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −76.07 (s, 3F); HRMS: calcd. for $C_{17}H_{11}NOClF_3$ + H: 338.0560; found: 338.0560.

5i: 47 mg, 69% yield; colorless solid; mp: 126−128 °C; IR (KBr): 2926, 2858, 1705, 1385, 1254, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04−7.96 (m, 2H), 7.89 (t, 2H, J = 6.9 Hz), 7.66 (td, 1H, J = 7.6, 1.0 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.04 (t, 1H, J = 7.8 Hz), 4.75 (dd, 1H, J = 13.9, 7.0 Hz), 3.62−3.51 (m, 1H), 3.05−2.82 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.1, 141.4, 140.3, 138.0, 132.8, 132.1, 131.5, 130.4, 128.2, 127.6, 124.9 (q, J = 288.3 Hz), 124.5, 124.3, 103.4, 66.6 (q, J = 30.1 Hz), 36.0, 35.7; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −75.67 (s, 3F); HRMS: calcd. for $C_{17}H_{11}NOIF_3$ + H: 429.9916; found: 429.9934.

5k: 54 mg, 86% yield; pale yellow liquid; IR (Neat): 2919, 2851,1705, 1517, 1265, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (brs, 1H), 6.61 (s, 1H), 4.38 (dd, 1H, J = 13.5, 7.0 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.34−3.22 (m, 1H), 2.97−2.64 (m, 4H), 2.51−2.39 (m, 1H), 2.22−2.08 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.0, 149.4, 148.1, 127.0, 126.8 (q, J = 288.4 Hz), 124.0, 111.5, 109.0, 64.9 (q, J = 27.9 Hz), 56.2, 55.9, 35.3, 30.4, 29.4, 27.2; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −78.25 (s, 3F); HRMS: calcd. for $C_{15}H_{16}NO_3F_3$ + H: 316.1161; found: 316.1153.

5l: 51 mg, 78% yield; colorless liquid; IR (Neat): 2919, 2851,1705, 1517, 1265, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 1H), 6.61 (s, 1H), 5.06 (dd, 1H, J = 13.2, 5.2 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.00 (td, 1H, J = 13.0, 3.3 Hz), 2.90−2.72 (m, 2H), 2.70−2.59 (m, 2H), 2.51−2.39 (m, 1H), 2.11−1.97 (m, 1H), 1.93−1.74 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.3, 149.0, 147.8, 128.1, 126.4 (q, J = 290.0 Hz), 124.6, 111.7, 108.9, 63.6 (q, J = 26.0 Hz), 56.2, 55.9, 36.3, 33.2, 31.2, 28.2, 16.6; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −70.60 (s, 3F); HRMS: calcd. for $C_{16}H_{18}NO_3F_3$ + H: 330.1317; found: 330.1327.

5n: 48 mg, 72% yield; colorless liquid; IR (Neat): 1739, 1460, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.82−7.77 (m, 1H), 7.72−7.68 (m, 1H), 7.65 (td, 1H, J = 7.4, 1.3 Hz), 7.61 (td, 1H, J = 7.4, 1.3 Hz), 7.36−7.26 (m, 4H), 4.51−4.43 (m, 1H), 4.43−4.37 (m, 1H), 4.36−4.30 (m, 1H), 3.37 (dd, 1H, J = 13.6, 6.2 Hz), 2.94 (dd, 1H, J = 13.6, 9.0 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.1, 140.4, 137.1, 133.9, 133.6 132.6, 131.9, 129.3, 129.0, 128.8, 127.0, 125.0, 124.1, 123.9 (q, J = 288.2 Hz), 97.7 (q, J = 33.5 Hz), 77.4, 58.4, 40.5; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −80.54 (s, 3F); HRMS: calcd. for $C_{18}H_{14}NO_2F_3$ + Na: 356.0874; found: 356.0891.

Synthesis of 7. The product **7** was isolated (245 mg, 93% yield) as a white solid from **6** employing the procedure developed for the synthesis of **2**. mp: 166−168 °C; IR (KBr): 3252, 2862, 1703, 1498, 1377, 1156, 763, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 1H, J = 7.4 Hz), 7.60 (td, 1H, J = 0.7, 7.48 Hz), 7.46 (t, 1H, J = 7.1 Hz), 7.37 (d, 1H, J = 7.4 Hz), 7.34−7.27 (m, 3H), 7.20−7.14 (m, 2H), 4.95 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.6, 140.2, 134.0, 133.4, 131.4, 131.2, 129.3, 128.7, 128.6, 124.1, 122.7 (q, J = 287.5 Hz), 89.2 (q, J = 32.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −80.30 (s, 3F); HRMS: calcd. for $C_{15}H_{10}NO_2F_3$ + H: 294.0742; found: 294.0728.

Synthesis of 9. Employing the acid-mediated cyclization procedure, **9** was isolated (43 mg, 62% yield) from **7** (1 equiv) and *N*-methylindole **8** (1 equiv). mp: 170−172 °C; IR (KBr): 2858, 1713, 1486, 1377, 1353, 1166, 712, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 7.4 Hz), 7.55 (td, 1H, J = 7.4, 0.9 Hz), 7.46 (td, 1H, J = 7.5, 1.2 Hz), 7.29 (d, 1H, J = 7.7 Hz), 7.24 (d, 1H, J = 8.2 Hz), 7.17−7.07 (m, 5H), 6.79−6.74 (m, 1H), 6.72−6.67 (m, 2H), 6.32 (d, 1H, J = 8.1 Hz), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.6, 142.7, 137.1, 135.7, 133.0, 132.0, 130.3, 130.1 (q, J = 3.3 Hz), 129.1, 128.8, 128.2, 125.7, 125.0 (q, J = 287.1 Hz), 124.8, 124.4, 122.6, 120.5, 119.7, 109.8, 104.9, 71.6 (q, J = 29.0 Hz), 33.3; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −72.68 (s, 3F); HRMS: calcd. for $C_{24}H_{17}N_2OF_3$ + H: 407.1371; found: 407.1386.

Synthesis of 11. Employing the acid-mediated cyclization procedure, **11** was isolated (65 mg, 92% yield) from **7** (1 equiv) and 1,3-dimethoxybenzene (1 equiv). mp: 182−184 °C; IR (KBr): 2941, 2842, 1702, 1607, 1360, 1164, 1039, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92−7.87 (m, 1H), 7.49−7.43 (m, 2H), 7.43−7.37 (m, 1H), 7.38−7.15 (m, 4H), 6.90−6.85 (m, 2H), 6.41 (dd, 1H, J = 8.8, 2.5 Hz), 6.33 (d, 1H, J = 2.5 Hz), 3.74 (s, 3H), 3.21 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.4, 161.8, 159.4, 144.0, 136.3, 133.0, 132.3, 130.2 (q, J = 3.7 Hz), 129.3, 128.9, 128.5, 127.9, 124.8 (q, J = 286.7 Hz), 123.7, 122.7, 113.7, 104.3, 100.3, 73.1 (q, J = 27.3 Hz), 55.5, 54.4; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −80.18 (s, 3F); HRMS: calcd. for $C_{23}H_{18}NO_3F_3$ + H: 414.1317; found: 414.1329.

General Procedure for the Synthesis of Trifluoromethylated Harmicine, Cripsine, and Related Compounds. Lactam **3** or **5** (0.13 mmol) was dissolved in dry THF (2 mL) under a N_2 atmosphere and cooled to 0 °C. Next, $LiAlH_4$ (15 mg, 0.40 mmol) was added portionwise; after the addition, the reaction mixture was heated at reflux for 4 h. The reaction mixture was cooled to rt, quenched with aqueous Na_2SO_4, stirred for 15 min at room temperature, and then filtered. The solid residue was washed with ethyl acetate, filtered, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the crude product by column chromatography using ethyl acetate/hexane as eluent afforded the reduced products in good yield.

12: 30 mg, 82% yield; pale yellow liquid; IR (Neat): 3418, 2939, 1458, 1323, 1295, 1179 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (brs, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.22 (td, 1H, J = 8.0, 1.0 Hz), 7.13 (td, 1H, J = 8.0, 1.0 Hz), 3.40−3.29 (m, 2H), 3.15−3.09 (m, 1H), 3.00−2.90 (m, 2H), 2.63−2.53 (m, 2H), 2.03−1.91 (m, 2H), 1.81−1.74 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.5, 130.4, 127.2 (q, J = 284.6 Hz), 126.5, 122.9, 119.8, 118.8, 111.6, 111.2, 63.8 (q, J = 28.3 Hz), 51.3, 44.2, 35.3, 23.8, 16.0; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −79.50 (s, 3F); HRMS: calcd. for $C_{15}H_{15}N_2F_3$ + H: 281.1266; found: 281.1254.

13: 32 mg, 80% yield; pale yellow liquid; IR (Neat): 2925, 2852, 1514, 1259, 1138, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (brs, 1H), 6.60 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.39 (ddd, 1H, J = 12.6, 8.4, 4.5 Hz), 3.28−2.21 (m, 1H), 2.94−2.76 (m, 4H), 2.73−2.61 (m, 2H), 2.10−1.95 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.5, 147.6, 129.5, 127.6 (q, J = 285.7 Hz), 126.4, 111.4, 110.9, 66.9 (q, J = 26.3 Hz), 56.2, 55.9, 54.0, 46.3, 36.9, 25.1, 23.7 ; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −79.02 (s, 3F); HRMS: calcd. for $C_{15}H_{18}NO_2F_3$ + H: 302.1368; found: 302.1381.

14: 35 mg, 75% yield; orange solid; mp: 124−126 °C; IR (KBr): 2933, 2361, 1518, 1464, 1261, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75−7.67 (m, 1H), 7.34−7.25 (m, 3H), 7.25−7.18 (m, 1H), 6.58 (s, 1H), 4.40 (d, 1H, J = 13.1 Hz), 4.27 (d, 1H, J = 13.1 Hz), 3.89 (s, 3H), 3.83 (s, 3H), 3.64−3.51 (m, 1H), 3.32−3.21 (m, 1H), 3.09 (ddd, 1H, J = 16.4, 11.9, 5.5 Hz), 2.48 (ddd, 1H, J = 16.4, 4.0, 1.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.8, 147.4, 140.1, 139.8, 131.0, 129.0, 128.6, 127.4, 126.7 (q, J = 286.2 Hz), 123.9, 122.9, 111.8, 111.2, 71.3 (q, J = 28.4 Hz), 56.2, 55.8, 43.6, 22.5; ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$): δ −75.82 (s, 3F); HRMS: calcd. for $C_{19}H_{18}NO_2F_3$ + H: 350.1368; found: 350.1363.

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■ ASSOCIATED CONTENT

Supporting Information

Supporting Information containing ^{1}H and ^{13}C NMR spectra of all the new compounds and crystallographic data of compound **3a** is provided. 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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