JOC*Note*

An Efficient Synthesis of Enantiomerically Enriched Trifluoromethylated 1,2-Diols and 1,2-Amino Alcohols with Quaternary Stereocenters by Diastereoselective Addition of $TMSCF_3$ to Chiral 2-Acyl-1,3-perhydrobenzoxazines

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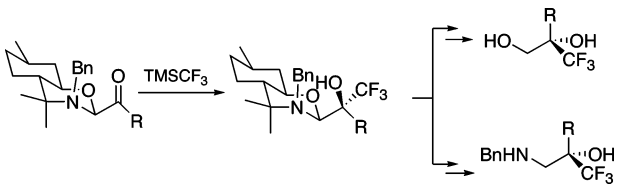

$TMSCF_3$ adds to chiral 2-acyl-1,3-perhydrobenzoxazines with total diastereoselectivity leading to quaternary trifluoromethyl alcohols. Further transformation of the addition products yields enantiomerically enriched trifluoromethylated 1,2-diols and 1,2-amino alcohols.

Organofluorine compounds show remarkable physical, chemical, and biological properties, and they have been used in the development of pharmaceuticals, agrochemicals, and materials.[1] Trifluoromethylated derivatives have special lipophilicity and metabolic characteristics.[1b,2] For these reasons, their synthesis has attracted considerable attention,[3] albeit some of the reported methods require many synthetic steps or not easily available trifluoromethylated compounds.

One of the most useful method to introduce a trifluoromethyl group consists on the nucleophilic addition of $TMSCF_3$, induced by a fluoride ion, to aldehydes, ketones, esters, and related compounds.[4] Although the asymmetric version of these reactions is less common,[5] some routes to enantiopure fluorinated amino acids,[6] amino alcohols,[7] and related compounds[8] have recently been described.

Nucleophilic trifluoromethylation using $TMSCF_3$ as reagent needs activation of the reagent, and although both Lewis bases[9] or fluorine-containing additives[10] have been used, the latter gave better results. The diastereoselectivity of the reaction has also been studied on different substrates and varies from moderate to good depending on the structure of the carbonyls.[11] On the other hand, some α-trifluromethylated alcohols have been prepared, in moderate ee, by enantioselective addition of $TMSCF_3$ to ketones and aldehydes catalyzed by chiral ammonium fluorides.[12]

Continuing our interest in the synthesis of fluorinated derivatives,[13] we present now a facile and direct entry to enantiomerically enriched trifluoromethyl 1,2-diols and 1,2-amino alcohols based on the diastereoselective addition of

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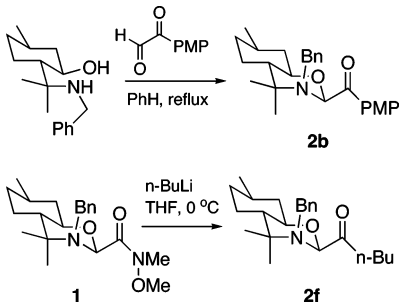
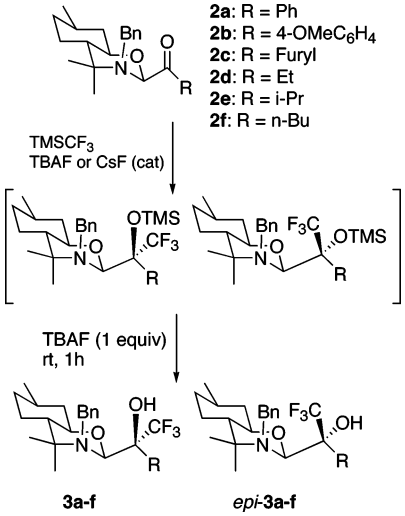
SCHEME 1. Synthesis of 2-Acyl-1,3-perhydrobenzoxazines 2b and 2f



SCHEME 2. Synthesis of Trifluoromethyl Alcohols 3a−f



$TMSCF_3$ to an acyl group placed at C-2 in a chiral 1,3-perhydro benzoxazine derived from (−)-8-benzylamino menthol.[14] Further transformations of the addition products allows for the synthesis of enantioenriched diols and amino alcohols with a quaternary stereocenter in good yields. Our synthetic strategy uses easily available (−)-8-benzylamino menthol[14] and commercial or previously prepared glyoxal derivatives.

The starting 2-acyl-1,3-perhydro benzoxazines **2a**,[14] **2c**,[15] **2d**,[16] and **2e**[16] have been previously described, while compound **2b** was synthesized by condensation of (−)-8-benzylamino-menthol with 4-methoxyphenylglyoxal hydrate[17] in refluxing benzene and **2f** by reaction of the Weinreb amide **1**[15] with *n*-butyllithium (Scheme 1).

The feasibility of the reaction was first explored on aromatic (**2a**) and aliphatic (**2e**) derivatives. To this end, a solution of either **2a** or **2e** in THF or diethyl ether was reacted with $TMSCF_3$ (1.5 equiv) in the presence of a catalytic amount (2.5% mol) of tetrabutylammonium fluoride (TBAF) or CsF at 0 °C for 1.5−2 h. Once the starting compound had disappeared, 1 equiv of TBAF was added, and the mixture was stirred for 1 h at room temperature to transform the formed TMS-ethers into the final alcohols **3a**−**f** (Scheme 2).

Under these conditions the trifluoromethylated alcohols **3a** and **3e** were obtained in very good yields and good to total diastereoselectivity, although both the yield and diastereoselectivity were slightly higher when THF, instead of Et_2O was used as solvent (compare entry 9 vs 10 in Table 1). In addition, CsF was a better catalyst than TBAF increasing the yields of the reactions probably as a consequence of the hygroscopic character of the ammonium fluoride.[4b] The diastereoselection was also improved by using anhydrous CsF as catalyst. The reaction of **2a** and **2e** with $TMSCF_3$ and CsF yielded **3a** and **3e** as single compounds, whereas TBAF led to mixtures of these compounds and the diastereoisomers *epi*-**3a** and *epi*-**3e**.

The use of THF as solvent and CsF as catalyst allows for the trifluoromethylation of both aromatic and aliphatic derivatives **2a**−**f**, leading to **3a**−**f** in excellent yields and high diastereoselectivity (Table 1).

All of the alcohols were isolated and purified by column chromatography or recrystallization, and the stereochemistry of the formed quaternary stereocenter was determined as *S* by X-ray diffraction analysis[18] for the aryl (**3b**), isopropyl (**3e**), and butyl (**3f**) derivatives and extended for all the compounds.

The stereochemistry of the single diastereoisomers formed can be explained by considering the proposed mechanism for the trifluoromethylation of carbonyl compounds,[4b] as a consequence of a 1,2-stereoinduction processes. The addition occurs on the less hindered *Re* face of the carbon−oxygen double bond, in agreement with the Felkin−Anh models summarized in Figure 1, and previously proposed for the reaction of $TMSCF_3$ with imines.[4g]

Compounds **3a**−**f** were easily transformed into the final products in one or two steps. The conversion of these derivatives

TABLE 1. Trifluoromethylation of 2-Acyl-1,3-perhydrobenzoxazines

entry	ketone	solvent/catalyst	products (ratio)[a]	products (yield, %)[b]
1	**2a**	Et_2O/TBAF	**3a**/*epi*-**3a** (21:1)	**3a** (80)
2	**2a**	THF/TBAF	**3a**/*epi*-**3a** (22:1)	**3a** (82)
3	**2a**	THF/CsF	**3a**/*epi*-**3a** (>50:<1)[c]	**3a** (95)
4	**2b**	THF/TBAF	**3b**/*epi*-**3b** (>50:<1)[c]	**3b** (85)
5	**2b**	THF/CsF	**3b**/*epi*-**3b** (>50:<1)[c]	**3b** (93)
6	**2c**	THF/CsF	**3c**/*epi*-**3c** (>50:<1)[c]	**3c** (96)
7	**2d**	THF/TBAF	**3d**/*epi*-**3d** (12:1)	**3d** (82), *epi*-**3d** (6)
8	**2d**	THF/CsF	**3d**/*epi*-**3d** (>50:<1)[c]	**3d** (90)
9	**2e**	Et_2O/TBAF	**3e**/*epi*-**3e** (11:1)	**3e** (85), *epi*-**3e** (3)
10	**2e**	THF/TBAF	**3e**/*epi*-**3e** (18:1)	**3e** (87), *epi*-**3e** (2)
11	**2e**	Et_2O/CsF	**3e**/*epi*-**3e** (>50:<1)[c]	**3e** (93)
12	**2e**	THF/CsF	**3e**/*epi*-**3e** (>50:<1)[c]	**3e** (95)
13	**2f**	THF/TBAF	**3f**/*epi*-**3f** (32:1)	**3f** (92), *epi*-**3f** (2)
14	**2f**	THF/CsF	**3f**/*epi*-**3f** (>50:<1)[c]	**3f** (94)

[a] Determined by integration of the signals of ^1H NMR or ^{19}F NMR spectra of the reaction mixtures. [b] Isolated products. [c] Only one diastereoisomer was observed in the ^1H NMR or ^{19}F NMR spectra of the reaction mixtures.

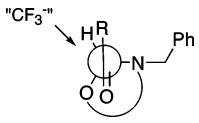


FIGURE 1. Felkin−Anh model for the diastereoselective trifluoromethylation.

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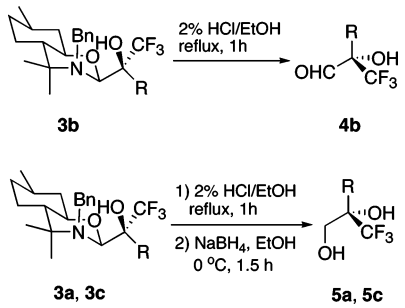
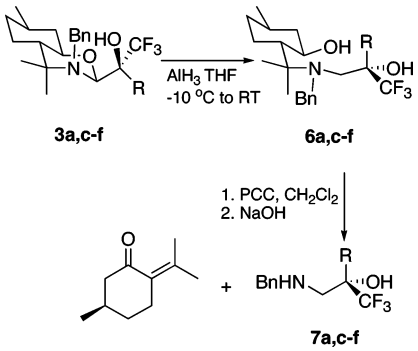
(18) For ORTEP representations of the X-ray diffraction analyses of compounds **3b**, **3e**, and **3f**, see the Supporting Information.

SCHEME 3. Synthesis of Trifluoromethylated Hydroxy Aldehydes and 1,2-Diols



SCHEME 4. Synthesis of Trifluoromethylated 1,2-Amino Alcohols



into α-hydoxy acids as previously described[14] was not possible because hydrolytic workup followed by oxidation with sodium hypochlorite led to a very complex mixture of compounds. Instead, the triflurometylated α-hydroxy aldehyde **4b** was obtained in 64% yield from **3b** by hydrolysis with 2% HCl in refluxing ethanol for 1 h. The same treatment applied to **3a** and **3c**, followed by reduction of the reaction mixtures with sodium borohydride in ethanol at 0 °C for 1.5 h, yielded trifluoromethylated 1,2-diols **5a**[19] and **5c** in 62% and 60% yield, respectively (Scheme 3). (−)-8-Benzylaminomenthol was recovered in 90% from the aqueous phase by neutralization.

A different approach was used for the synthesis of enantiomerically enriched trifluoromethyl-1,2-amino alcohols. In this case, compounds **3a**,**c**−**f** were subjected to reductive ring opening to **6a**,**c**−**f** by reaction with in situ prepared aluminum hydride in THF at −10 °C. Oxidation of these amino menthol derivatives with PCC in methylene chloride, followed by treatment with a solution of NaOH led to 1,2-amino alcohol derivatives **7a**,**c**−**f** in 42−60%, and (+)-pulegone (Scheme 4). The stereochemical integrity and the configuration of the stereocenter was established for **7d**[20] by comparison of the optical rotation with that previously described, and generalized for all the final compounds.

In summary, the described strategy allows for the preparation of enantiomerically enriched trifluoromethylated 1,2-amino alcohols and 1,2-diols with quaternary stereocenters by total diastereoselective addition of $TMSCF_3$ to chiral 2-acyl-1,3-perhydro benzoxazines. Aryl, heteroaryl, and alkyl groups can be introduced as substituents at the quaternary carbon atom in good yields from easily accessible starting reagents.

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Experimental Section

Synthesis of Trifluoromethyl Alcohols 3a−f. General Method. To a solution of ketone **2** (2 mmol) and CsF (0.05 mmol) in THF (50 mL), cooled to 0 °C, under argon was added dropwise a solution of trifluoromethyltrimethylsilane ($TMSCF_3$) in THF (1.5 mL, 3 mmol), and the mixture was stirred at that temperature until the reaction was finished (TLC). Subsequently, TBAF (2 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. THF was removed under vacuum, and the residue was purified by flash chromatography on silica gel using hexanes−ethyl acetate 8:1 as eluent.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2′-yl)-2,2,2-trifluoro-1-phenylethanol (3a). Yield: 95%. White solid. Mp: 109−110 °C (from ethanol). $[\alpha]^{23}_D$ −3.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.64 (s, 3H); 0.80−1.04 (m, 2H); 0.96 (d, 3H, *J* = 6.5 Hz); 1.19 (q, 1H, *J* = 11.2 Hz); 1.33 (s, 3H); 1.52−1.71 (m, 4H); 2.01 (m, 1H); 3.68 (d, 1H, *J* = 17.5 Hz); 3.76 (td, 1H, J_1 = 10.6 Hz, J_2 = 3.9 Hz); 4.17 (s, 1H, OH), 4.39 (d, 1H, *J* = 17.5 Hz); 5.53 (s, 1H); 6.32 (d, 2H, *J* = 6.8 Hz), 6.81−6.89 (m, 3H); 7.21−7.23 (m, 3H); 7.43−7.46 (m, 2H). ^{19}F NMR (δ): −78.3 (s, 3F). ^{13}C NMR (δ): 22.2; 22.4; 24.7; 27.3; 31.4; 35.0; 41.2; 43.5; 47.3; 58.7; 78.1; 78.3 (q, $^2J_{CF}$ = 26.4 Hz); 84.9; 124.9 (2C); 125.9 (3C); 127.1 (3C); 128.0 (2C); 133.6; 143.3. IR (KBr): 3486; 3070; 3028; 1603; 1455; 1375; 1314; 756; 708; 660 cm^{-1}. MS (*m*/*z*): 448 (M + 1, 57), 294 (100), 272 (87). Anal. Calcd for $C_{26}H_{32}F_3NO_2$: C, 69.78; H, 7.21; N, 3.13. Found: C, 69.66; H, 7.18; N, 3.32.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2′-yl)-2,2,2-trifluoro-1-(4-methoxyphenyl)-ethanol (3b). Yield: 93%. White solid. Mp: 184−185 °C (from ethanol). $[\alpha]^{23}_D$ +7.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.68 (s, 3H); 0.93−1.00 (m, 2H); 0.97 (d, 3H, *J* = 6.4 Hz); 1.18 (q, 1H, *J* = 11.7 Hz); 1.34 (s, 3H); 1.50−1.75 (m, 4H); 2.01 (m, 1H); 3.67 (d, 1H, *J* = 17.6 Hz); 3.75 (s, 3H); 3.76 (td, 1H, J_1 = 10.6 Hz, J_2 = 4.0 Hz); 4.14 (s, 1H); 4.37 (d, 1H, *J* = 17.6 Hz); 5.48 (s, 1H); 6.40−6.42 (m, 2H); 6.72 (m, 2H); 6.87−7.28 (m, 3H); 7.33 (d, 2H, *J* = 8.5 Hz). ^{19}F NMR (δ): -78.8 (s, 3F). ^{13}C NMR (δ): 22.2; 22.4; 24.8; 27.1; 31.4; 35.1; 41.2; 43.6; 47.1; 55.1; 58.6; 78.0; 78.3 (q, $^2J_{CF}$ = 26.5 Hz); 84.9; 113.2; 124.9; 126.0; 127.1; 128.3 (9C); 125.7; 143.4; 159.6 (3C). IR (KBr): 3521; 3086; 3058; 1615; 1586; 1516; 1462; 1388; 1376; 1314; 1299; 1251; 939; 834; 804; 756; 701 cm^{-1}. MS (*m*/*z*): 478 (M + 1, 100), 324 (38), 272 (66). Anal. Calcd for $C_{27}H_{34}F_3NO_3$: C, 67.91; H, 7.18; N, 2.93. Found: C, 67.76; H, 6.99; N, 2.98.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2′-yl)-2,2,2-trifluoro-1-(furan-2-yl)ethanol (3c). Yield: 96%. Yellow oil. $[\alpha]^{23}_D$ +3.2 (*c* = 0.84, $CHCl_3$). ^{1}H NMR (δ): 0.70 (s, 3H); 0.71−1.05 (m, 2H); 0.95 (d, 3H, *J* = 6.5 Hz); 1.17 (q, 1H, *J* = 11.9 Hz); 1.32 (s, 3H); 1.51−1.73 (m, 4H); 1.96 (m, 1H); 3.73 (td, 1H, J_1 = 10.6 Hz, J_2 = 3.9 Hz); 3.77 (d, 1H, *J* = 17.6 Hz); 4.00 (br s, 1H); 4.49 (d, 1H, *J* = 17.6 Hz); 5.45 (s, 1H); 6.13 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.8 Hz), 6.20 (dd, 1H, J_1 = 3.2 Hz, J_2 = 0.8 Hz), 6.66 (dd, 2H, J_1 = 8.0 Hz, J_2 = 1.8 Hz); 6.98−7.24 (m, 3H); 7.41 (dd, 1H, J_1 = 1.8 Hz, J_2 = 0.8 Hz). ^{19}F NMR (δ): -79.1 (s, 3F). ^{13}C NMR (δ): 22.2; 22.5; 24.7; 26.9; 31.4; 35.0; 41.1; 43.6; 47.4; 58.6; 78.0; 83.9; 110.1; 110.6; 125.1; 126.3 (2C); 127.2 (2C); 142.4; 143.6; 147.1. ^{13}C NMR (acetone-d_6, δ): 22.6; 23.0; 25.5; 27.5; 32.1; 35.8; 42.1; 44.4; 48.3; 59.4; 78.0 (q); 78.7; 85.1; 110.7; 111.4; 125.9; 127.4 (2C); 128.1 (2C); 143.6; 145.3; 149.6. IR (film): 3505; 3045; 3020; 1600; 1450; 1382; 1368; 1315; 1263; 1240; 1190; 730; 710; 690 cm^{-1}. Anal. Calcd for $C_{24}H_{30}F_3NO_3$: C, 65.89; H, 6.91; N, 3.20. Found: C, 65.71; H, 7.06; N, 3.04.

(2*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-2-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2′-yl)-1,1,1-trifluorobutan-2-ol (3d). Yield: 90%. Colorless oil. $[\alpha]^{23}_D$ +10.8 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (δ): 0.90−1.04 (m, 2H); 0.93 (s, 3H); 1.01 (d, 3H, *J* = 6.5 Hz); 1.12 (td, 3H, J_1 = 6.6 Hz, J_2 = 1.1 Hz); 1.20 (q, 1H, *J* = 11.8

Hz); 1.40 (s, 3H); 1.50−1.80 (m, 6H); 2.00 (m, 1H); 3.55 (s, 1H); 3.71 (td, 1H, J_1 = 10.6 Hz, J_2 = 3.9 Hz); 4.03 (d, 1H, J = 18.4 Hz); 4.73 (d, 1H, J = 18.4 Hz); 5.08 (s, 1H); 7.22 (t, 1H, J = 7.2 Hz); 7.34 (dd, 2H, J_1 = 7.6 Hz, J_2 = 7.2 Hz); 7.43 (d, 2H, J = 7.6 Hz). ^{19}F NMR (δ): -76.5 (s, 3F). ^{13}C NMR (δ): 7.79; 22.2; 22.4; 24.4; 24.8; 26.8; 31.4; 35.1; 41.2; 43.5; 47.5; 58.8; 77.8 (q, $^2J_{CF}$ = 24.7 Hz); 77.9; 83.4; 125.7; 126.3 (2C); 127.9 (2C); 143.8. IR (film): 3537; 3080; 3063; 1604; 1493; 1453; 1390; 1373; 1308; 1245; 1192; 755; 724; 698 cm^{-1}. Anal. Calcd for $C_{22}H_{32}F_3NO_2$: C, 66.14; H, 8.07; N, 3.51. Found: C, 66.32; H, 7.91; N, 3.66.

(2*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-2-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2′-yl)-1,1,1-trifluoro-3-methylbutan-2-ol (3e). Yield: 95%. White solid. Mp: 117−118 °C (from ethanol). $[\alpha]^{23}_D$ +3.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.84−1.00 (m, 5H); 0.84 (s, 3H); 0.95 (d, 3H, J = 6.6 Hz); 1.08−1.20 (m, 4H); 1.32 (s, 3H); 1.40−1.71 (m, 4H); 1.93 (m, 1H); 2.22 (m, 1H); 3.55 (s, 1H); 3.63 (td, 1H, J_1 = 10.8 Hz, J_2 = 4.0 Hz); 3.94 (d, 1H, J = 18.3 Hz); 4.59 (d, 1H, J = 18.3 Hz); 5.02 (s, 1H); 7.15 (t, 1H, J = 7.1 Hz); 7.24−7.29 (m, 2H); 7.34 (d, 2H, J = 6.9 Hz). ^{19}F NMR (δ): −71.7 (s, 3F). ^{13}C NMR (δ): 16.4; 17.4; 22.2; 22.4; 24.8; 27.0; 30.1; 31.4; 35.1; 41.2; 43.5; 47.7; 59.1; 78.2; 79.1 (q, $^2J_{CF}$ = 23.6 Hz); 84.4; 125.8; 126.3 (2C); 128.0 (2C); 143.9. IR (KBr): 3517; 3080; 1603; 1493; 1458; 1373; 1363; 1315; 1247; 1190; 1167; 779; 756; 719; 697 cm^{-1}. Anal. Calcd for $C_{23}H_{34}F_3NO_2$: C, 66.80; H, 8.29; N, 3.39. Found: C, 66.70; H, 8.19; N, 3.48.

(2*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-2-(3-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benz[*e*][1,3]oxazin-2'-yl)-1,1,1-trifluorohexan-2-ol (3f). Yield: 94%. White solid. Mp: 108−109 °C (from methanol). $[\alpha]^{23}_D$ +9.1 (c = 0.88, $CHCl_3$). ^{1}H NMR (δ): 0.94−1.09 (m, 2H); 0.97 (t, 3H, J = 6.0 Hz); 0.97 (s, 3H); 1.03 (d, 3H, J = 6.5 Hz); 1.17−1.38 (m, 4H), 1.42 (s, 3H); 1.59−1.80 (m, 7H); 2.02 (m, 1H); 3.55 (s, 1H); 3.72 (td, 1H, J_1 = 10.7 Hz, J_2 = 3.8 Hz); 4.04 (d, 1H, J = 18.4 Hz); 4.75 (d, 1H, J = 18.4 Hz); 5.06 (s, 1H); 7.23 (t, 1H, J = 7.3 Hz); 7.35 (t, 2H, J = 7.3 Hz); 7.46 (d, 2H, J = 7.3 Hz). ^{19}F NMR (δ): −76.5 (s, 3F). ^{13}C NMR (δ): 14.0; 22.2; 22.5; 23.0; 24.8; 25.0; 26.7; 31.3; 31.4; 35.1; 41.2; 43.6; 47.3; 58.8; 77.9; 83.8; 125.7; 126.4 (2C); 127.8 (2C); 143.6. IR (Nujol): 3545; 3080; 1600; 1490; 1450; 1375; 1315; 1180; 1160; 755; 725; 700 cm^{-1}. Anal. Calcd for $C_{24}H_{36}F_3NO_2$: C, 67.42; H, 8.49; N, 3.28. Found: C, 67.25; H, 8.36; N, 3.26.

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Supporting Information Available: Experimental details and full characterization including copies of ^{13}C NMR spectra for all the compounds. ORTEP representations of the X-ray structures for **3b**,**e**,**f** and CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

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