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Concise Synthesis of Enantiopure α-Trifluoromethyl Alanines, Diamines, and Amino Alcohols via the Strecker-type Reaction

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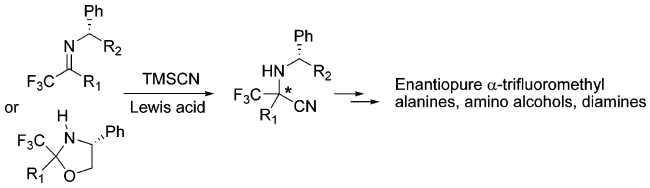

Diastereomerically pure α-trifluoromethyl α-amino nitriles obtained by Strecker-type reactions from chiral CF_3 imines and iminium proved to be very attractive versatile intermediates for the synthesis of various α-trifluoromethyl amino compounds. From these synthons, both enantiomers of α-trifluoromethyl alanine, trifluoromethyl 1,2-diamines, and amino alcohols were conveniently obtained in enantiopure form in high yields in a few steps.

α-Trifluoromethyl α-amino acids (α-Tfm AAs), trifluoromethylated 1,2-amino alcohols, and 1,2-diamines are very attractive target molecules for the design of biologically active molecules.[1] This is mainly due to the specific properties of fluorine atoms producing significant changes in the physical, chemical, and biological properties of molecules.[2] Curiously, although the Strecker-type reaction is extensively used in the nonfluorinated series for the stereoselective synthesis of α-amino acids,[3] this strategy has been very rarely reported in the fluorinated series.[4,5] Different methods are known for the stereoselective synthesis of trifluoromethyl 1,2-diamines,[6] but to our knowledge, their synthesis by reduction of α-trifluoromethyl α-amino nitriles has never been reported. In the course of our studies, we have already reported that chiral trifluoromethyl iminiums are effective intermediates for the stereoselective synthesis of various α-trifluoromethylated amino compounds.[4a,7] We now report the straightforward synthesis of enantiopure α-trifluoromethyl alanines, amino alcohols, and 1,2-diamines from α-amino nitriles obtained by Strecker-type reaction starting from chiral CF_3 imines or oxazolidines.

The Strecker-type reaction from CF_3 imines or iminium has been mainly reported in the racemic series,[8] and to our knowledge, the synthesis of enantiopure α-amino nitriles through resolution is not documented in the literature. In this work, we first investigated the asymmetric Strecker-type reaction with various chiral trifluoromethylated *N*-benzylimines (Table 1).

These diastereomerically pure (*E*)-imines were very conveniently prepared from trifluoroacetaldehyde hemiacetal or trifluoromethyl ketones and (*S*)-α-methylbenzylamine or (*R*)-phenylglycinol and derivatives. These chiral auxiliaries are inexpensive and easily removable to get the target free amino compounds. In all cases, the Strecker-type reaction with TMSCN required a Lewis acid activation of the fluorinated aldimines or ketimines to occur. The reaction was very efficiently promoted in mild conditions with a catalytic amount of $Yb(OTf)_3$, which

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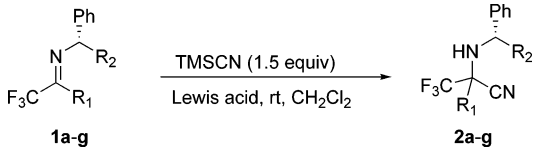
TABLE 1. Strecker-type Reactions of Imines 1a−g

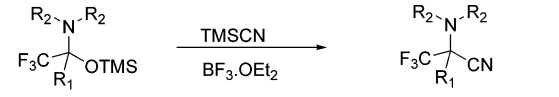


1a-g **2a-g**

entry	imine (R_1, R_2)	Lewis acid	product	yield (%)[a]	dr[b]
1	**1a** (H, CH_3)	Yb(OTf)$_3$[c]	**2a**	80	50:50
2	**1b** (CH_3, CH_3)	Yb(OTf)$_3$[d]	**2b**	80	77:23
3	**1c** (Ph, CH_3)	Yb(OTf)$_3$[c,e]	**2c**	90	75:25
4	**1c** (Ph, CH_3)	$MgBr_2$[f]	**2c**	93	67:33
5	**1d** (H, CH_2OMe)	Yb(OTf)$_3$[c]	**2d**	58	50:50
6	**1d** (H, CH_2OMe)	$MgBr_2$[f]	**2d**	62	80:20
7	**1e** (CH_3, CH_2OH)	Yb(OTf)$_3$[c]	**2e**	92	55:45
8	**1f** (CH_3, $CH_2OTBDMS$)	Yb(OTf)$_3$[c]	**2f**	75	75:25
9	**1f** (CH_3, $CH_2OTBDMS$)	$MgBr_2$[f]	**2f**	93	68:32
10	**1g** (CH_3, CH_2ODPMS)	Yb(OTf)$_3$[c]	**2g**	93	60:40

[a] Isolated yield. [b] Measured by ^{19}F NMR of the crude reaction mixture. [c] 0.1 equiv. [d] 0.2 equiv. [e] The reaction performed with Et_2AlCN (1.5 equiv) as the cyanide donor and Yb(OTf)$_3$ (0.1 equiv) gave **2c** in 90% yield and 76:24 dr. [f] 1.5 equiv.

SCHEME 1



3a: R_1=H, R_2=Bn
3b: R_1=Ph, R_2=CH_3

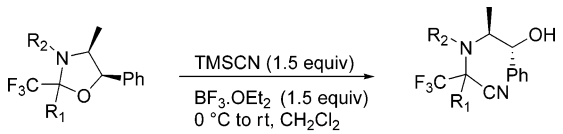
4a: R_1=H, R_2=Bn (91%)
4b: R_1=Ph, R_2=CH_3 (87%)

is a very easy to handle Lewis acid. The expected amino nitriles were obtained in high yields with a low to moderate diastereoselectivity. However, in most cases (Table 1, entries 1−4, 7, and 10), each diastereomer was efficiently obtained in diastereomerically pure form after silica gel separation. The diastereoselectivity could be slightly improved by using (*R*)-α-methoxymethylbenzylimine and $MgBr_2$ (1.5 equiv) as the Lewis acid (Table 1, entry 6). The chelation of both nitrogen and oxygen by the magnesium should explain the diastereoselectivity increase because this effect was not observed with Yb(OTf)$_3$ (Table 1, entry 5). No enhancement of the stereoselectivity was achieved by the introduction of a more hindered silylated substituent on the benzylic side chain (Table 1, entries 8−10).

The Strecker-type reaction was also performed starting from the silylated hemiacetal of fluoral **3a** and the silylated hemiacetal of trifluoroacetophenone **3b** under $BF_3{\cdot}OEt_2$ activation (Scheme 1). The corresponding α-amino nitriles **4a** and **4b** were obtained in 91 and 87% yields, respectively.

To investigate the scope of this reaction in the asymmetric series, we turned our attention to chiral 2-trifluoromethyloxazolidines, which are stable fluorinated chiral iminium precursors under Lewis acid activation.[4a,7] These oxazolidines were very conveniently prepared from fluoral or trifluoromethyl ketones and commercially available amino alcohols.[9] The oxazolidines were obtained in high yield as stable diastereomeric mixtures. In a preliminary account,[4a] we have reported that the same iminium is formed in situ starting from both oxazolidines under a Lewis acid activation. So their separation is useless, and the Strecker-type reaction can be carried out on the mixture of oxazolidines. The Strecker-type reactions from (−)-ephedrine- and (−)-norephedrine-derived oxazolidines were first investigated (Table 2). The corresponding α-amino nitriles were obtained in high yields (80−90%).

TABLE 2. Strecker-type Reactions of Oxazolidines 5a−c Derived from (−)-Ephedrine and (−)-Norephedrine



5a-c **6a-c**

entry	oxazolidine (R_1, R_2)	dr oxazolidines	product	yield (%)[a]	dr[b]
1	**5a** (H, CH_3)	79:21	**6a**	80	63:37
2	**5b** (H, H)	85:15	**6b**	90	66:34
3	**5c** (CH_3, H)	60:40	**6c**	90	67:33

[a] Isolated yield. [b] Measured by ^{19}F and ^1H NMR of the crude reaction mixture.

To anticipate a convenient removal of the chiral auxiliary for the synthesis of free amino compounds, the reactivity of (*R*)-phenylglycinol-based oxazolidines was then studied. The phenylglycinol side chain can be easily removed by Pb(OAc)$_4$ treatment or hydrogenolysis, and this strategy has been widely used in the nonfluorinated series for the stereoselective synthesis of α-amino acids from oxazolidines[10] or imines.[11] The Strecker-type reaction of various (*R*)-phenylglycinol-based trifluoromethylated oxazolidines occurred in high yields (84−97%) provided that the oxazolidines were activated with a stoichiometric amount of $BF_3{\cdot}OEt_2$ or a catalytic amount of TMSOTf (Table 3). Unlike the corresponding more reactive imines, no reaction occurred in the presence of a catalytic amount of Yb(OTf)$_3$ (Table 3, entry 1). The same diastereomeric ratio of α-amino nitriles **8a** was obtained, whatever the diastereomeric ratio of the starting oxazolidines **7a** (Table 3, entries 2−5). This result confirms that the same iminium intermediate should be formed from both oxazolidines, and consequently, a tedious separation of the oxazolidines is useless. The diastereoselectivity of this Strecker-type reaction was increased compared to that of the corresponding trifluoroacetaldehyde imines **1a**,**d** (Table 1). With the same substrate **7a**, the diastereoselectivity of the Strecker reaction proved to be higher than the allylation and propargylation reactions we already reported.[4a] The (*R*,*R*) configurational assignment of the major **8a** diastereomer is in accordance with the less hindered *re* face attack of the intermediate iminium.[4a,7] The configurations of the amino nitriles were determined by correlation with the corresponding amino acid configuration (vide infra). The diastereoselectivity decreased for the *N*-benzyl oxazolidine **7b** (Table 3, entry 6), and no reaction occurred from the *N*-benzoyl oxazolidine **7c** (Table 3, entry 7). With this substrate, the oxazolidine ring opening

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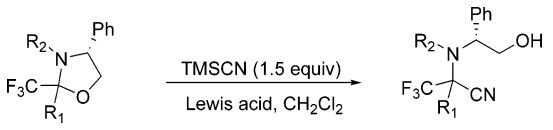
TABLE 3. Strecker-type Reactions of Oxazolidines 7a−e Derived from (*R*)-Phenylglycinol



7a-e **8a-d, 2e**

entry	oxazolidine (R_1, R_2)	dr	Lewis acid	product	yield (%)[a]	dr[b]
1[c]	**7a** (H, H)	62:38	$Yb(OTf)_3$[d,e]			
2	**7a** (H, H)	62:38	$BF_3{\cdot}OEt_2$[f]	**8a**	90	83:17
3	**7a** (H, H)	62:38	TMSOTf[g]	**8a**	87	82:18
4	**7a** (H, H)	87:13	TMSOTf[g,h,i]	**8a**	87	81:19
5	**7a** (H, H)	20:80	TMSOTf[g,i]	**8a**	84	83:17
6	**7b** (H, Bn)	67:33	$BF_3{\cdot}OEt_2$[f]	**8b**	87	50:50
7[c]	**7c** (H, Bz)	100:0	$BF_3{\cdot}OEt_2$[f]			
8	**7d** (Ph, H)	71:29	$BF_3{\cdot}OEt_2$[f]	**8d**	97	72:28
9	**7e** (CH_3, H)	100:0	$BF_3{\cdot}OEt_2$[f]	**2e**	91	54:46

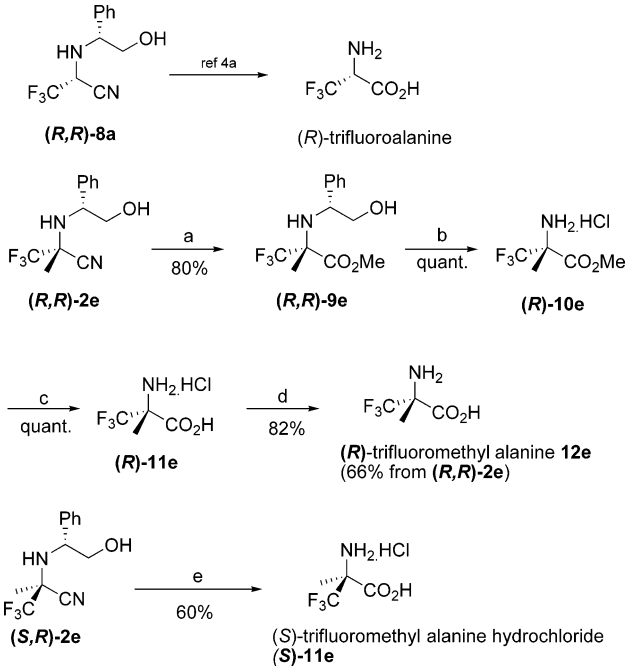
[a] Isolated yield. [b] Measured by ^{19}F and ^1H NMR of the crude reaction mixture. [c] No reaction. [d] 0.2 equiv. [e] No reaction occurred also with $La(OTf)_3$ (0.2 equiv) and $Ti(OiPr)_4$ (1.5 equiv). [f] 1.5 equiv, 0 °C to rt. [g] 0.1 equiv, −78 °C to rt. [h] Same yield and diastereoselectivity was achieved with 1.5 equiv. [i] Similar diastereoselectivity was achieved with $BF_3{\cdot}Et_2O$.

should be prevented by the combined electron-withdrawing effect of the trifluoromethyl group and the amide function. The Strecker-type reaction was then successfully extended to the trifluoromethyl ketone-derived oxazolidines **7d**,**e**, giving the corresponding quaternary amino nitriles **8d** and **2e** in high yields (Table 3, entries 8 and 9). A very interesting feature of all these (*R*)-phenylglycinol-based amino nitriles was that both diastereomers were very easily separated by chromatography on silica gel (eluent: petroleum ether/ethyl acetate 85:15). For example, with this eluent system, the R_f value difference between (*R*,*R*)-**2e** and (*S*,*R*)-**2e** was 0.27. Even if the stereoselectivity of the Strecker reaction was low, it constitutes a powerful strategy for the synthesis of both amino nitrile diastereomers in enantiopure form from the unique (*R*)-phenylglycinol chiral auxiliary.

We already reported that the α-amino nitrile (*R*,*R*)-**8a** was a precursor of enantiomerically enriched (*R*)-trifluoroalanine.[4a] We wish to report here the straightforward synthesis of enantiopure (*R*)- and (*S*)-α-trifluoromethyl alanine from the corresponding α-amino nitriles (Scheme 2). Several biological applications of enantiomerically pure α-trifluoromethyl alanine were recently reported,[1g,12] and its efficient preparation in enantiopure form is of considerable interest.[13]

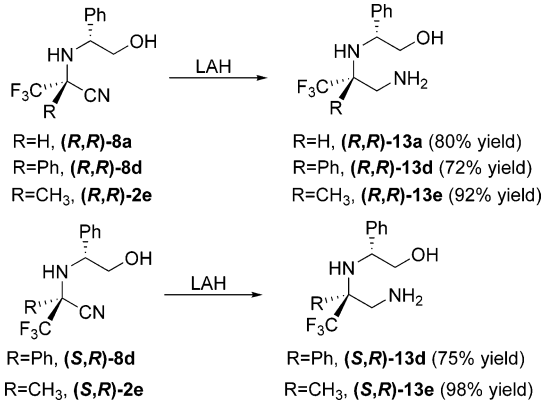
The (*R*)-α-trifluoromethyl alanine **12e** was obtained in 66% yield from the amino nitrile (*R*,*R*)-**2e** through a three-step procedure involving the methanolysis of the nitrile, hydrogenolysis of the phenylglycinol side chain, and hydrolysis of the ester function. The (*S*)-α-trifluoromethyl alanine hydrochloride (*S*)-**12e** was obtained in 60% yield in only one step by concentrated HCl treatment of the amino nitrile (*S*,*R*)-**2e**. The removal of the side chain and hydrolysis of the nitrile occurred

SCHEME 2[a]



[a] Reagents and conditions: (a) MeOH, HCl_g, 6 h reflux; (b) H_2, $Pd(OH)_2$, MeOH then 1 N HCl; (c) 6 N HCl, AcOH; (d) propene oxide; (e) concentrated HCl, 14 h reflux.

SCHEME 3



at same time. The optical rotation and the spectroscopic data of (*R*)-**11e** and (*S*)-**11e** were identical to those reported in the literature.[13a]

Our second objective to exhibit the high versatility of chiral α-trifluoromethyl α-amino nitriles was to demonstrate their easy transformation into enantiopure diamines and amino alcohols. These target compounds are interesting fluorinated synthons and potential ligands for organometallic chemistry. The lithium aluminum hydride reduction of diastereomerically pure isolated α-amino nitriles **8a**,**d** and **2e** gave the corresponding diastereomerically pure diamino alcohols **13a**,**d**,**e** in 72−98% isolated yield (Scheme 3). As both (*R*,*R*) and (*S*,*R*) starting materials are readily available, both diastereomers of diamino alcohol **13d**,**e** were obtained. Furthermore, these two diamino alcohols proved to be very easily converted into the corresponding diastereomerically pure (*R*,*R*) and (*S*,*R*) amino diols **14e** through a diazotization reaction (Scheme 4).

To obtain the corresponding novel enantiopure unprotected fluorinated diamines, the removal of the phenylglycinol side

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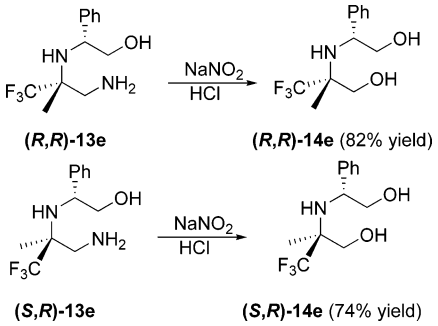
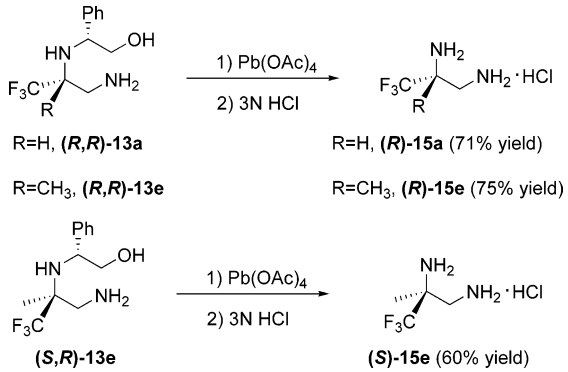
SCHEME 4



SCHEME 5



chain was carried out. This was done in good yields by Pb(OAc)$_4$ treatment of the diamino alcohols **13a**,**e** followed by 3 N HCl hydrolysis. The target α-trifluoromethyl diamines (*R*)-**15a**, (*R*)-**15e**, and (*S*)-**15e** were conveniently obtained in enantiopure form as their hydrochlorides (Scheme 5).

In conclusion, we have developed a straightforward synthetic route for the synthesis of both enantiomers of α-trifluoromethyl alanine and various enantiopure diamines and amino alcohols from trifluoromethyl α-amino nitriles as key intermediates. Despite the moderate diastereoselectivity of the Strecker-type reaction, the high efficiency of the chromatographic separation of each α-amino nitrile diastereomer assisted by the (*R*)-phenylglycinol side chain allowed the very convenient synthesis of enantiopure compounds.

Experimental Section

Representative Procedure for the Preparation of Amino Nitriles from Oxazolidines: 3,3,3-Trifluoro-2-((1*R*)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile (2e). To a solution of oxazolidines **7e** (1.15 g, 5 mmol) in dichloromethane (50 mL) under argon were added cyanotrimethylsilane (0.94 mL, 7.5 mmol) and BF_3·OEt_2 (0.9 mL, 7.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature until disappearance of the starting material (14 h, GC monitoring). The reaction mixture was then poured into a saturated aqueous solution of $NaHCO_3$ (25 mL). The aqueous layer was extracted with dichloromethane (3 × 25 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (85:15 petroleum ether/ethyl acetate) gave pure isolated fractions of (*R*,*R*)-**2e** (634 mg, 49%) and (*S*,*R*)-**2e** (540 mg, 42%). **(*R*,*R*)-2e**: R_f = 0.46. Pale yellow oil; $[\alpha]^{20}_D$ −144.6° (*c* 1.0, $CHCl_3$); IR (neat) 3329, 3032, 2937, 1603, 1455, 1174 cm^{-1}; ^{1}H NMR δ 1.33 (s, 3H), 1.86 (dd, *J* = 7.3, 4.4 Hz, 1H), 2.84 (s, 1H), 3.51 (ddd, *J* = 11.2, 9.2, 7.3 Hz, 1H), 3.81 (dt, *J* = 11.2, 4.4 Hz, 1H), 4.12 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR δ 20.2, 59.9 (q, *J* = 30.3 Hz), 61.2, 66.8, 116.5, 123.1 (q, *J* = 283.6 Hz), 127.0, 128.0, 128.7, 140.3; ^{19}F NMR δ −79.8 (s); MS (EI 70 eV) *m*/*z* 258 (M^+), 227, 200 (100), 162, 120, 77. Anal. Calcd for $C_{12}H_{13}F_3N_2O$: C, 55.81; H, 5.07; N, 10.85. Found: C, 55.45; H, 5.15; N, 10.51. **(*S*,*R*)-2e**: R_f = 0.19. Yellow solid; mp 81−83 °C; $[\alpha]^{20}_D$ −93° (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 1.75 (s, 3H), 1.88 (dd, *J* = 6.6, 5.6 Hz, 1H), 2.45 (d, *J* = 6.0 Hz, 1H), 3.59 (ddd, *J* = 11.3, 7.8, 5.6 Hz, 1H), 3.83 (ddd, *J* = 11.3, 6.6, 4.5 Hz, 1H), 4.15 (ddd, *J* = 7.8, 6.0, 4.5 Hz, 1H), 7.30−7.50 (m, 5H); ^{13}C NMR δ 20.3, 58.3 (q, *J* = 30.3 Hz), 60.9, 66.8, 116.2, 123.0 (q, *J* = 285.0 Hz), 126.9, 127.9, 128.5, 139.2; ^{19}F NMR δ −78.6 (s).

Representative Procedure for the Reduction of Amino Nitriles: 3,3,3-Trifluoro-2-((1*R*)-2-hydroxy-1-phenylethylamino)-propylamine ((*R*,*R*)-13a). To a solution of amino nitrile (*R*,*R*)-**8a** (240 mg, 1 mmol) in dry diethyl ether (27 mL) was added $LiAlH_4$ (160 mg, 4 mmol) at 0 °C. The mixture was stirred for 24 h at room temperature, and the reaction mixture was hydrolyzed by successive addition of water (0.2 mL), 15% KOH (0.2 mL), and water (0.4 mL). The resulting precipitate was filtered on Celite. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization in pentane to give (*R*,*R*)-**13a** (198 mg, 80%) as a white solid: mp 95−96 °C; $[\alpha]^{20}_D$ −38.7° (*c* 1.1, $CHCl_3$); IR (KBr) 3625, 3344, 3010, 2930, 1454, 1219 cm^{-1}; ^{1}H NMR δ 2.84 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.09 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.25 (qdd, *J* = 8.1, 7.6, 4.2 Hz, 1H), 3.68 (dd, *J* = 11.3, 7.8 Hz, 1H), 3.80 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.00 (dd, *J* = 7.8, 3.8 Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR δ 38.9, 58.6 (q, *J* = 26.5 Hz), 62.6, 67.1, 126.1 (q, *J* = 282.7 Hz), 127.3, 127.6, 128.4, 140.2; ^{19}F NMR δ −75.4 (d, *J* = 8.1 Hz); MS (EI 70 eV) *m*/*z* 248 (M^+), 217, 189, 168 (100), 121, 77. Anal. Calcd for $C_{11}H_{15}F_3N_2O$: C, 53.22; H, 6.09; N, 11.28. Found: C, 53.48; H, 6.27; N, 11.18.

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Supporting Information Available: General experimental methods, complete experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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