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Unexpected and Expeditious Entry into Trifluoromethyl Aziridines from Substituted β-Dicarbonyl Compounds

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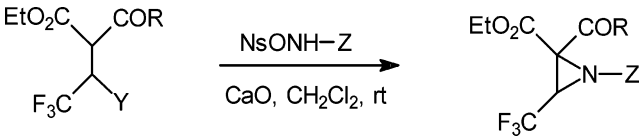

One-pot aziridinations were obtained starting from substituted 2,2,2-trifluoroethyl β-dicarbonyl compounds with nosyloxycarbamates in the presence of an excess of CaO as base. The unexpected ring closure reaction takes place at room temperature, leading to the *N*-protected α-trifluoromethyl aziridines with good yields. The reaction pathway seems to be influenced by the choice of the base.

The presence of fluorine in organic molecules is often associated with unusual reactivity, because of differences between physical and chemical properties of fluorinated compounds and their hydrogen analogues.[1]

The influence of fluorine on the stability and properties of organic compounds is well-known. Moreover, the incorporation of a fluorinated moiety into organic molecules frequently leads to novel applications in various fields.[2] Therefore, a wide variety of methods have been developed for the preparation of various types of fluorine-incorporated compounds.[3] Among the latter, organic molecules containing a nitrogen in the α- and/or β-position with respect to the carboxylic group have recently been recognized as attractive starting materials for obtaining biologically active substances such as enzyme inhibitors or peptide isosteres.[4]

Recently, we reported the synthesis of α-trifluoromethyl β-amino esters and 2-(trifluoromethyl)aziridine-1,2-dicarboxylates by amination reactions of 2-(trifluoromethyl)acrylates with ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrophenylsulfonyl).[5]

Continuing our studies on the use of this carbamate to synthesize fluorinated amino compounds, we serendipitously found that aziridine **6a**[6] can also be obtained by a one-pot reaction starting directly from **2**, a precursor of alkene **1**,[7] in the presence of CaO at room temperature (Scheme 1).

Being interested in this unexpected result, we at first attempted the same reaction in the presence of different bases. Et_3N in homogeneous conditions gave a more complex reaction mixture, whereas other inorganic bases we previously used, such as Cs_2CO_3, K_2CO_3,[8] or NaH,[6] failed to give the expected product. Only LiOH[9] gives aziridine **6a**, but in lower yields. These results suggest a possible role for the metal in the carbon−nitrogen bond formation reaction.[10]

Then, we decided to extend aziridination reactions to other analogous substrates by using different alkyl nosyloxycarbamates in the presence of CaO. The results are reported in Table 1.

As shown by the results, changing the leaving groups (Y) in the starting malonate or acetoacetate substrate does not seem to greatly influence the reaction outcome, but interesting changes are seen with the choice of nosyloxycarbamate. In fact, *tert*-butyl nosyloxycarbamate (NsONHBoc) did not lead to the aziridine, which instead was obtained in good yield starting from alkene **1**[6] by aza-MIRC (Michael-initiated ring closure)[11] reaction. This last observation suggests that alkene **1** is not an intermediate in aminations of substituted 2,2,2-trifluoroethyl β-dicarbonyl compounds **2**−**5**. According to this hypothesis, unreacted **2** was quantitatively recovered after being stirred for 48 h in CH_2Cl_2 in the presence of CaO.

Finally, by comparing reactivity with respect to **1**,[6] we found that the synthesis of aziridines **6a**−**d** from sub-

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(1) (a) Liebman, J. E. In *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH: New York, 1988. (b) Smart, B. E., Ed. *Chem. Rev.* **1996**, *96* (5), special issue. (c) Müller, K., Ed. *ChemBioChem* **2004**, *5* (5), special issue.

(2) (a) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*: *Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (b) Smart, B. E. *J. Fluorine Chem*. **2001**, *109*, 3−11.

(3) (a) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Wiley: Chichester, U.K., 1999. (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha and Gordon and Breach Science: Tokyo, 1998. (c) Qiu, X.; Meng, W.; Qing, F. *Tetrahedron* **2004**, *60*, 6711−6745. (d) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev*. **2004**, *104*, 1−16. (e) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917−1936.

(4) (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed.* **1993**, *32*, 1244−1267. (b) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088−6089. (c) *Fluorine-Containing Amino Acids*: *Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, U.K., 1995. (d) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* **1998**, *98*, 763−795.

(5) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197−200.

(6) Fioravanti, S.; Colantoni, D.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 3296−3298.

(7) Blond, G.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2001**, *66*, 4826−4830. We had to use more drastic reaction conditions than those reported in order to obtain the alkene (see Supporting Information).

(8) Barani, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 11235−11238.

(9) Fioravanti, S.; Olivieri, L.; Pellacani, L.; Tardella, P. A. *J. Chem. Res., Synop*. **1998**, 338−339.

(10) For a recent review of metal-mediated aziridinations, see: Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669.

(11) (a) Little, D. R.; Dawson, J. R. *Tetrahedron Lett*. **1980**, *21*, 2609−2612. (b) Stevens, C. V.; Van Heecke, G.; Barbero, C.; Patora, K.; De Kimpe, N.; Verhe, R. *Synlett* **2002**, 1089−1092. (c) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, 4549−4552. (d) Pohlman, M.; Kazmaier, U.; Lindner, T. *J. Org. Chem.* **2004**, *69*, 6909−6912. (e) Matsumoto, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett*. **2004**, *6*, 4367−4369 and references therein.

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SCHEME 1. Direct Aziridination of 2

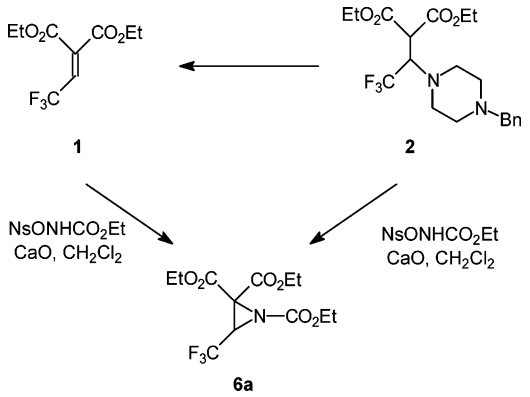
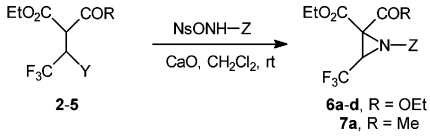
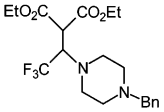
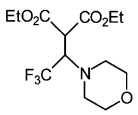
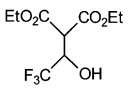
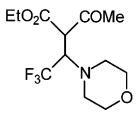


TABLE 1. One-Pot Aziridination of 2,2,2-Trifluoroethyl *β*-Dicarbonyl Compounds



Z = **a**: CO_2Et; **b**: Boc; **c**: Cbz, **d**: Fmoc

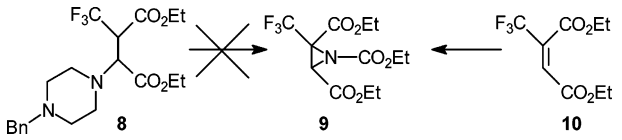
Substrate	Z	Aziridine	Molar ratio[a]	Time (h)	Yield (%)
 **2**	CO_2Et	**6a**	1:6:4	8	78
	Boc	**6b**	1:8:6	48	-
	Cbz	**6c**	1:6:4	12	72
	Fmoc	**6d**	1:6:4	8	68
 **3**	CO_2Et	**6a**	1:8:6	8	68
	Boc	**6b**	1:8:6	48	-
	Cbz	**6c**	1:7:5	12	75
	Fmoc	**6d**	1:8:6	8	70
 **4**	CO_2Et	**6a**	1:6:4	7	73
 **5**	CO_2Et	**7a**[b]	1:8:6	9	58

[a] Substrate:CaO:NsONH−Z. [b] Starting from a diastereomeric mixture of **5** (dr = 57/43), we obtained aziridines **7a** with a dr = 75/25, as determined on the crude mixture by ^{19}F NMR spectra and by analytical HPLC data (eluent, hexane/ethyl acetate = 90:10).

strates **2**−**4** required a greater excess of reagents, especially of base.

It is probable that the aminating species involved in these aziridination reactions are the nitrenes generated by α-elimination of the corresponding carbamates.[8,12] The intermediacy of the same nitrenes was recently proposed by us to explain the synthesis of vinyl carbamates obtained in amination reactions of EWG-substituted

SCHEME 2. Attempted Aziridination of Diethyl 2-(4-Benzylpiperazin-1-yl)-3-(trifluoromethyl)succinate



α-trifluoromethyl enoates,[6] and by other authors in the elegant synthesis of a marine natural product.[13] The unreactivity of NsONHBoc is also in agreement with the nitrene hypothesis because, as is known, this carbamate undergoes a very fast Lossen-type transposition after deprotonation, leading to the corresponding isocyanate.[14]

As is known, *β*-dicarbonyl compounds react with electrophilic reagents in the same[15] or in analogous conditions.[14b,16] Moreover, the aminated intermediate of hydroxy malonate **4**[17] could behave like *β*-amino alcohols, common precursors of aziridines.[18,19] Furthermore, it is reported that the nucleophilic substitution of the hydroxyl group in the CF_3−CH(OH) unit can be easily obtained only in intramolecular substitutions.[20]

Therefore, in the reactions reported here, the formation of the aziridine ring could be explained by electrophilic amination of the enolates of compounds **2**−**5**, followed by a ring closure reaction. To test the importance of the CF_3 group, we tried the synthesis of the same nonfluorinated substrates, but all our attempts to isolate the products failed.[21]

In a further attempt, we performed the reaction of $NsONHCO_2Et$ and CaO with diethyl 2-(4-benzylpiperazin-1-yl)-3-(trifluoromethyl)succinate **8**, an isomer of substrate **2**.

As expected,[22] **8** did not give the corresponding aziridine **9**, obtained with the same reagents but starting from alkene **10**[6] (Scheme 2).

After 36 h of stirring, we recovered only the same unreacted **8** and diethyl hydrazine-1,2-dicarboxylate (EtO_2CNH−$NHCO_2Et$), a product commonly detected in reactions involving ethoxycarbonylnitrene (NCO_2Et).[12]

(12) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630−3637.

(13) Jacquot, D. E. N.; Zöllinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295−2298.

(14) (a) Pihuleac, J.; Bauer, L. *Synthesis* **1989**, 61−64. (b) Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *64*, 5896−5903. (c) Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2003**, *5*, 1019−1021.

(15) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **2001**, *42*, 1171−1173.

(16) (a) Marchi, C.; Trepat, E.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **2002**, *58*, 5699−5708. (b) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, *12*, 2115−2118. (c) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193−2196. (d) Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Synthesis* **2005**, 957−960.

(17) During the synthesis of alkene **1** (see ref 7), we also found compound **4** in the crude mixture. For experimental details, see Experimental Section and Supporting Information.

(18) (a) Pousset, C.; Larchevêque, M. *Tetrahedron Lett.* **2001**, *43*, 5257−5260. (b) Kawamoto, A.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1916−1928.

(19) (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. (b) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519−1559.

(20) Katagiri, T.; Uneyama, K. *Chirality* **2003**, *15*, 4−9.

(21) Experimental Section of: Oh, H. K.; Lee, J. M.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3806−3810.

(22) Calcium oxide promoted aza-Michael 1,4-addition of $NsONHCO_2$-Et on 2-(trifluoromethyl)acrylates, giving *N*,*N*-disubstituted α-trifluoromethyl *β*-amino esters, but it was not able to promote the ring closure; see ref 5.

In conclusion, unexpected behavior of these reported 2,2,2-trifluoroethyl compounds confirms the surprises that can emerge when studying fluorinated compound reactivity in simple reactions.[23] Furthermore, nosyloxycarbamates also continue to show an unforeseen reactivity often dependent on reaction partners and conditions.

Experimental Section

Synthesis of Diethyl {[2,2,2-Trifluoro-1-(morpholin-4-yl)]ethyl}malonate (3). According to the reported procedure,[7] to a solution of [2,2,2-trifluoro-1-(morpholin-4-yl)]ethanol[24] (0.37 g, 2 mmol) and diethyl malonate (0.16 g, 1 mmol) in THF (2 mL) was added *t*-BuOK (0.02 g, 0.2 mmol) at room temperature, and then the reaction mixture was heated to 80 °C for 24 h. After being cooled, the crude mixture was evaporated and purified by flash chromatography (hexane/ethyl acetate = 90:10); **3** was recovered as pure product in 64% yield.

3: colorless oil; IR 1748, 1734 cm^{-1}; ^1H NMR δ 1.22 (t, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 2.60−2.68 (m, 2 H), 2.86−2.96 (m, 2 H), 3.45−3.58 (m, 4 H), 3.76 (d, J = 11.1 Hz, 1 H), 3.84−3.95 (m, 1 H), 4.12−4.23 (m, 4 H); ^{13}C NMR δ 13.1, 14.3, 50.1, 52.3, 62.0, 62.1, 64.6 (q, J_{CF} = 26.0 Hz), 67.5, 125.7 (q, J_{CF} = 291.0 Hz), 165.5, 166.5; ^{19}F NMR δ −67.8 (d, J_{HF} = 8.9 Hz); GC/MS 327 (M^+, 4), 258 (14), 169 (10), 168 (100), 167 (13), 140 (12), 124 (18), 86 (26); HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_{13}H_{20}F_3NNaO_5$ 350.1191, found 350.1185.

Synthesis of Diethyl [(2,2,2-Trifluoro-1-hydroxy)ethyl]-malonate (4). To a stirred solution of trifluoroacetaldehyde methyl hemiacetal (0.13 g, 1.0 mmol) and diethyl malonate (0.16 g, 1.0 mmol) in CH_2Cl_2 (3 mL/mmol) was added DABCO (0.03 g, 0.25 mmol). After 24 h, the crude mixture was evaporated and purified by flash chromatography (hexane/ethyl acetate = 95:5); **4** was recovered as pure product in 52% yield. **4** was also found as byproduct (31% yield) during the synthesis of **1** (see Supporting Information).

4: colorless oil; IR 3476 (br), 1750, 1734 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.2 Hz, 3 H), 1.31 (t, J = 7.2 Hz, 3 H), 3.71 (d, J = 4.2 Hz, 1 H), 4.23−4.33 (m, 4 H), 4.56 (d, J = 9.0 Hz, 1 H), 4.61−4.68 (m, 1 H); ^{13}C NMR δ 13.9, 14.0, 50.5, 62.6, 62.7, 70.0 (q, J_{CF} = 32.3 Hz), 123.9 (q, J_{CF} = 281.8 Hz), 165.4, 167.8; ^{19}F NMR δ −78.9 (d, J_{HF} = 5.9 Hz); GC/MS 259 (M^+ + 1, <1), 213 (33), 189 (28), 185 (30), 169 (11), 165 (12), 160 (33), 157 (10), 143 (11), 141 (16), 133 (15), 123 (100), 117 (40), 115 (41), 89 (37), 88 (10), 87 (23), 86 (10), 71 (59), 69 (30), 45 (17), 43 (24), 42 (11); HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_9H_{13}F_3NaO_5$ 281.0613, found 281.0618.

Synthesis of Ethyl 2-Acetyl-4,4,4-trifluoro-3-(morpholin-4-yl)butanoate (5). Starting from ethyl acetoacetate and according to the procedure for the synthesis of **3**, we obtained **5** as a mixture of diastereomers (dr = 57/43, determined by ^{19}F NMR) in 58% yield, after purification by flash chromatography (hexane/ethyl acetate = 85:15).

5: colorless oil; IR 1740, 1719 cm^{-1}; ^1H NMR δ 1.22 (t, J = 7.2 Hz, major), 1.26 (t, J = 7.2 Hz, 3 H), 2.21 (s, major), 2.23 (s, 3 H), 2.60−2.69 (m, 2 H), 2.83−2.94 (m, 2 H), 3.43−3.58 (m, 4 H), 3.78 (d, J = 11.4 Hz, major), 4.01 (d, J = 11.1 Hz, 1 H), 3.88−3.97 (m, 1 H), 4.13−4.23 (m, 4 H); ^{13}C NMR δ 13.8, 14.1, 26.7, 29.8, 49.9, 50.1, 59.5 (q, J_{CF} = 1.1 Hz), 59.6, 62.0, 62.2, 63.9 (q, J_{CF} = 26.0 Hz), 64.6 (q, J_{CF} = 26.1 Hz), 67.4, 67.6, 125.8 (q, J_{CF} = 291.0 Hz), 126.0 (q, J_{CF} = 291.6 Hz), 165.6, 166.5, 197.7, 198.1; ^{19}F NMR δ −67.6 (d, J_{HF} = 6.2 Hz, major), −67.3 (d, J_{HF} = 5.9 Hz); GC/MS 297 (M^+, 4), 258 (14), 169 (10), 168 (100), 167 (13), 140 (12), 124 (18), 86 (26); HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_{12}H_{18}F_3NNaO_4$ 320.1086, found 320.1083.

General Procedure for the Synthesis of Aziridines 6a−d and 7a. To a stirred solution of 1 mmol of substrate (**2**−**5**) in CH_2Cl_2 (2 mL/mmol) were added CaO and NsONH-Z portionwise during the times and in the molar ratios reported in Table 1. The reaction was monitored by TLC or GC; then the mixture was quickly filtered through a 3 in. plug of silica gel (hexane/ethyl acetate = 95:5), and the solvents were evaporated under reduced pressure. Products were purified by flash chromatography (hexane/ethyl acetate = 80:20). **6a**−**d** were reported before.[6]

Diethyl 2-Acetyl-3-(trifluoromethyl)aziridine-1,2-dicarboxylate (7a): dr = 75/25; colorless oil; IR 1751, 1736, 1716 cm^{-1}; ^1H NMR δ 1.23−1.31 (m, 6 H), 2.38 (s, major), 2.49 (s, 3 H), 3.69−3.75 (m, 1 H), 4.14−4.30 (m, 4 H); ^{13}C NMR δ 13.7, 13.8, 13.9, 14.0, 27.8, 27.9, 45.2 (q, J_{CF} = 41.8 Hz), 60.4, 61.1, 63.9, 64.0, 64.9, 121.2 (q, J_{CF} = 275.4 Hz), 153.5, 157.0, 163.6, 165.7, 194.4; ^{19}F NMR δ −70.1 (major), −70.4; GC/MS 297 (M^+, 6), 196 (17), 184 (17), 156 (68), 154 (12), 152 (15), 110 (100), 43 (44); HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_{11}H_{14}F_3NNaO_5$ 320.0722, found 320.0729.

Synthesis of Diethyl 2-(4-Benzylpiperazin-1-yl)-3-(trifluoromethyl)succinate 8. To a stirred solution of diethyl 2-(trifluoromethyl)maleate **10** (0.24 g, 1 mmol) in 5 mL of Et_2O at room temperature was added 1-benzylpiperazine (0.19 g, 1.1 mmol); after 1.5 h the mixture was filtered through a 3 in. plug of silica gel (hexane/ethyl acetate = 90:10). After evaporation of solvents under reduced pressure, **8** was purified by precipitation from pentane (dr = 58/42 determined by ^{19}F NMR).

8: white foam; IR 1735 cm^{-1}; ^1H NMR δ 1.24−1.31 (m, 6 H), 2.30−2.52 (m, 6 H), 2.72−2.86 (m, 2 H), 3.45 (s), 3.48 (s, major, 2 H), 3.62−3.74 (m), 3.82−3.93 (m, major, 1 H), 3.74 (d, J = 12.0 Hz, major), 3.97 (d, J = 11.7 Hz, 1 H), 4.15−4.30 (m, 4 H), 7.27−7.31 (m, 5 H); ^{13}C NMR δ 13.7, 14.1, 14.2, 14.3, 49.4 (q, J_{CF} = 25.8 Hz), 49.6 (br), 51.4 (q, J_{CF} = 26.6 Hz), 53.2, 53.3, 61.0, 61.1, 61.7, 62.0, 62.8, 62.9, 64.1 (q, J_{CF} = 2.6 Hz), 65.0, 123.7 (q, J_{CF} = 280.8 Hz), 123.8 (q, J_{CF} = 281.0 Hz), 126.9, 127.0, 128.1, 129.0, 129.1, 137.7, 138.0, 165.0 (q, J_{CF} = 3.5 Hz), 166.2 (q, J_{CF} = 3.2 Hz), 166.8, 168.8; ^{19}F NMR δ −66.4 (d, J_{HF} = 9.0 Hz, major), −64.5 (d, J_{HF} = 9.0 Hz); GC/MS (major) 416 (M^+, 14), 344 (12), 343 (60), 261 (11), 252 (11), 175 (26), 146 (11), 132 (14), 91 (100); HR-MS (ES Q-TOF) calcd for $C_{20}H_{27}F_3N_2NaO_4$ 439.1821, found 439.1817.

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Supporting Information Available: General experimental methods; ^1H NMR or ^{13}C NMR spectra for compounds **3**−**5**, **7a**, and **8**; and ^{19}F NMR spectra for **5**, **7a**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Seebach, D. *Angew. Chem., Int. Ed.* **1990**, *29*, 1320−1367.
(24) Billard, T.; Langlois, B. R.; Blond, G. *Tetrahedron Lett.* **2000**, *41*, 8777−8780.