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# Diastereoselective Friedel–Crafts reaction of α-trifluoromethyl imines derived from chiral amines

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**Abstract**—The Friedel–Crafts reactions of chiral *N*-(2,2,2-trifluoroethylidene)-1-arylethylamines **1a** and **1b** with various electron-rich aromatic compounds were examined. The reactions proceeded readily at room temperature in the presence of $BF_3{\cdot}Et_2O$. Substituted products **2**–**12** were obtained in low to very high stereoselectivities (up to 100% d.e.). The absolute configuration of compound **12** was determined by X-ray analysis. Moreover, the chiral auxiliary from compounds **3** and **12** was selectively removed by palladium-catalyzed hydrogenolysis. 

## 1. Introduction

The development of diastereo- and enantioselective synthetic methods for the preparation of amines remains an important goal in modern organic synthesis and various methods have been investigated,[1] with the addition of nucleophiles to imines being one of the most important.[2] Nucleophilic addition of some organometallic reagents to an imine bearing a chiral auxiliary affords the amine in high stereoselectivity (>99% d.e).[3] The inexpensive and commercially available optically active 1-phenylethylamine and 1-(1-naphthyl)ethylamine are widely used and efficient chiral auxiliaries.[4]

α-Trifluoromethylated amines are important building blocks for pharmaceutical research due to their unusual physical, chemical and biological properties.[5] To date, literature reports regarding the preparation of α-trifluoromethylated amines mainly involve (1) the reductive amination of α-trifluoromethylated ketones;[6] (2) the 1,3-hydrogen shift of *N*-benzyl perfluroalkylated imines;[7] (3) ene reactions of *N*-tosyl trifluoromethylated imines[8] and (4) nucleophilic additions of trimethyl(trifluoromethyl)silane to nitrones,[9] imines[10] and *N*-tosyl aldimines.[11] In addition, trifluoroacetimidoyl halides are very useful in preparing α-trifluoromethylated amine derivatives.[12]

Because of its importance in the drug industry, the direct asymmetric synthesis of chiral α-trifluoromethylated amines is still of great interest. Some of the main procedures developed recently are the asymmetric nucleophilic addition of chiral sulfoxides to *N*-anisyl α-trifluoromethyl imines,[13] the enantioselective 1,3-hydrogen shift of perfluroalkylated imines bearing a chiral 1-phenylethyl group[14] and the stereoselective nucleophilic addition of $TMSCF_3$ to chiral *N*-(*tert*-butylsulfinyl)imines.[15] In addition, the enzymatic resolution of (±)-1-phenyl-2,2,2-trifluoroethyamine has been reported.[16]

In contrast to the considerable progress with methodologies for nucleophilic additions to imines, there have been only very few reports regarding the reaction of aromatic compounds with imines, according to our knowledge, only the Cu(I)-catalyzed enantioselective substitution of pyrrole, indole and *N*,*N*-dimethylanilines with *N*-tosylimino or *N*-ethoxycarbonylimino esters of ethyl glyoxylate has been reported.[17] Although the Friedel–Crafts reaction with hexafluoroisopropylideneimine, was first reported in 1968,[18] the reaction has a narrow spectrum of application because of the vigorous reaction conditions. Our recent work demonstrated that *N*-alkyl α-trifluoromethylated imines are reactive enough to undergo $BF_3$-catalyzed Friedel–Crafts reaction with various electron-rich heteroaromatic compounds and benzene derivatives at room temperature.[19] We therefore realized that it is possible to directly synthesize chiral 1-aryl-2,2,2-trifluoroethylamines by using α-trifluoromethylated imines bearing a chiral auxilliary. In the study reported herein, we carried out the Friedel–Crafts reaction by choosing chiral imine **1**, which is useful in the preparation of α-trifluoromethylated amino acids,[20] as the starting material. Subse-

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quent experiments clearly showed that the Friedel–Crafts reaction with chiral imine **1** is an efficient way to prepare *N*-alkyl 1-aryl-2,2,2-trifluoroethylamines with high diastereoselectivity. Our new preparative method also has the advantage of directly introducing trifluoromethyl and amine functional groups into the aromatic compound stereoselectively at the same time.

## 2. Results and discussion

Chiral imines **1a** and **1b** were prepared by refluxing trifluoroacetaldehyde ethyl hemiacetal and (*S*)-1-phenylethylamine or (*R*)-1-(1-naphthyl)ethylamine in toluene. The imines were easily obtained by removal of the solvent under reduced pressure and were used without purification.

The reactions of chiral imine **1** with various aromatic compounds were examined in the presence of $BF_3{\cdot}Et_2O$ because the α-trifluoromethylimine did not react with aromatic compounds such as indole in the absence of a Lewis acid. The results are given in Table 1.

The reaction of **1a** with indole proceeded smoothly in $CH_2Cl_2$ at 10°C, giving the substituted product **2** (Scheme 1). The yield of **2** depended markedly on the molar ratio of indole to $BF_3{\cdot}Et_2O$, a high yield of **2** being obtained with an addition about 50 mol% of $BF_3{\cdot}Et_2O$ (entries 1–3). The same conditions were used for the corresponding reaction of reactive pyrrole and (*N*,*N*-dimethyl)aniline, yielding good yields of products **4** and **5** (Fig. 1), respectively (entries 5 and 9). No substitution reaction occurred with (*N*,*N*-dimethyl)-4-methylaniline (entry 10), and the reactions with thiophene, phenols and 2-naphthol with **1a** went very slowly under these conditions (entries 7 and 8). Therefore, about 100 mol% of $BF_3{\cdot}Et_2O$ was used in these reactions. As a consequence, the yields of substituted products **6** and **8**–**12** (Fig. 1) were markedly improved (entries 8, 11–13). Similar reactions of **1b** with indole, pyrrole and 2-naphthol were carried out under the same conditions, respectively (entries 4, 6 and 14).

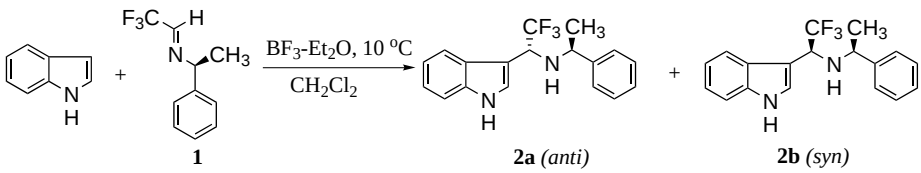
The substituted product was easily separated from the unreacted starting materials by column chromatography, but it was difficult to separate the diastereomers of the product using this method. Diastereomer analysis was therefore carried out by $^{19}F$ NMR because the chemical shifts of the fluorine atoms are easily distinguished. The diastereomer ratios found are given in Table 1. In addition, products **2**–**5** and **12** were also analyzed by HPLC. The ratios found were consistent with those in Table 1.

On the basis of these results, we considered that the main factors affecting the diastereoselectivity of the substitution are the steric hindrance of the reactants

**Table 1.** Reaction of arenes with imine **1** in $CH_2Cl_2$ at 10°C

| Entry | Arene | Imine | $BF_3$[a] (mol%) | Time (h) | Product (%)[b] | *anti*:*syn*[c] | $[\alpha]_D^{20}$ ($CHCl_3$)[d] |
|---|---|---|---|---|---|---|---|
| 1 | Indole | **1a** | 10 | 4 | **2** (21) | 95:5 | |
| 2 | Indole | **1a** | 20 | 4 | **2** (54) | 92:8 | |
| 3 | Indole | **1a** | 50 | 4 | **2** (94) | 9:1 | −10.2 |
| 4 | Indole | **1b** | 50 | 4 | **3** (92) | >99:1 | +5.6 |
| 5 | Pyrrole | **1a** | 50 | 4 | **4** (78) | 78:22 | −11.4 |
| 6 | Pyrrole | **1b** | 50 | 4 | **5** (82) | 82:18 | +7.4 |
| 7 | Thiophene | **1a** | 50 | 48 | **6** (18) | 64:36 | −4.5 |
| 8 | Thiophene | **1a** | 100 | 48 | **6** (46) | 64:36 | −4.5 |
| 9 | $PhNMe_2$ | **1a** | 50 | 12 | **7** (68) | 4:1 | −18.0 |
| 10 | 4-$PhMeNMe_2$ | **1a** | 50 | 12 | None | | |
| 11 | Phenol | **1a** | 100 | 48 | **8** (57) | 1:1 | −7.8 |
| | | | | | **9** (10) | 97:3 | −3.5 |
| 12 | 4-Cresol | **1a** | 100 | 60 | **10** (52) | 97:3 | −10.2 |
| 13 | 2-Naphthol | **1a** | 100 | 48 | **11** (86) | 89:11 | −2.3 |
| 14 | 2-Naphthol | **1b** | 100 | 48 | **12** (71) | >99:1 | −18.9 |

[a] Molar ratio of $BF_3$:arene.
[b] Isolated yields.
[c] Determined by $^{19}F$ NMR.
[d] Data for isolated products.




**Scheme 1.**

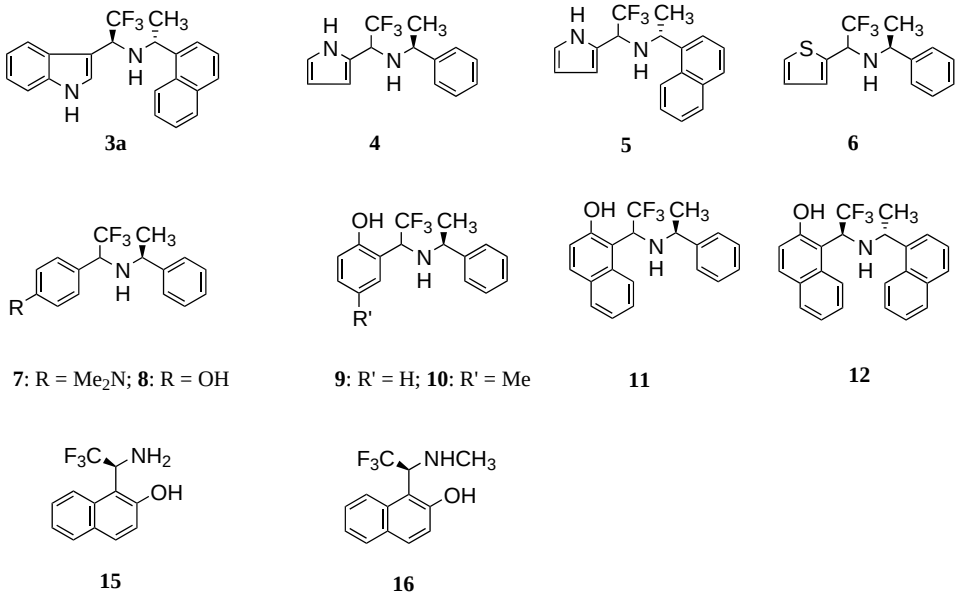



**Figure 1.**

and the reactivity of arenes toward electrophile. For instance, high diastereoselectivity was observed in the reaction with the bulky indole (entry 3) as compared to that with the pyrrole (entry 5). Similarly, the reaction of bulky imine **1b** gave a higher diastereoselectivity than that using the imine **1a** (entries 3–6). In contrast, the effect of the reactivity of aromatic compounds on diastereoselectivity was clearly shown by comparing the results for the reactions with pyrrole and with thiophene. With thiophene the reaction proceeded much more slowly than that with pyrrole under the same conditions (entries 5 and 7), and afforded amine **6** with lower diastereoselectivity (Table 1). Similarly, the reaction of **1a** with (*N*,*N*-dimethyl)aniline provided only *p*-substituted amine **7** in the *anti*:*syn* ratio of 4:1 (entry 9), whereas the corresponding reaction with phenol gave *p*-substituted amine **8** without diastereoselectivity (entry 11). The high electrophilic reactivity of aromatic compounds clearly favors the diastereoselective formation of amines.

A plausible explanation for the effect of reactivity on diastereoselectivity, based on the Hammond postulate, can be proposed. In the case of a reactive arene, the reaction passes through an early transition state, which should be rather close in energy to the reactant, so that its geometry is predicted to resemble the energetically most preferable conformer of the imine (TS I, Fig. 2). The arene therefore prefers to attack the carbon center of C=N bond from the *re* face because there is less steric hindrance than from the *si* face, and the (1*R*,1′*S*) diastereomer (*anti* isomer) is the main product. The reaction of a less reactive arene has a late transition state, in which the arene molecule is much closer to the carbon center of the C=N bond. In this case, the attack of the arene molecule from the less hindered side (*si* face, TS (II)) becomes more important, the transition state (II) being competitive in energy to the TS (I), which results in lowered the diastereoselectivity.

Another problem is the formation of the *o*-substituted product **9** with high diastereoselectivity in the reaction with phenol (entry 11). As shown in Table 1, *p*-substitution occurred preferentially, indicative that the reactivity of the *o*-position is much lower than that of the *p*-position. Because of the formation of *p*-substituted product **8** without diastereoselectivity, the transition state (I) for *p*-substitution may be very close in energy to the transition state (II). A low diastereoselective *o*-substitution therefore was estimated, although the steric hindrance at the *o*-position is somewhat greater than that at the *p*-position. On the basis of this analysis, we speculate that the highly diastereoselective formation of the *o*-substituted product might proceed via

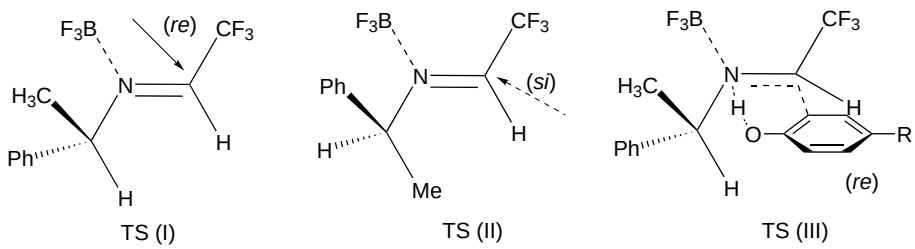



**Figure 2.** Transition state models for the diastereoselective Friedel–Crafts reaction of imine.

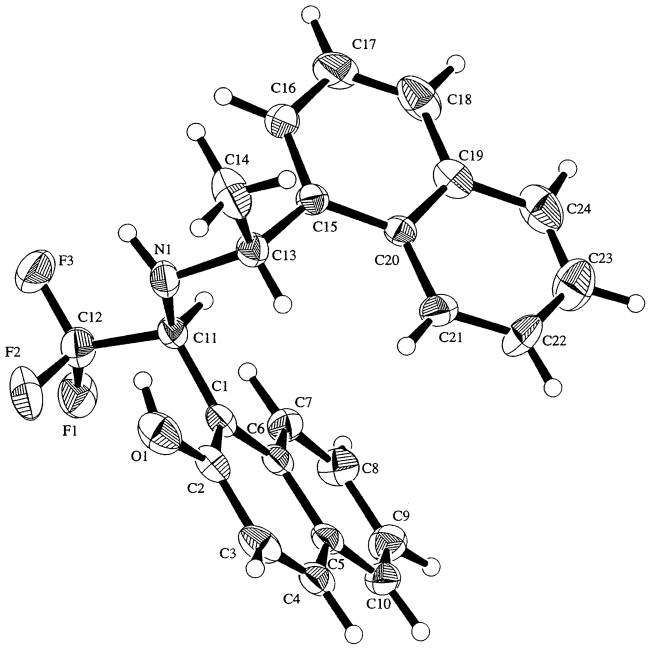



**Figure 3.** X-Ray structure of compound **12**.

a six-membered transition state (III), as shown in Fig. 2. Diastereoselective *o*-substitution was also observed in the corresponding reaction with *p*-cresol (entry 12). In addition, only the 1-substituted products **11** and **12** were obtained in high diastereoselectivity in the respective reactions of **1a** and **1b** with 2-naphthol (entries 13 and 14). The absolute configuration of **12** is shown to be (1*S*,1′*R*), as determined by X-ray crystallography analysis (Fig. 3).[21] This configuration is consistent with that deduced from Fig. 2.

We also investigated the removal of the chiral auxiliary from the amines listed in Fig. 1 by palladium-catalyzed hydrogenolysis. Hydrogenolysis of amine **3a** or **12** was carried out in methanol at room temperature under a hydrogen atmosphere in the presence of Pd/C. Under these conditions, the reaction of **3a** proceeded readily, and the chiral 1-(α-naphthyl)ethyl group was removed selectively, yielding 2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl-amine **13** (86%) and a *N*-methylated product methyl-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]-amine **14** (8%) (Scheme 2). A similar reaction of **12** gave 1-(1-amino-2,2,2-trifluoro)ethyl-naphthalen-2-ol **15** (72%) and 1-(2,2,2-trifluoro-1-methylamino)ethyl-naphthalen-2-ol **16** (20%). HPLC analysis showed that no detectable racemization occurred during the hydrogenolysis of **3a** or **12**. In contrast, only about 20% of **11** was converted to products under the same conditions, indicative that removal of the chiral 1-phenylethyl group from **11** was much more difficult than that of the chiral 1-(α-naphthyl)ethyl group from **12**. In this case, compound **15** was the main product, and small amounts of 1-(2,2,2-trifluoroethyl)-naphthalen-2-ol and the *N*-methylated product **16** also were detected by $^{19}F$ NMR and MS analyses. The mechanism by which the *N*-methylated products **14** and **16** are formed is now under investigation.

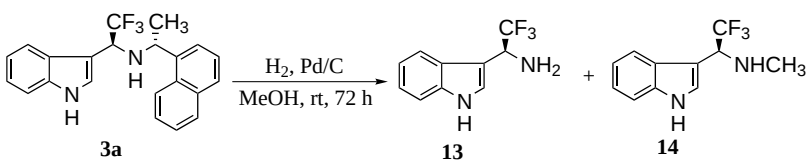
## 3. Conclusion

We consider that the $BF_3$-catalyzed highly diastereoselective Friedel–Crafts reaction with chiral α-trifluoromethyl imines is a new method to prepare chiral *N*-alkyl 1-aryl-2,2,2-trifluoroethylamines. The diastereoselectivity was obviously affected by steric factors and the reactivity of the aromatic compound. The unexpectedly high diastereoselectivity for *o*-substitution products of phenols and 2-naphthol might be attributed to the six-membered transition state (III). Selective removal of the chiral auxilliary by palladium-catalyzed hydrogenolysis allows us to prepare chiral 1-aryl-2,2,2-trifluoroethyl amines conveniently. The practical use of compounds **11** and **12** as the chiral auxiliary and the bioactivity of chiral amines **13**–**16** is now being investigated.

## 4. Experimental

### 4.1. General

IR spectra were recorded on a Shimadzu FTIR-8600PC instrument. $^1H$ NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard at 90 MHz on a Hitachi R-90H FT spectrometer and at 299.95 MHz on a Varian INOVA-300 FT spectrometer. $^{19}F$ NMR spectra were recorded with hexafluorobenzene as an internal standard at 84.7 and at 282.22 MHz on the same spectrometers. Mass spectra (70 eV) were measured on a Shimadzu QP-5000 instrument. High-resolution mass spectra were measured on a JEOL JMS-SX102A MS spectrometer. Melting points were measured in a glass capillary on a heating block, and are uncorrected. HPLC analysis was performed in a Shimatzu LC-10VP apparatus equipped with a chiral column (Daicel OD-R). Optical rotations were measured in $CHCl_3$ or EtOH solution in a 1 dm cell with a JASCO DIP-370 digital polarimeter.




**Scheme 2.**

### 4.2. Preparation of imines 1a and 1b

Trifluoroacetaldehyde ethyl hemiacetal (4.32 g, 30 mmol) was added to a solution of (*S*)-1-phenylethylamine (3.63 g, 30 mmol) or (*R*)-1-(1-naphthyl)ethylamine (0.51 g, 30 mmol) in toluene (25 mL) dried over 4 Å molecular sieves. The mixture was stirred at room temperature for 15 min, and then stirred under reflux for 2 h. The solvent was evaporated under reduced pressure giving the imine as a crude oil. This imine was used without purification.

### 4.3. General procedure for the Friedel–Crafts reaction with imine 1

Boron trifluoride etherate complex (0.21 g, 1.5 mmol) was added to a solution of indole (0.35 g, 3 mmol) and imine **1a** (0.60 g, 3 mmol) in dried $CH_2Cl_2$ (10 mL) at 0°C, and the mixture stirred at 10°C for 4 h. Distilled water (10 mL) was added, and the mixture neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer extracted twice with ethyl acetate. The organic phases were combined, dried over anhydrous $MgSO_4$, and subjected to evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluted with 1:5 (v/v) of ethyl acetate:hexane) giving **2** as a colorless oil in 94% yield.

The Friedel–Crafts reactions of other arenes were completed in the same way. The spectrum data for all the main diastereomers are listed below. Only the distinguishable NMR data of the minor diastereomer is given below.

**4.3.1. (1-Phenylethyl)-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)-ethyl]-amine, (1*R*,1′*S*)-2 (major isomer)**. Colorless oil. IR (KBr) $\nu_{max}$ = 3420, 3030, 2966, 2928, 1558, 1456, 1340, 1271, 1172, 1115, 764, 744, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.31 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 1.92 (s, br, 1H, *NH*), 3.71 (q, $J$ = 6.8 Hz, 1H, $CH_3CH$), 4.15 (q, $J$ = 7.7 Hz, 1H, $CF_3CH$), 7.13–7.65 (m, 5H, Ar*H*), 7.28 (s, 5H, Ph*H*), 8.20 (s, br, 1H, *NH*). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.64 (d, $J$ = 7.7 Hz, 3F, $CF_3$). MS $m/z$ 318 (M$^+$, 31), 249(76), 198 (42), 145 (47), 106 (100). Anal. calcd for $C_{18}H_{17}F_3N_2$: C, 67.91; H, 5.38; N, 8.80. Found: C, 67.75; H, 5.42; N, 8.51%. **(1*S*,1′*S*)-2 (minor isomer)**: $^{19}$F NMR ($CDCl_3$) $\delta$ 88.56 (d, $J$ = 7.7 Hz, 3F, $CF_3$).

**4.3.2. [1-(1-Naphthyl)ethyl]-[2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyl]-amine, (1*S*,1′*R*)-3**. White crystals, mp 115–116°C. IR (KBr) $\nu_{max}$ = 3412, 3314, 3030, 2966, 2928, 1559, 1458, 1336, 1261, 1194, 1113, 806, 785, 748 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 2.10 (s, br, 1H, *NH*), 4.26 (q, $J$ = 7.1 Hz, 1H, $CF_3CH$), 4.56 (q, $J$ = 6.4 Hz, 1H, $CH_3CH$), 6.88–8.10 (m, 13H, *NH* and Ar*H*). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.30 (d, $J$ = 7.1 Hz, 3F, $CF_3$). MS $m/z$ 368 (M$^+$, 59), 299 (39), 251 (8), 198 (39), 170 (68), 156 (100). Anal. calcd for $C_{22}H_{19}F_3N_2$: C, 71.73; H, 5.20; N, 7.60. Found: C, 72.03; H, 5.28; N, 7.43%.

**4.3.3. (1-Phenylethyl)-[2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)-ethyl]-amine, (1*R*,1′*S*)-4 (major isomer)**. Colorless oil. IR (KBr) $\nu_{max}$ = 3422, 3030, 2968, 2868, 1456, 1362, 1263, 1175, 1136, 1113, 727, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 1.86 (s, br, 1H, *NH*), 3.62 (q, $J$ = 6.6 Hz, 1H, $CH_3CH$), 3.96 (q, $J$ = 7.3 Hz, 1H, $CF_3CH$), 6.14 (m, 2H, Ar*H*), 6.81 (m, 1H, Ar*H*), 7.29 (s, 5H, Ph*H*), 8.36 (br, 1H, *NH*). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.16 (d, $J$ = 7.3 Hz, 3F, $CF_3$). MS $m/z$ 268 (M$^+$, 23), 201 (27), 199 (34), 120 (60), 105 (100). Anal. calcd for $C_{14}H_{15}F_3N_2$: C, 62.68; H, 5.64; N, 10.44. Found: C, 62.53; H, 5.72; N, 10.29%. **(1*S*,1′*S*)-4 (minor isomer)**: $^1$H NMR ($CDCl_3$) $\delta$ 1.36 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 4.10 (q, $J$ = 7.3 Hz, 1H, $CF_3CH$). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.27 (d, $J$ = 7.3 Hz, 3F, $CF_3$).

**4.3.4. [1-(1-Naphthyl)ethyl]-[2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethyl]amine, (1*S*,1′*R*)-5 (major isomer)**. White crystals, mp 69–71°C. IR (KBr) $\nu_{max}$ = 3439, 3333, 3030, 2982, 2961, 1595, 1515, 1373, 1360, 1259, 1188, 1176, 1113, 800, 783, 731 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.46 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 2.03 (s, br, 1H, *NH*), 4.04 (q, $J$ = 7.5 Hz, 1H, $CF_3CH$), 4.56 (q, $J$ = 6.6 Hz, 1H, $CH_3CH$), 6.06 (m, 1H, Ar*H*), 6.17 (m, 1H, Ar*H*), 6.78 (m, 1H, Ar*H*), 7.25–7.96 (m, 7H, Np*H*), 8.36 (br, 1H, *NH*). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.45 (d, $J$ = 7.3 Hz, 3F, $CF_3$). MS $m/z$ 318 (M$^+$, 18), 251 (8), 170 (10), 155 (100). Anal. calcd for $C_{18}H_{17}F_3N_2$: C, 67.91; H, 5.38; N, 8.80. Found: C, 67.68; H, 5.47; N, 8.77%. **(1*R*,1′*R*)-5 (minor isomer)**: $^{19}$F NMR ($CDCl_3$) $\delta$ 88.21 (d, $J$ = 7.3 Hz, 3F, $CF_3$).

**4.3.5. (1-Phenylethyl)-(2,2,2-trifluoro-1-thiophen-2-yl-ethyl)amine, (1*R*,1′*S*)-6 (major isomer)**. Colorless oil. IR (KBr) $\nu_{max}$ = 3440, 3030, 2966, 2928, 1558, 1541, 1508, 1456, 1375, 1338, 1261, 1163, 1136, 1119, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 1.90 (s, br, 1H, *NH*), 4.10 (q, $J$ = 6.6 Hz, 1H, $CH_3CH$), 4.26 (q, $J$ = 7.7 Hz, 1H, $CF_3CH$), 6.99 (m, 2H, Ar*H*), 7.29 (s, 6H, Ar*H* and Ph*H*). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.00 (d, $J$ = 7.7 Hz, 3F, $CF_3$). MS $m/z$ 285 (M$^+$, 5), 270 (100), 216 (24), 165 (99), 105 (96). Anal. calcd for $C_{14}H_{14}F_3NS$: C, 58.93; H, 4.95; N, 4.91. Found: C, 58.84; H, 5.18; N, 5.00%. **(1*R*,1′*S*)-6 (minor isomer)**: $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 3.80 (q, $J$ = 6.6 Hz, 1H, $CH_3CH$). $^{19}$F NMR ($CDCl_3$) $\delta$ 86.92 (d, $J$ = 7.7 Hz, 3F, $CF_3$).

**4.3.6. (1-Phenylethyl)-[2,2,2-trifluoro-1-(4-*N*,*N*-dimethyl-aminophenyl)ethyl]-amine, (1*R*,1′*S*)-7 (major isomer)**. Colorless oil. IR (KBr) $\nu_{max}$ = 3439, 3030, 2982, 2961, 2866, 1616, 1526, 1456, 1362, 1263, 1165, 1107, 813, 764, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.30 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 1.88 (s, br, 1H, *NH*), 2.92 (s, 6H, $NCH_3$), 3.60 (q, $J$ = 6.8 Hz, 1H, $CH_3CH$), 3.74 (q, $J$ = 7.9 Hz, 1H, $CF_3CH$), 6.68 (d, 2H, $J$ = 8.6 Hz, Ar*H*), 7.11 (d, 2H, $J$ = 8.6 Hz, Ar*H*), 7.26 (s, 5H, Ph*H*). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.24 (d, $J$ = 7.9 Hz, 3F, $CF_3$). MS $m/z$ 322 (M$^+$, 41), 253 (72), 202 (62), 149 (100), 105 (93). Anal. calcd for $C_{18}H_{21}F_3N_2$: C, 67.06; H, 6.57; N, 8.69. Found: C, 66.89; H, 6.63; N, 8.65%. **(1*S*,1′*S*)-7 (minor isomer)**: $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 2.90 (s, 6H, $NCH_3$), 3.94 (q, $J$ = 7.9 Hz, 1H,

$CF_3CH$), 6.65 (d, 2H, $J=8.6$ Hz, Ar$H$), 7.24 (s, 5H, Ph$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.59 (d, $J=7.9$ Hz, 3F, $CF_3$).

**4.3.7. 4-[2,2,2-Trifluoro-1-(1-phenylethylamino)ethyl]-phenol, (1*R*,1′*S*)-8**. Colorless oil. IR (KBr) $\nu_{max}=3366$, 3030, 2972, 2866, 1616, 1600, 1518, 1474, 1364, 1261, 1171, 1121, 827, 764, 702 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.29 (d, $J=6.3$ Hz, 3H, $CH_3$), 2.05 (s, 1H, $NH$), 3.57 (q, $J=6.3$ Hz, 1H, $CH_3CH$), 3.90 (q, $J=7.3$ Hz, 1H, $CF_3CH$), 6.83 (d, 2H, $J=8.3$ Hz, Ar$H$), 7.15 (d, 2H, $J=8.3$ Hz, Ar$H$), 7.25 (s, 5H, Ph$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.45 (d, $J=7.9$ Hz, 3F, $CF_3$). MS $m/z$ 295 (M$^+$, 13), 280 (100), 226 (67), 175 (52), 122 (50), 106 (96). Anal. calcd for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74. Found: C, 65.04; H, 5.63; N, 4.75%. **(1*S*,1′*S*)-8**: $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (d, $J=6.3$ Hz, 3H, $CH_3$), 4.13 (q, $J=7.3$ Hz, 1H, $CF_3CH$), 6.76 (d, 2H, $J=8.3$ Hz, Ar$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.50 (d, $J=7.9$ Hz, 3F, $CF_3$).

**4.3.8. 2-[2,2,2-Trifluoro-1-(1*S*-phenylethylamino)ethyl]-phenol, (1*R*,1′S)-9 (major isomer)**. Colorless oil. IR (KBr) $\nu_{max}=3327$, 3032, 2972, 2880, 1618, 1589, 1491, 1473, 1456, 1381, 1364, 1267, 1173, 1128, 758, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.44 (d, $J=6.6$ Hz, 3H, $CH_3$), 3.90 (q, $J=6.6$ Hz, 1H, $CH_3CH$), 4.45 (q, $J=7.7$ Hz, 1H, $CF_3CH$), 6.73–7.25 (m, 4H, Ar$H$), 7.26 (s, 5H, Ph$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.96 (d, $J=7.7$ Hz, 3F, $CF_3$). MS $m/z$ 295 (M$^+$, 20), 280 (14), 191 (8), 122 (15), 105 (100). Anal. calcd for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74. Found: C, 64.99; H, 5.68; N, 4.66%. **(1*S*,1′*S*)-9 (minor isomer)**: $^{19}$F NMR ($CDCl_3$) $\delta$ 87.23 (d, $J=7.7$ Hz, 3F, $CF_3$).

**4.3.9. 4-Methyl-2-[2,2,2-trifluoro-1-(1*S*-phenylethylamino)ethyl]-phenol, (1*R*,1′*S*)-10 (major isomer)**. White crystals, mp 101–103°C. IR (KBr) $\nu_{max}=3340$, 3304, 3022, 2978, 2922, 1600, 1504, 1448, 1363, 1269, 1151, 1124, 1113, 820, 762, 700 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.47 (d, $J=6.8$ Hz, 3H, $CH_3$), 2.21 (s, 3H, Ar$CH_3$), 2.27 (s, br, 1H, $NH$), 3.70 (q, $J=6.8$ Hz, 1H, $CH_3CH$), 3.87 (q, $J=7.7$ Hz, 1H, $CF_3CH$), 6.58 (s, 1H, Ar$H$), 6.80 (d, 1H, $J=8.3$ Hz, Ar$H$), 7.15 (m, 3H, Ph$H$ and Ar$H$), 7.33 (m, 3H, Ph$H$), 10.40 (s, 1H, ArO$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 87.19 (d, $J=7.7$ Hz, 3F, $CF_3$). MS $m/z$ 309 (M$^+$, 38), 205 (22), 136 (42), 105 (100). Anal. calcd for $C_{17}H_{18}F_3NO$: C, 66.01; H, 5.87; N, 4.53. Found: C, 66.06; H, 5.93; N, 4.63%. **(1*S*,1′*S*)-10 (minor isomer)**: $^{19}$F NMR ($CDCl_3$) $\delta$ 87.99 (d, $J=7.7$ Hz, 3F, $CF_3$).

**4.3.10. 1-[2,2,2-Trifluoro-1-(1-phenylethylamino)ethyl]-naphth-2-ol, (1*R*,1′*S*)-11 (major isomer)**. White crystals, mp 112–113°C. IR (KBr) $\nu_{max}=3340$, 3298, 3059, 3030, 2968, 2930, 1622, 1601, 1585, 1521, 1470, 1454, 1379, 1263, 1240, 1180, 1163, 1113, 953, 874, 820, 750, 698 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.53 (d, $J=6.8$ Hz, 3H, $CH_3$), 2.45 (d, br, $J=12.1$ Hz, 1H, $NH$), 3.74 (dq, $J=12.1$ Hz, 6.8 Hz, 1H, $CH_3CH$), 4.86 (q, $J=7.5$ Hz, 1H, $CF_3CH$), 6.93–7.35 (m, 4H, Ar$H$), 7.27 (s, 5H, Ph$H$), 7.77 (m, 2H, Ar$H$), 11.85 (s, 1H, ArO$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.27 (d, $J=7.5$ Hz, 3F, $CF_3$). MS $m/z$ 345 (M$^+$, 54), 241 (20), 172 (75), 105 (100). Anal. calcd for $C_{20}H_{18}F_3NO$: C, 69.56; H, 5.25; N, 4.06. Found: C, 69.48; H, 5.29; N, 4.29%. **(1*S*,1′*S*)-11 (minor isomer)**: $^{19}$F NMR ($CDCl_3$) $\delta$ 88.84 (d, $J=7.5$ Hz, 3F, $CF_3$).

**4.3.11. 1-[2,2,2-Trifluoro-1-(1-naphth-1-yl-ethylamino)-ethyl]-naphth-2-ol, (1*S*,1′*R*)-12**. White crystals, mp 175°C. IR (KBr) $\nu_{max}=3340$, 3313, 3058, 2988, 1624, 1603, 1520, 1470, 1452, 1381, 1259, 1165, 1109, 950, 864, 827, 800, 783, 752 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 1.66 (d, $J=6.8$ Hz, 3H, $CH_3$), 2.80 (d, br, $J=11.6$ Hz, 1H, $NH$), 4.70 (dq, $J=11.6$ Hz, 6.8 Hz, 1H, $CH_3CH$), 4.87 (q, $J=7.7$ Hz, 1H, $CF_3CH$), 6.83–7.85 (m, 13H, Ar$H$), 11.98 (s, 1H, ArO$H$). $^{19}$F NMR ($CDCl_3$) $\delta$ 88.33 (d, $J=7.7$ Hz, 3F, $CF_3$). MS $m/z$ 395 (M$^+$, 48), 241 (12), 177 (17), 155 (100), 128 (21). Anal. calcd for $C_{24}H_{20}F_3NO$: C, 72.90; H, 5.10; N, 3.54. Found: C, 72.78; H, 5.12; N, 3.64%.

### 4.4. Synthesis of (*S*)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)-ethylamine, 13

A mixture of **3a** (0.42 g, 1.14 mmol) and palladium on charcoal (5%, 0.42 g) in methanol (10 mL) was stirred for 72 h under a hydrogen atmosphere at room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate concentrated by evaporation under reduced pressure. The residue was isolated on a silica gel column eluted with ethyl acetate/hexane (v/v: 1/5–1/2). The first eluted material was 1-ethylnaphthalene (0.16 g, 90% from **3a**), the second methylamine **14** (0.021 g, 8% from **3a**), and the third amine **13** (0.21 g, 86% from **3a**). Compound **13**: colorless needles (recrystallization from $CHCl_3$); $[\alpha]_D^{20}=+0.7$ ($c$ 1.1, EtOH). Mp 130–131°C. $^1$H NMR (acetone-$d_6$) $\delta$ 2.30 (s, br, 2H, $NH_2$), 4.84 (q, $J=7.7$ Hz, 1H, $CF_3CH$), 7.10–7.60 (m, 4H, Ar$H$), 7.75 (m, 1H, Ar$H$), 10.35 (s, br, 1H, $NH$). $^{19}$F NMR (acetone-$d_6$) 87.42 (d, $J=7.7$ Hz, 3F, $CF_3$). MS m/e 214 (M$^+$, 33), 197 (44), 145 (100), 118 (76). Anal. calcd for $C_{10}H_9F_3N_2$: C, 56.06; H, 4.24; N, 13.08. Found: C, 56.34; H, 4.25; N, 12.82%. Compound **14**: white needles, $[\alpha]_D^{20}=+3.6$ ($c$ 0.5, $CHCl_3$). Mp 102–103°C. $^1$H NMR ($CDCl_3$) $\delta$ 1.78 (s, br, 1H, $CH_3NH$), 2.50 (s, 3H, $CH_3$), 4.39 (q, $J=7.7$ Hz, 1H, $CF_3CH$), 7.15–7.44 (m, 4H, Ar$H$), 7.70 (m, 1H, Ar$H$), 8.42 (s, br, 1H, $NH$). $^{19}$F NMR ($CDCl_3$) 87.90 (d, $J=7.7$ Hz, 3F, $CF_3$). MS m/e 228 (M$^+$, 39), 198 (19), 159 (100), 117 (34). Anal. calcd for $C_{11}H_{11}F_3N_2$: C, 57.89; H, 4.86; N, 12.28. Found: C, 57.84; H, 4.85; N, 12.23%.

### 4.5. Synthesis of (*S*)-1-(1-Amino-2,2,2-trifluoro-ethyl)-naphthalen-2-ol, 15

Compound **12** (0.25 g, 0.63 mmol) was hydrogenated in methanol (10 mL) in the presence of palladium on charcoal (5%, 0.16 g) according to the same procedures. The residue was isolated by silica gel column chromatography, eluting with ethyl acetate/hexane (v/v: 1/5–1/3). The first eluted material was 1-ethylnaphthalene (0.090 g, 91% from **12**), the second methylamine **16** (0.032 g, 20% from **12**), and the third amine **15** (0.11 g, 72% from **12**). Compound **15**: colorless needles, $[\alpha]_D^{20}=$

+3.3 (*c* 0.6, $CHCl_3$). Mp 106–107°C. $^1H$ NMR ($CDCl_3$) $\delta$ 2.02 (s, br, 2H, $NH_2$), 5.60 (q, $J=7.0$ Hz, 1H, $CF_3CH$), 7.11 (d, $J=9.0$ Hz, 1H, Ar*H*), 7.39 (m, 3H, Ar*H*), 7.76 (d, $J=8.8$ Hz, 2H, Ar*H*), 11.13 (s, br, 1H, Ar*OH*). $^{19}F$ NMR ($CDCl_3$) 86.66 (d, $J=7.0$ Hz, 3F, $CF_3$). MS m/e 241 ($M^+$, 31), 196 (28), 172 (100), 146 (22), 127 (55). Anal. calcd for $C_{12}H_{10}F_3NO$: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.80; H, 4.17; N, 5.76%. Compound **16**: colorless needles, $[\alpha]_D^{20}=+1.0$ (*c* 0.8, $CHCl_3$). Mp 135–136°C. $^1H$ NMR ($CDCl_3$) $\delta$ 2.51 (s, 3H, $CH_3$), 5.13 (q, $J=7.2$ Hz, 1H, $CF_3CH$), 7.10 (d, $J=9.0$ Hz, 1H, Ar*H*), 7.39 (m, 3H, Ar*H*), 7.78 (d, $J=8.6$ Hz, 2H, Ar*H*). $^{19}F$ NMR ($CDCl_3$) 88.12 (d, $J=7.2$ Hz, 3F, $CF_3$). MS m/e 255 ($M^+$, 27), 196 (19), 186 (100), 177 (12), 146 (12). Anal. calcd for $C_{13}H_{12}F_3NO$: C, 61.17; H, 4.74; N, 5.49. Found: C, 61.19; H, 4.72; N, 5.44%.

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