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Short Communication

Construction of pyrrole- and indole-fused CF_3-piperazine derivatives

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A B S T R A C T

A series of pyrrole- and indole-fused trifluoromethyl-functionalized piperazine derivatives were constructed in moderate to good yields with excellent chemoselectivities via a Pictet-Spengler reaction under mild and operationally simple conditions. The synthetic utility of this protocol was further extended by the facile preparation of indole-fused CF_3-1,4-diazocane and enantioenriched CF_3-piperazines via a vinylogous Pictet-Spengler reaction and an asymmetric Pictet-Spengler reaction, respectively.

1. Introduction

Piperzines are frequently found *N*-heterocyclic motifs within many biologically active natural products and medicinally relevant compounds [1]. As a result, significant attention has been devoted on the preparation of various structurally diversified paperzine derivatives in the past few decades [2]. In this context, the trifluoromethyl-functionalized piperzines have emerged as an attractive type of useful scaffolds in drug discovery owing to the unique CF_3 effect on the physicochemical and pharmaceutical properties of organic molecules [3–4]. For instance, it has been demonstrated that the introduction of a CF_3 group at amine's vicinal positions can potentially result in lower basicity, higher metabolic stability, and decreased acute toxicity [5]. However, the synthesis of CF_3-piperazine derivatives with increased molecular complexity, such as the fused variants, has remained as an unmet challenge. Indeed, to the best of our knowledge, only Nenajdenko and coworkers have reported the preparation of pyrrole-fused CF_3-piperazines via a Pictet-Spengler reaction (Scheme 1a) [6–7]. Despite the advance, the practicality of this method is largely restricted due to the length synthesis of starting materials, long reaction time, and limited substrate scope. Therefore, with our continuing interest in the chemistry of CF_3-containing heterocycles [8], herein we report the facile construction of both pyrrole- and indole-fused CF_3-piperazine derivatives via a Pictet-Spengler reaction under mild and operationally simple conditions (Scheme 1b). Furthermore, this approach has also been successfully extended to provide indole-fused CF_3-1,4-diazocane and enantioenriched CF_3-piperazines via a novel vinylogous Pictet-Spengler reaction and an asymmetric Pictet-Spengler reaction, respectively [9].

2. Results and discussion

On the basis of our precedent studies on the reaction development of trifluoroacetaldehyde methyl hemiacetal (TFMH **1**) [10], *N*-aminoethylpyrrole **2a** was chosen as the model substrate to react with TFMH under acidic conditions. Pleasingly, the desired CF_3-piperazine **3a** was obtained in 40% yield when acetic acid was employed as the catalyst at room temperature (Table 1, entry 1). Encouraged by this result, a series of Brønsted acids were then evaluated in this Pictet-Spengler reaction (entries 2–4), among which the best result was identified with trifluoroacetic acid (75% yield, entry 3) [11]. It should be noted that Lewis acids such as aluminium chloride or boron trifluoride diethyl etherate could also catalyze this transformation, albeit with low yields (entries 5 and 6). Further optimizations including changing the additive, solvent, catalyst loadings, or reaction temperature, resulted in no significant improvements (entries 7–17). Finally, gram-scale experiment was also conducted and smoothly produced **3a** in 70% yield (entry 18), thus illustrating the robust nature of this protocol.

With the optimized conditions in hand, the generality of this reaction was examined by varying substituents on the pyrrole ring. As shown in Scheme 2, 2-methyl, 2-ethyl, and 2,4-dimethyl-substituted *N*-aminoethylpyrroles all underwent the Pictet − Spengler reaction with TFMH uneventfully, thus giving rise to the corresponding CF_3-piperazines **3b** − **3d** in 63 − 77% yields. It should be noted that no formation of the undesired Friedel–Crafts side-product was observed for all the pyrrole-derived substrates. Notably, the indole core represents a privileged type of hetreocycles in natural products, pharmaceuticals, and materials [12]. However, the synthesis of indole-fused CF_3-piperazines

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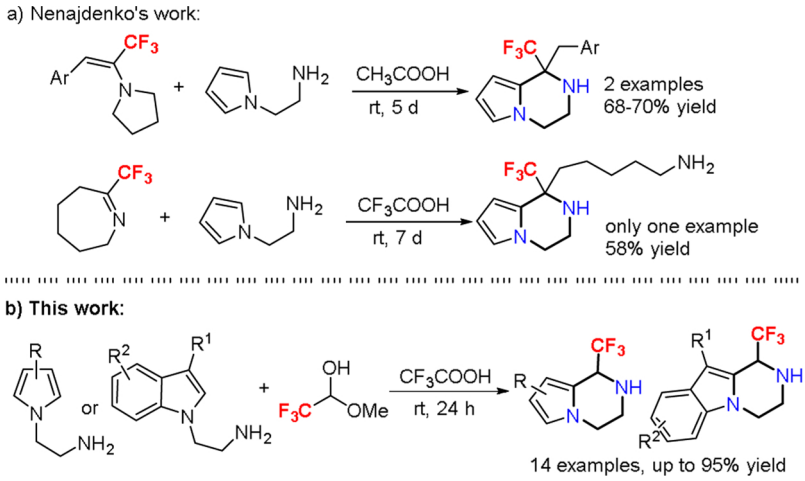
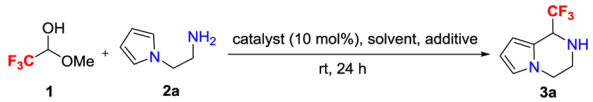


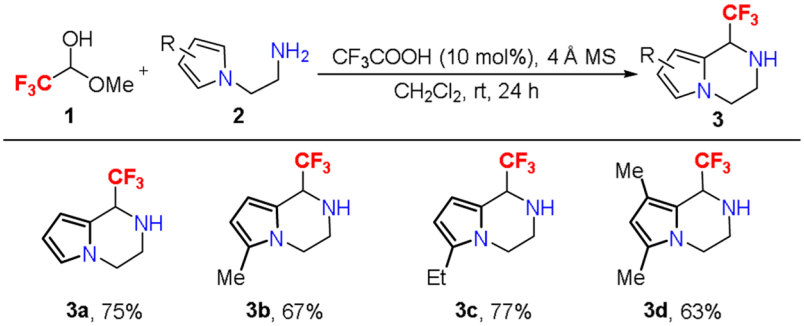
Scheme 1. Construction of CF_3-piperazine derivatives via the Pictet-Spengler reaction.

Table 1
Optimizations for the Pictet − Spengler reaction between *N*-aminoethylpyrrole **2a** and TFMH **1** [a].

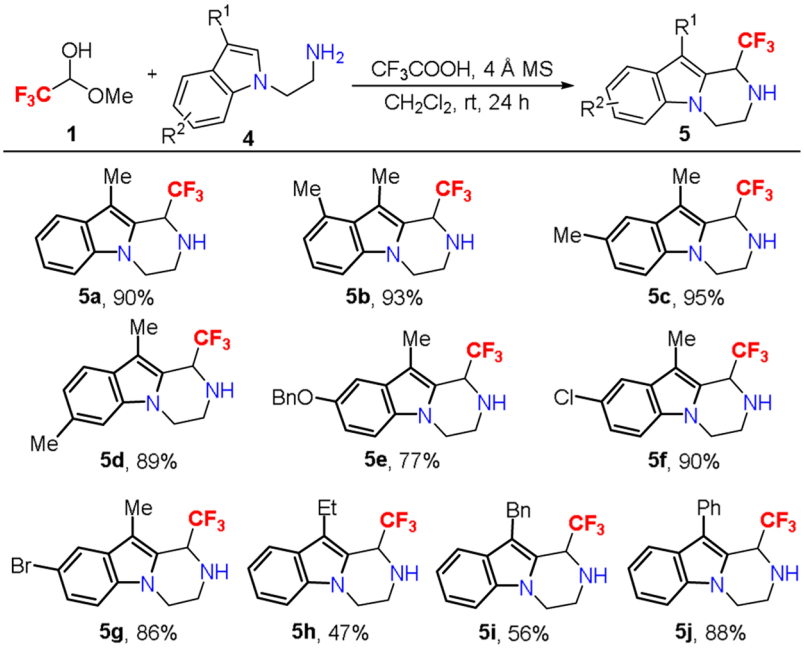


Entry	Catalyst	Solvent	Additive	Yield (%)[b]
1	CH_3COOH	CH_2Cl_2	4 Å MS	40
2	H_3PO_4	CH_2Cl_2	4 Å MS	70
3	CF_3COOH	CH_2Cl_2	4 Å MS	75
4	*p*-$MeC_6H_4SO_3H$	CH_2Cl_2	4 Å MS	39
5	$AlCl_3$	CH_2Cl_2	4 Å MS	29
6	BF_3•Et_2O	CH_2Cl_2	4 Å MS	28
7	CF_3COOH	CH_2Cl_2	Na_2SO_4	66
8	CF_3COOH	CH_2Cl_2	3 Å MS	56
9	CF_3COOH	CH_2Cl_2	5 Å MS	63
10	CF_3COOH	CH_2Cl_2	–	55
11	CF_3COOH	$CHCl_3$	4 Å MS	55
12	CF_3COOH	toluene	4 Å MS	59
13	CF_3COOH	THF	4 Å MS	55
14	CF_3COOH	EtOAc	4 Å MS	59
15[c]	CF_3COOH	CH_2Cl_2	4 Å MS	66
16[d]	CF_3COOH	CH_2Cl_2	4 Å MS	60
17[e]	CF_3COOH	CH_2Cl_2	4 Å MS	55
18[f]	CF_3COOH	CH_2Cl_2	4 Å MS	70

[a] Reaction conditions: **1** (1 mmol, 2 equiv), **2a** (0.5 mmol, 1 equiv), catalyst (10 mol%), and additive (250 mg) in indicated solvent (3 mL) at rt for 24 h.
[b] Isolated yield.
[c] catalyst (5 mol%).
[d] catalyst (20 mol%).
[e] 50 °C.
[f] 5 mmol scale of **2a** was employed.



Scheme 2. Synthesis of pyrrole-fused CF_3-piperazine derivatives.



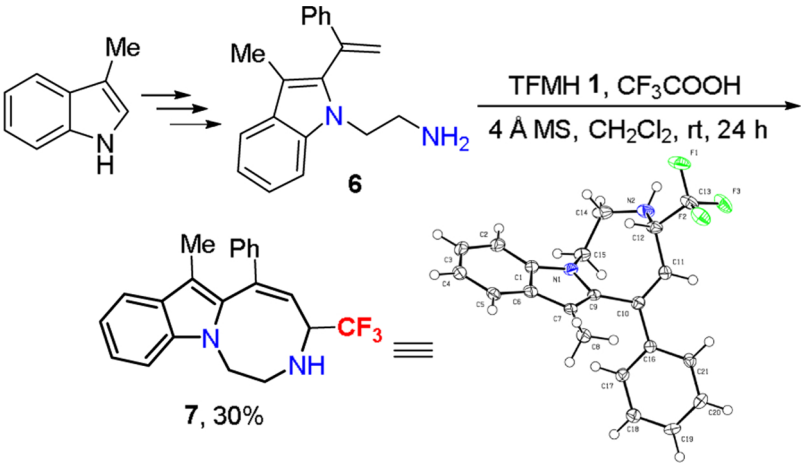
Scheme 3. Synthesis of indole-fused CF_3-piperazine derivatives.

haven't been reported until now. With this concern in mind, a series of *N*-aminoethylindoles were subsequently subjected to the aforementioned Pictet − Spengler reaction under otherwise identical conditions. To our great delight, a broad range of CF_3-containing indole-fused piperazine derivatives **5a − 5 j** were obtained in 47 − 95% yields (Scheme 3). For instance, electron-donating groups on the 3-methylindole motif at different positions rendered cyclization products in high yields with exclusive chemoselectivities (**5b − 5e**). The halogen-substituted substrates are also compatible in this transformation and produced compounds **5f** and **5 g** in 90% and 86% yield, respectively, thereby may offering new possibilities for downstream cross-coupling-type manipulations [13]. Furthermore, the indole partners bearing different substitution patterns at the 3-positions, including ethyl, benzyl, and phenyl, all proved to be viable substrates and delivered **5 h − 5 j** in decent to good yields with excellent chemoselectivities.

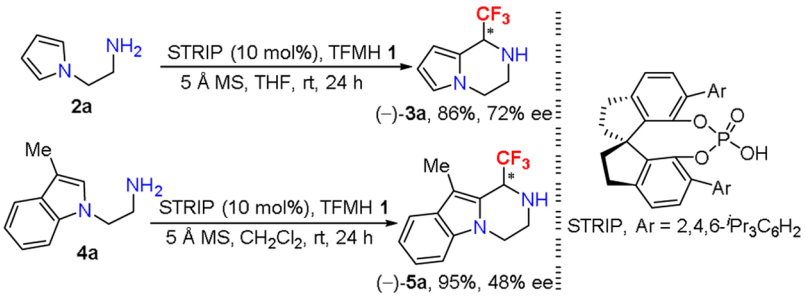
Subsequently, the synthetic utility of this method was further demonstrated by a novel vinylogous Pictet-Spengler reaction (Scheme 4). The *N*-aminoethyl-2-vinylindole **6** was prepared in a few steps from 3-methylindole according to know procedures [14]. Treatment of compound **6** with TFMH and trifluoroacetic acid at room temperature could smoothly furnish the indole-fused CF_3-1,4-diazocane **7**, albeit with plain yield. The molecular structure of this compound was unambiguously confirmed by X-ray crystallographic analysis [15].

Finally, a preliminary optimization on the enantioselective variant of this intramolecular Pictet-Spengler reaction was also conducted. To our delight, enantioenriched pyrrole-fused CF_3-piperazine **3a** could be afforded with 72% ee in an improved yield compared with the racemic version (86% vs 75%, Scheme 5) when 3,3′-bis(2,4,6-triisopropylphenyl)-substituted spirocyclic phosphoric acid (STRIP) was employed as the chiral Brønsted acid. The extension of this asymmetric protocol to the generation of enantioenriched indole-fused CF_3-piperazine **5a** was found to be with limited success (95%, 48% ee, Scheme 5), thus deserving further systematic evaluations. Nevertheless, these promising initial results highlight the high potential of this approach for the rapid construction of chiral CF_3-piperazine derivatives.

In conclusion, we have developed an efficient method for the construction of both pyrrole and indole-fused CF_3-piperazines from trifluoroacetaldehyde methyl hemiacetal and *N*-aminoethyl heterocyclic components. This facile protocol takes advantages of trifluoroacetic acid as a practical catalyst for the Pictet-Spengler reaction, featuring broad substrate scope and operational convenience. Notably, a novel vinylogous Pictet-Spengler reaction also proved workable and generated the



Scheme 4. Synthesis of indole-fused CF_3-1,4-diazocane via the vinylogous Pictet-Spengler reaction.



Scheme 5. Synthesis of enantioenriched CF_3-piperazine derivatives via enantioselective Pictet-Spengler reaction.

corresponding indole-fused CF_3-1,4-diazocane. Furthermore, two representative enantioenriched CF_3-piperazines were obtained via the chiral phosphoric acid-catalyzed asymmetric Pictet-Spengler reaction. Further investigations including the substrate scope expansion and mechanistic studies are ongoing in our laboratory, the results of which will be reported in due course.

3. Experimental section

3.1. General information

^{1}H, ^{13}C and ^{19}F were recorded on Bruker AV 400 MHz instrument at 400 MHz (^{1}H NMR), 101 MHz (^{13}C NMR), as well as 376 MHz (^{19}F NMR). Chemical shifts were reported in ppm down field from internal Me_4Si and external CCl_3F, respectively. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad). Coupling constants were reported in Hertz (Hz). MS were recorded on a VG ZABHS spectrometer with the ESI resource. High resolution mass spectrometry (HRMS) spectra were obtained on a Bruker miorOTOF-QII instrument. X-ray structural analysis was conducted on the Bruker APEX-II CCD instrument. Optical rotations were determined using an Autopol IV-T. HPLC analyses were carried out on a HewlettPackard Model HP 1200 instrument. Infrared spectroscopies (IR) were conducted on a bruker vertex70 instrument.

Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium/benzophenone prior to use; CH_2Cl_2 was distilled from CaH_2; All purchased reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm Qingdao Haiyang silica gel plates. Silica gel (200–300 mesh) (from Qingdao Haiyang Chem. Company, Ltd.) was used for flash chromatography. Various substituted 3-methyl-1*H*-indoles, 3-ethyl-1*H*-indole, 3-phenyl-1*H*-indole, 3-benzyl-1*H*-indole, aminoethyl pyrroles [16][7i] were prepared according to the reported procedures.

3.2. General Procedure for Synthesis of N-aminoethyl pyrroles 2 and N-aminoethyl indoles 4

To a solution of the corresponding pyrrole or indole derivative (10 mmol) in MeCN (30 ml) was added sodium hydroxide (2.00 g, 50 mmol) and tetrabutylamonium hydrogen sulfate (0.17 g, 0.5 mmol). After the solution was stirred at room temperature for 30 min, 2-chloroethylamine hydrochloride (1.39 g, 12 mmol) was added. Then the reaction mixture was refluxed for 24 h. The mixture was poured into water (100 mL), extracted with diethyl ether, dried under $MgSO_4$, and concentrated under reduced pressure to give a crude product. The crude was then purified by flash column chromatography on silica gel (eluted with petroleum ether / ethyl acetate = 1 : 1) to give the pure product.

3.2.1. 2-(3-ethyl-1H-inden-1-yl) ethan-1-amine (4 h)

yellow oil; 4.76 g; 85% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.9 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.29 – 7.21 (m, 1 H), 7.21 – 7.09 (m, 1 H), 6.95 (s, 1 H), 4.14 (t, J = 5.9 Hz, 2 H), 3.10 (t, J = 5.9 Hz, 2 H), 2.85 (q, J = 7.5 Hz, 2 H), 1.40 (t, J = 7.5 Hz, 3 H), 1.10 (s, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.6, 128.1, 124.6, 121.6, 119.3, 118.7, 117.7, 109.3, 49.4, 42.3, 18.3, 14.7. **HRMS** (ESI) found *m/z* 189.1386 $[M+H]^+$, calcd for $C_{12}H_{17}N_2$ 189.1392. **IR** (cm^{-1}): 2962, 2361, 1597, 1466, 1370, 1077, 737, 693 cm^{-1}.

3.2.2. 2-(1H-pyrrol-1-yl) ethan-1-amine (4i)

yellow oil; 0.86 g; 89% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.9 Hz, 1 H), 7.40 – 7.30 (m, 5 H), 7.30 – 7.19 (m, 3 H), 7.14 (t, J = 7.4 Hz, 1 H), 6.88 (s, 1 H), 4.17 (s, 2 H), 4.12 (t, J = 5.9 Hz, 3 H), 3.09 (t, J = 5.9 Hz, 2 H), 1.08 (s, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.4, 136.7, 128.8, 128.4, 128.2, 126.4, 126.0, 121.8, 119.5, 119.1, 114.7, 109.4, 49.5, 42.3, 31.6. **HRMS** (ESI) found *m/z* 251.1549 $[M+H]^+$, calcd for $C_{17}H_9N_2$ 251.1548. **IR** (cm^{-1}): 2902, 2361, 1466, 1331, 1074, 735, 699 cm^{-1}.

3.3. General procedure for the synthesis of pyrrole- and indole-fused CF_3-piperazine derivatives 3 and 5

To a 10 mL Schlenk flask equipped with a stirring bar was added aminoethyl pyrroles **2** or **4** (0.5 mmol, 1.0 equiv), trifluoroacetaldehyde methyl hemiacetal **1** (95 μL, 1.0 mmol, 2.0 equiv), 4 Å molecular sieves (250 mg), and CH_2Cl_2 (3.0 mL). Then, trifluoroacetic acid (7.4 μL, 0.05 mmol, unless otherwise noted) was added to the mixture. The resulting mixture was stirred at room temperature until the completion of the reaction (monitored by TLC). The mixture was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether / ethyl acetate = 10 / 1) to give the desired product **3** or **5**.

3.3.1. 1-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo [1,2-a] pyrazine (3a)

white solid; 71.3 mg; 75% yield; m.p.: 76 – 78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.64 (t, J = 2.4 Hz, 1 H), 6.21 – 6.18 (m, 1 H), 6.17 – 6.16 (m, 1 H), 4.62 (q, J = 7.6 Hz, 1 H), 4.03 – 3.89 (m, 1 H), 3.45 – 3.39 (m, 1 H), 3.23 – 3.13 (m, 1 H), 1.97 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.56 (d, J = 7.6 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 125.5 (q, J = 281.9 Hz), 120.6, 119.5, 108.4, 106.8, 54.3 (q, J = 30.4 Hz), 45.4, 41.1. **HRMS** (ESI) found *m/z* 191.0800 $[M+H]^+$, calcd for $C_8H_{10}N_2F_3$ 191.0796. **IR** (cm^{-1}): 2360, 1267, 1158, 1115, 1076, 847, 755, 725, 675 cm^{-1}.

3.3.2. 6-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo [1,2-a] pyrazine (3b)

yellow solid; 68.4 mg; 67% yield; m.p.: 52–53 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.10 – 6.06 (m, 1 H), 5.91 (d, J = 3.5 Hz, 1 H), 4.60 (q, J = 7.6 Hz, 1 H), 3.85 – 3.79 (m, 1 H), 3.77 – 3.69 (m, 1 H), 3.47 – 3.37 (m, 1 H), 3.24 – 3.13 (m, 1 H), 2.20 (s, 3 H), 2.04 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.51 (d, J = 7.6 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 128.5, 125.6 (q, J = 282.4 Hz), 118.4, 106.33, 106.0 (d, J = 1.5 Hz), 54.4 (q, J = 30.4 Hz), 42.6, 40.9, 11.6. **HRMS** (ESI) found *m/z* 205.0951 $[M+H]^+$, calcd for $C_9H_{12}N_2F_3$ 205.0953. **IR** (cm^{-1}): 2361, 1266, 1156, 1115, 1086, 1060, 1026, 912, 852, 754, 722, 682, 625 cm^{-1}.

*3.3.3. 6-ethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo [1,2-a] pyrazine (**3c**)*

yellow solid; 84.0 mg; 77% yield; m.p.: 39–40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 5.96 (d, J = 2.9 Hz, 1 H), 4.63 (q, J = 7.5 Hz, 1 H), 3.90 – 3.80 (m, 1 H), 3.80 – 3.72 (m, 1 H), 3.49 – 3.35 (m, 1 H), 3.26 – 3.14 (m, 1 H), 2.57 (q, J = 7.4 Hz, 2 H), 2.10 (s, 1 H), 1.28 (t, J = 7.4 Hz, 3 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -75.47 (d, J = 7.5 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.8, 125.6 (q, J = 282.0 Hz), 118.5, 105.9 (d, J = 1.4 Hz), 104.5, 54.4 (q, J = 30.2 Hz), 42.6, 40.9, 19.2, 12.7. **HRMS** (ESI) found m/z 219.1119 $[M+H]^+$, calcd for $C_{10}H_{14}N_2F_3$ 219.1109. **IR** (cm^{-1}): 2360, 1265, 1157, 1130, 1090, 1061, 1040, 910, 854, 754, 723, 682, 625 cm^{-1}.

*3.3.4. 6,8-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo [1,2-a] pyrazine (**3d**)*

yellow solid; 68.7 mg; 63% yield; m.p.: 39–40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (s, 1 H), 4.50 (q, J = 8.0 Hz, 1 H), 3.85 – 3.79 (m, 1 H), 3.69 – 3.59 (m, 1 H), 3.52 – 3.43 (m, 1 H), 2.16 (s, 3 H), 2.01 (s, 3 H), 0.83 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.58 (d, J = 7.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 128.7, 126.5 (q, J = 285.8 Hz), 116.7, 114.9, 112.4, 108.5, 52.5 (q, J = 29.9 Hz), 42.5, 39.6, 11.5. **HRMS** (ESI) found m/z 219.1117 $[M+H]^+$, calcd for $C_{10}H_{14}N_2F_3$ 219.1109. **IR** (cm^{-1}): 2360, 1266, 1115, 1085, 1059, 1026, 911, 852, 755,721, 682, 625 cm^{-1}.

*3.3.5. 10-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5a**)*

white solid; 114.4 mg; 90% yield; m.p.: 97–98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.9 Hz, 1 H), 7.23 (d, J = 8.1 Hz, 1 H), 7.20 – 7.14 (m, 1 H), 7.12 – 7.04 (m, 1 H), 4.67 (q, J = 8.1 Hz, 1 H), 4.18 – 4.10 (m, 1 H), 3.81 – 3.71 (m, 1 H), 3.65 – 3.42 (m, 1 H), 3.27 – 3.09 (m, 1 H), 2.22 (s, 3 H), 1.97 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.42 (d, J = 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1, 128.6, 126.3 (q, J = 286.5 Hz), 123.2, 122.2, 119.9, 119.1, 110.2, 109.1, 52.7 (q, J = 29.9 Hz), 42.5, 39.3, 9.0. **HRMS** (ESI) found m/z 255.1120 $[M+H]^+$, calcd for $C_{13}H_{14}N_2F_3$ 255.1109. **IR** (cm^{-1}): 2360, 1451, 1319, 1255, 1136, 1082, 1011, 966, 883, 748, 684, 624, 543 cm^{-1}.

*3.3.6. 9,10-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5b**)*

white solid; 124.8 mg; 93% yield; m.p.: 136–137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2 H), 6.90 – 6.82 (m, 1 H), 4.74 (q, J = 8.1 Hz, 1 H), 4.21 – 4.13 (m, 1 H), 3.84 – 3.74 (m, 1 H), 3.71 – 3.57 (m, 1 H), 3.29 – 3.20 (m, 1 H), 2.74 (s, 3 H), 2.47 (s, 2 H), 2.27 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.30 (d, J = 7.7 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 131.8, 129.2 (q, J = 286.5 Hz), 126.9, 123.1, 122.3, 121.6, 111.1, 107.1, 52.4 (q, J = 29.8 Hz), 42.5, 39.3, 20.6, 12.0 (q, J = 2.2 Hz). **HRMS** (ESI) found m/z 269.1277 $[M+H]^+$, calcd for $C_{14}H_{16}N_2F_3$ 269.1266. **IR** (cm^{-1}): 2361, 1307, 1255, 1165, 1128, 1084, 861, 774, 748, 699, 649 cm^{-1}.

*3.3.7. 8,10-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5c**)*

white solid; 127.4 mg; 95% yield; m.p.: 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 7.19 (d, J = 8.3 Hz, 1 H), 7.07 (dd, J = 8.3, 1.2 Hz, 1 H), 4.73 (q, J = 8.2 Hz, 1 H), 4.21 – 4.14 (m, 1 H), 3.86 – 3.75 (m, 1 H), 3.68 – 3.58 (m, 1 H), 3.29 – 3.18 (m, 1 H), 2.47 (s, 3 H), 2.26 (s, 3 H), 1.57 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.46 (d, J = 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 129.2, 128.8, 126.4 (q, J = 286.4 Hz), 123.8, 123.3, 118.8, 109.7, 108.9, 52.7 (q, J = 30.0 Hz), 42.6, 39.4, 21.7, 9.0 (q, J = 2.2 Hz). **HRMS** (ESI) found m/z 269.1278 $[M+H]^+$, calcd for $C_{14}H_{16}N_2F_3$ 269.1266. **IR** (cm^{-1}): 2969, 2360, 1343, 1247, 1116, 794, 702, 575 cm^{-1}.

*3.3.8. 7,10-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5d**)*

white solid; 119.4 mg; 89% yield; m.p.: 71–72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 1 H), 7.09 (s, 1 H), 6.99 (d, J = 7.5 Hz, 1 H), 4.72 (q, J = 8.1 Hz, 1 H), 4.20 – 4.12 (m, 1 H), 3.84 – 3.75 (m, 1 H), 3.68 – 3.57 (m, 1 H), 3.28 – 3.20 (m, 1 H), 2.50 (s, 3 H), 2.26 (s, 3 H), 1.57 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.54 (d, J = 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.6, 132.1, 126.4 (q, J = 286.7 Hz), 126.5, 122.4, 121.6, 118.8, 110.0, 109.2, 52.7 (q, J = 30.0 Hz), 42.5, 39.4, 22.0, 9.0 (q, J = 2.3 Hz). **HRMS** (ESI) found m/z 269.1276 $[M+H]^+$, calcd for $C_{14}H_{16}N_2F_3$ 269.1266. **IR** (cm^{-1}): 2360, 1456, 1343, 1303, 1247, 1116, 793, 634, 576 cm^{-1}.

*3.3.9. 8-(benzyloxy)-10-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5e**)*

white solid; 138.7 mg; 77% yield; m.p.: 72–74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3 Hz, 2 H), 7.44 (t, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.2 Hz, 1 H), 7.22 (d, J = 8.8 Hz, 1 H), 7.17 (d, J = 1.9 Hz, 1 H), 7.03 (dd, J = 8.7, 2.1 Hz, 1 H), 5.17 (s, 2 H), 4.72 (q, J = 8.1 Hz, 1 H), 4.20 – 4.05 (m, 1 H), 3.83 – 3.70 (m, 1 H), 3.69 – 3.56 (m, 1 H), 3.22 (d, J = 12.3 Hz, 1 H), 2.29 (s, 3 H), 2.24 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.32 (d, J = 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 137.8, 132.7, 128.8, 128.7, 127.9, 127.7, 126.3 (q, J = 287.2 Hz), 123.9, 113.0, 109.9, 109.7, 102.7, 71.2, 52.6 (q, J = 30.0 Hz), 42.5, 39.2, 9.0 (q, J = 2.3 Hz). **HRMS** (ESI) found m/z 361.1534 $[M+H]^+$, calcd for $C_{20}H_{20}N_2OF_3$ 361.1528. **IR** (cm^{-1}): 2360, 1453, 1344, 1255, 1118, 1023, 933, 832, 796, 731, 695 cm^{-1}.

*3.3.10. 8-chloro-10-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5f**)*

0.5 equivalent of trifluoroacetic acid (18 μL, 0.25 mmol) was employed for the preparation of this compound; white solid; 129.9 mg; 90% yield; m.p.: 121–122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.22 – 7.13 (m, 2 H), 4.73 (q, J = 7.8 Hz, 1 H), 4.18 – 4.11 (m, 1 H), 3.88 – 3.72 (m, 1 H), 3.69 – 3.57 (m, 1 H), 3.26 (d, J = 11.9 Hz, 1 H), 2.30 (s, 1 H), 2.25 (s, 3 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.32 (d, J = 8.0 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.5, 129.6, 126.2 (q, J = 286.6 Hz), 125.6, 124.6, 122.5, 118.7, 110.1, 109.8, 52.7 (q, J = 30.1 Hz), 42.6, 39.1, 8.9 (q, J = 2.3 Hz). **HRMS** (ESI) found m/z 289.0733 $[M+H]^+$, calcd for $C_{13}H_{13}N_2F_3Cl$ 289.0719. **IR** (cm^{-1}): 2361, 1452, 1247, 1117, 865, 792, 668 cm^{-1}.

*3.3.11. 8-bromo-10-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5 g**)*

0.5 equivalent of trifluoroacetic acid (18 μL, 0.25 mmol) was employed for the preparation of this compound; white solid; 143.3 mg; 86% yield; m.p.: 114–115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 1.5 Hz, 1 H), 7.31 (dd, J = 8.6, 1.8 Hz, 1 H), 7.16 (d, J = 8.6 Hz, 1 H), 4.73 (q, J = 8.1 Hz, 1 H), 4.24 – 4.09 (m, 1 H), 3.87 – 3.76 (m, 1 H), 3.68 – 3.57 (m, 1 H), 3.26 (d, J = 12.3 Hz, 1 H), 2.30 (s, 1 H), 2.24 (s, 3 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.33 (d, J = 7.8 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 130.2, 126.2 (q, J = 287.9 Hz). 125.0, 124.4, 121.8, 113.1, 110.6, 109.8, 52.7 (q, J = 30.1 Hz), 42.6, 39.1, 8.9 (q, J = 2.2 Hz). **HRMS** (ESI) found m/z 355.0035 $[M + Na]^+$, calcd for $C_{13}H_{12}BrN_2F_3$ Na 355.0028. **IR** (cm^{-1}): 2967, 2360, 1450, 1337, 1244, 1115, 1092, 913, 867, 824, 791, 717, 657, 605 cm^{-1}.

*3.3.12. 10-ethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5 h**)*

0.5 equivalent of trifluoroacetic acid (18 μL, 0.25 mmol) was employed for the preparation of this compound; yellow oil; 63.0 mg; 47% yield; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 1 H), 7.33 – 7.19 (m, 2 H), 7.18 – 7.10 (m, 1 H), 4.75 (q, J = 8.2 Hz, 1 H), 4.23 – 4.11 (m, 1 H), 3.87 – 3.76 (m, 1 H), 3.70 – 3.50 (m, 1 H), 3.22 (d, J = 12.6 Hz, 1 H), 2.92 – 2.63 (m, 2 H), 2.37 (s, 1 H), 1.28 (t, J = 7.5 Hz, 3 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.52 (d, J = 8.2 Hz). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 137.5, 127.7, 126.0 (q, J = 286.5 Hz), 122.5, 122.2, 119.8, 119.7, 116.8, 109.3, 52.7 (q, J = 29.9 Hz), 42.5, 39.2, 17.9, 14.9. **HRMS** (ESI) found *m/z* 291.1085 $[M + Na]^+$, calcd for $C_{14}H_{15}F_3N_2Na$ 291.1080. **IR** (cm^{-1}): 2968, 2360, 1453, 1350, 1255, 1119, 741 cm^{-1}.

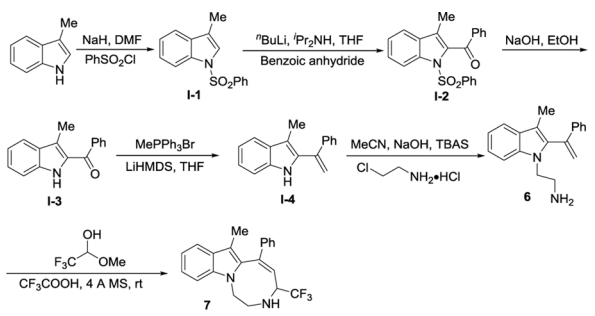
*3.3.13. 10-benzyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5i**)*

white solid; 92.5 mg; 56% yield; m.p.: 90–92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 1 H), 7.26 – 7.21 (m, 3 H), 7.21 – 7.14 (m, 3 H), 7.10 – 7.03 (m, 1 H), 4.67 (q, J = 8.1 Hz, 1 H), 4.31 – 4.21 (m, 1 H), 4.19 – 4.08 (m, 2 H), 3.96 – 3.87 (m, 1 H), 3.70 – 3.58 (m, 1 H), 3.29 – 3.21 (m, 1 H), 2.27 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -70.94 (d, J = 8.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.6, 137.3, 128.6, 128.5, 128.1, 126.2 (q, J = 286.6 Hz).126.1, 124.2, 122.3, 120.1, 119.9, 113.1, 109.2, 52.7 (q, J = 30.0 Hz), 42.5, 39.1, 30.2 (q, J = 2.2 Hz). **HRMS** (ESI) found *m/z* 331.1429 $[M+H]^+$, calcd for $C_{19}H_{18}N_2F_3$ 331.1422. **IR** (cm^{-1}): 2361, 1307, 1255, 1165, 1128, 1084, 861, 774, 748, 699, 649 cm^{-1}.

*3.3.14. -phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (**5 j**)*

0.5 equivalent of trifluoroacetic acid (18 µL, 0.25 mmol) was employed for the preparation of this compound; white solid; 139.2 mg; 88% yield; m.p.: 195–196 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 1 H), 7.46 (d, J = 4.2 Hz, 4 H), 7.42 – 7.27 (m, 3 H), 7.18 (t, J = 7.4 Hz, 1 H), 5.08 (q, J = 7.9 Hz, 1 H), 4.35 – 4.26 (m, 1 H), 4.09 – 3.97 (m, 1 H), 3.74 – 3.62 (m, 1 H), 3.32 (d, J = 12.5 Hz, 1 H), 2.27 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.36 (d, J = 7.9 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9, 134.7, 129.7, 128.9, 127.7, 126.8, 126.0 (q, J = 286.5 Hz). 123.2, 122.7, 120.7, 119.9, 117.12, 109.2, 52.6 (q, J = 30.1 Hz), 42.5, 39.3. **HRMS** (ESI) found *m/z* 317.1274 $[M+H]^+$, calcd for $C_{18}H_{16}N_2F_3$ 317.1266. **IR** (cm^{-1}): 2361, 1452, 1323, 1255, 1178, 1150, 1121, 1011, 889, 766, 750, 628, 565 cm^{-1}.

3.4. Synthesis of indole-fused CF_3-1,4-diazocane 7



Sodium hydride (60% dispersion in mineral oil, 1.3 g, 33 mmol) was added portionwise to a solution of 3-methylindole (4 g, 30 mmol) in DMF (50 mL), keeping the temperature below 30 °C. After stirring for 15 min at room temperature, a solution of phenylsulphonyl chloride (4.7 mL, 37 mmol) in DMF (20 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, then the solvent was evaporated under vacuo. The residue was quenched with water and extracted exhaustively over methylene dichloride. The combined organic layer was dried over sodium sulphate, then the solvent was removed under reduced pressure. The crude residue was purified by column chromatograph on silica gel (eluted with methylene dichloride / hexane = 1 / 1) to give the pure product 1-(phenylsulphonyl)-3 methylindole **I-1** (86% yield).

To a solution of LDA [prepared from diisopropylamine (3.89 g, 38.5 mmol) and ^{n}BuLi (25.7 mL of 1.5 M hexane solution, 38.5 mmol) in THF] was added a solution of 1-(phenylsulphonyl)-3 methylindole **I-1** (9.5 g, 35 mmol) in THF (60 mL) under ice cooling. The mixture was stirred at room temperature for 1 h and then a solution of benzoic anhydride (9.5 g, 42 mmol) in THF (60–100 mL) was added at −78 °C. The mixture was gradually warmed to room temperature. After the stirring had been continued at the same temperature for 10–14 h, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated to give (3-methyl-1-(phenylsulfonyl)-1*H*-indol-2-yl)(phenyl)-methanone **I-2** (52% yield).

A mixture of the obtained material **I-2**, 10% NaOH (30 mL), and ethanol (100 mL) was refluxed for 14 h. The solvent was evaporated and the resulting residue was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated to give (3-methyl-1*H*-indol-2-yl) (phenyl) methanone **I-3** (67% yield).

To a stirred solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (3.93 g, 11 mmol) and LiHMDS (10.67 mL of 1.0 M hexane solution, 11 mmol) in THF under ice cooling] was added a solution of **I-3** (9.4 mmol) in THF (30–60 mL) under ice cooling. The mixture was warmed to room temperature and kept under stirring for 14 h at the same temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4. The solvent was evaporated to give **I-4** (32% yield).

To a solution of previously prepared 3-methyl-2-(1-phenylvinyl)-1*H*-indole **I-4** (3 mmol) in MeCN (10 mL) was added sodium hydroxide (0.60 g, 15 mmol) and tetrabutylamonium hydrogen sulfate (TBAS, 51 mg, 0.15 mmol). After the solution was stirred at room temperature for 30 min, 2-chloroethylamine hydrochloride (0.42 g, 3.6 mmol) was added. Then the reaction mixture was refluxed for 24 h. The mixture was poured into water (100 mL), then extracted with ether, dried under $MgSO_4$ and concentrated under reduced pressure to give a crude product. The crude was then purified by flash column chromatography on silica gel (eluted with petroleum ether / ethyl acetate = 1 : 1) to give the pure product 2-(3-methyl-2-(1-phenylvinyl)-1*H*-indol-1-yl)ethan-1-amine **6** (93% yield).

To a 10 mL Schlenk flask equipped with a stirring bar was added 2-(3-methyl-2-(1-phenylvinyl)-1*H*-indol-1-yl) ethan-1-amine **6** (0.5 mmol, 1.0 equiv), trifluoroacetaldehyde methyl hemiacetal **1** (95 µL, 1.0 mmol, 2.0 equiv), 4 Å molecular sieves (250 mg), and CH_2Cl_2 (3.0 mL). Then, trifluoroacetic acid (22 µL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred at room temperature until the completion of the reaction (monitored by TLC, 24 h). Concentration under vacuum, and the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether / ethyl acetate = 10 / 1) to give the desired product **7**.

*3.4.1. 2-(3-methyl-2-(1-phenylvinyl)-1H-indol-1-yl) ethan-1-amine (**6**)*

yellow solid; 0.8 g; 93% yield; m.p.: 64–65 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 1 H), 7.49 – 7.36 (m, 7 H), 7.35 – 7.28 (m, 1 H), 6.21 (d, J = 1.4 Hz, 1 H), 5.59 (d, J = 1.4 Hz, 1 H), 3.97 (t, J = 6.6 Hz, 2 H), 2.92 (t, J = 6.6 Hz, 2 H), 2.49 (s, 3 H), 0.93 (s, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.1, 139.7, 136.6, 136.6, 128.6, 128.5, 128.2, 126.4, 121.8, 119.4, 119.1, 119.0, 110.2, 109.4, 47.2, 42.0, 9.3. **HRMS** (ESI) found *m/z* 277.1696 $[M+H]^+$, calcd for $C_{19}H_{20}N_2$ 277.1699. **IR** (cm^{-1}): 2360, 1680, 669, 755 cm^{-1}.

*3.4.2. (Z)-7-methyl-6-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydro- [1,4] diazocino [1,8-a] indole (**7**)*

white solid; 55.0 mg; 30% yield; m.p.: 167–168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 1 H), 7.41 – 7.27 (m, 7 H), 7.24 – 7.18 (m, 1 H), 6.42 (d, J = 9.2 Hz, 1 H), 4.52 (dd, J = 15.3, 4.0 Hz, 1 H), 3.97 (dd, J = 15.4, 10.5 Hz, 1 H), 3.46 (dd, J = 14.9, 4.1 Hz, 1 H), 3.39 – 3.26 (m, 1 H), 3.00 (dd, J = 14.8, 10.6 Hz, 1 H), 1.94 (s, 3 H), 1.61 (s, 1 H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -76.65 (d, J = 7.6 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.2, 137.7, 135.9, 133.4, 128.6, 128.3, 127.1, 125.3 (q, J = 280.8 Hz), 125.0, 122.3, 119.7, 119.1, 110.1,

109.0, 57.9 (q, J = 30.3 Hz), 48.6, 47.8, 9.3. **HRMS** (ESI) found m/z 357.1576 $[M+H]^+$, calcd for $C_{21}H_{20}F_3N_2$ 357.1573. **IR** (cm^{-1}): 2919, 2360, 1444, 1349, 1258, 1166, 1121, 1088, 967, 878, 792, 747, 720, 698, 570 cm^{-1}.

3.5. Synthesis of enantioenriched pyrrole- and indole-fused CF_3-piperazine 3a and 5a

To a 10 mL Schlenk flask equipped with a stirring bar was added aminoethyl pyrroles **2a** or **4a** (0.5 mmol, 1.0 equiv), trifluoroacetaldehyde methyl hemiacetal **1** (95 μL, 1.0 mmol, 2.0 equiv), 5 Å molecular sieves (250 mg), STRIP (36 mg, 0.05 mmol). Then, THF or CH_2Cl_2 (3.0 mL) was added to the mixture. The resulting mixture was stirred at room temperature until the completion of the reaction (monitored by TLC). The mixture was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (eluted with petroleum ether / ethyl acetate = 10 / 1) to give the desired product (–)-**3a** or (–)-**5a**.

3.5.1. (–)-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo [1,2-a] pyrazine ((–)-3a)

yellow solid; 81.8 mg; 86% yield; 72% ee; [determined by **HPLC** analysis Daicel Chirapak AD-H, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_1 = 8.2 min (major) and t_2 = 11.3 min (minor)]. $[\alpha]_D^{20}$ –29.6 (*c* 1.0, CH_2Cl_2).

3.5.2. (–)-10-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole ((–)5a)

yellow solid; 120.8 mg; 95% yield; 48% ee; [determined by **HPLC** analysis Daicel Chirapak AD-H, *n*-hexane/*i*-PrOH = 80/20, 254 nm UV detector, 1.0 mL/min, t_1 = 7.2 min (major) and t_2 = 10.2 min (minor)]. $[\alpha]_D^{20}$ –31.8 (*c* 1.0, CH_2Cl_2).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2019.109361.

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