Stereoselective and Enantioselective Synthesis of *anti*-1-(Trifluoromethyl) Amino Alcohols

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anti-(Trifluoromethyl) *β*-amino alcohols **2** have been prepared in good yields and with 90% diastereoisomeric excess through a reaction of 1-(trifluoromethyl) epoxy ethers **3** with dimethylaluminum amide, followed by the in situ chelation-controlled stereoselective reduction of the intermediate amino ketone. The salen-mediated chiral epoxidation of 1-(trifluoromethyl) enol ether **4a** led to the homochiral epoxy ethers **11a** and **12a** in a good enantiomeric excess. Reaction with dimethylaluminum amide followed by a reduction step provided the chiral amino alcohols **15a** and **16a**, respectively.

β-Amino alcohols are important targets that have found use in the treatment of a wide variety of human disorders[1] as peptidomimetic units and as chiral auxiliaries in organic synthesis.[2] For the same reasons, fluoroalkyl *β*-amino alcohols **1** and **2** aroused increasing interest. Moreover, fluoroalkyl *β*-amino alcohols are precursors of the corresponding fluoroalkyl peptidyl ketones, which have been shown to be effective inhibitors of proteolytic enzymes,[3] such as serine proteases[4] (chymotrypsin,[5] elastases,[6,7] trypsin,[8] thrombin,[9]), aspartyl proteases,[10,11] or cysteine proteases.[12] In some cases, fluoroalkyl *β*-amino alcohols are themselves inhibitors of the same enzymes.[6,11]

The interest in these fluoroalkyl *β*-amino alcohols aroused efforts for stereoselective and enantioselective synthetic methods.[7a,b,11,13] For our part, we have described stereoselective access to syn and anti isomers of trifluoromethyl *β*-amino alcohols based on the ring opening of epoxy ethers **3** with nitrogen nucleophiles, followed by different reduction of the resultant trifluoromethyl ketones, involving Felkin−Anh control for N,N-disubstituted amino trifluoromethyl ketones, leading to syn amino alcohols,[14,15] and chelation control for NH-Boc amino trifluoromethyl ketones, leading to anti amino alcohols.[15,16] However, disappointingly, ring opening with a chiral amine failed: chiral primary amines react at high temperature, providing N-monosubstituted ketones that, after enolization by 1−4 prototropy, undergo a rapid degradation. Some experiments performed with a chiral secondary amine showed a dramatic reduction in the rate of ring opening due to steric hindrance.

(1) Grayson, M., Ed. *Kirk-Othmer Encycl. Chem. Techno.* **1982**, *17*, 311−345.

(2) Tomioka, K. *Synthesis* **1990**, 541. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−68.

(3) Imperiali, B. *Synthetic Peptides in Biotechnology*; A. R. Liss, Inc.: New York, 1988; pp 97−129.

(4) Imperiali, B.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760−3767.

(5) Brady, K.; Liang, T. C.; Abeles, R. H. *Biochemistry* **1989**, *28*, 9066−9070. Liang, T. C.; Abeles, R. H. *Biochemistry* **1987**, *26*, 7603−7608. Brady, K.; Wei, A.; Ringe, D.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7600−7607. Brady, K.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7608−7617.

(6) (a) Dunlap, R. P.; Stone, P. J.; Abeles, R. H. *Biochem. Biophys. Res. Comm.* **1987**, *145*, 509−513. (b) Stein, R. L.; Strimpler, A. M.; Edwards, P. D., Lewis, J. J.; Mauger, R. C.; Schwartz, J. A.; Stein, M. M.; Trainor, D. A.; Wildonger, R. A.; Zottola, M. A. *Biochemistry* **1987**, *26*, 2682−2689. (c) Govardhan, C. P.; Abeles, R. H. *Arch. Biochem. Biophys.* **1990**, *280*, 137−146. (d) Warner, P.; Green, R. C.; Gomes, B.; Strimpler, A. M. *J. Med. Chem.* **1994**, *37*, 3090−3099. (e) Berstein, P. R.; Gomes, B. C.; Kosmider, B. J.; Vacek, E. P.; Williams, J. C. *J. Med. Chem.* **1995**, *38*, 212−215. (f) Veale, C. A.; Damewood, J. R.; Steelman, G. B.; Bryant, C.; Gomes, B.; Williams, J. C. *J. Med. Chem.* **1995**, *38*, 86−97. (g) Brown, F. J.; Andisik, D. W.; Berstein, P. R.; Bryant, C. B.; Ceccarelli, C.; Damewood, J. R.; Edwards, P. D.; Earley, R. A.; Feeney, S.; Green, R. C.; Gomes, B.; Kosmider, B. J.; Krell, R. D.; Shaw, A.; Steelman, G. B.; Thomas, R. M.; Vacek, E. P.; Veale, C. A.; Tuthill, P. A.; Warner, P.; Williams, J. C.; Wolanin, D. J.; Woolson, S. A. *J. Med. Chem.* **1994**, *37*, 1259−1261.

(7) (a) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394−407. (b) Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letts, G.; Rosenthal, A. S. *J. Med. Chem.* **1992**, *35*, 641−662. (c) Angelastro, M. R., Baugh, L. E.; Bey, P.; Burkhart, J. P.; Chen, T. M.; Durham, S. L.; Hare, C. M.; Huber, E. W.; Janusz, M. J.; Koehl, J. R.; Marquart, A. L.; Mehdi, S.; Peet, N. P. *J. Med. Chem.* **1994**, *37*, 4538−4554.

(8) Ueda, T.; Kam, C. M.; Powers, J. C. *Biochem. J.* **1990**, *265*, 539−545.

(9) Neises, B.; Ganzhorn, A. Eur. Pat. Appl. EP 503, 203, 1992; *Chem. Abstr.* **1993**, *118*, 148063y.

(10) (a) Sham, H. L.; Stein, H.; Rempel, C. A.; Cohen, J.; Plattner, J. J. *FEBS Lett.* **1987**, *220*, 299−301. (b) Tarnus, C.; Jung, M. J.; Rémy, J. M.; Baltzer, S.; Schirlin, D. *FEBS Lett.* **1989**, *249*, 47−50. (c) Thaisrivongs, S.; Pals, D. T.; Turner, S. R. in *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington D.C., 1991; pp 164−173.

(11) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1988**, *29*, 4665−4668. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W., Jr. *J. Med. Chem.* **1993**, *36*, 2431−2447.

(12) (a) Giordano, C.; Gallina, C.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.* **1989**, *24*, 357−362. (b) Smith, R. A.; Copp, L. J.; Donnelly, S. L.; Spencer, R. W.; Krantz, A. *Biochemistry* **1988**, *27*, 6568−6573.

(13) Imperiali, B.; Abeles, R. H. *Tetrahedron Lett.* **1986**, *27*, 135−138. Bergeson, S. H.; Schwartz, J. A.; Stein, M. M.; Wildonger, R. A.; Edwards, P. D.; Shaw, A.; Trainor, D. A.; Wolanin, D. J. U.S. Pat. 4,910,190, 1990; *Chem. Abstr.* **1991**, *114*, 120085m. Edwards, P. D. *Tetrahedron Lett.* **1992**, *33*, 4279−4282. Kolb, M.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 4437−4440. Kolb, M.; Barth, J.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 1579−1582. Kolb, M.; Neises, B.; Gerhart, F. *Liebigs Ann. Chem.* **1990**, 1−6.

(14) Bégué, J. P.; Bonnet-Delpon, D.; Sdassi, H. *Tetrahedron Lett.* **1992**, *33*, 1879−1882.

(15) Bégué, J. P.; Bonnet-Delpon, D.; Fischer-Durand N.; Reboud-Raveaux, M.; Amour, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1099−1110.

(16) Bégué, J. P.; Bonnet-Delpon, D. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; Washington, DC, 1996; Chapter 4, pp 59−72.

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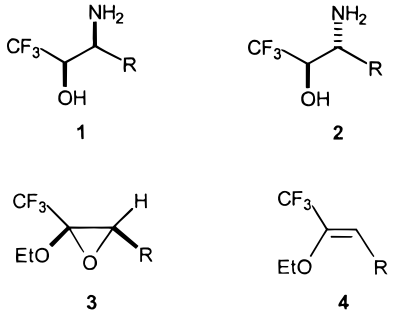


Figure 1.

We thus had to find a nitrogen-containing reagent that could effect the ring opening of epoxy ethers with introduction of a chiral amine but avoid any prototropy or enolization. Aluminum amides appeared to be good candidates for this purpose: first, as Lewis acids, they can facilitate the reaction under mild conditions; second, the aluminum takes the place of the mobile hydrogen in the amino ketone product and can favor the chelation control in the reduction step.

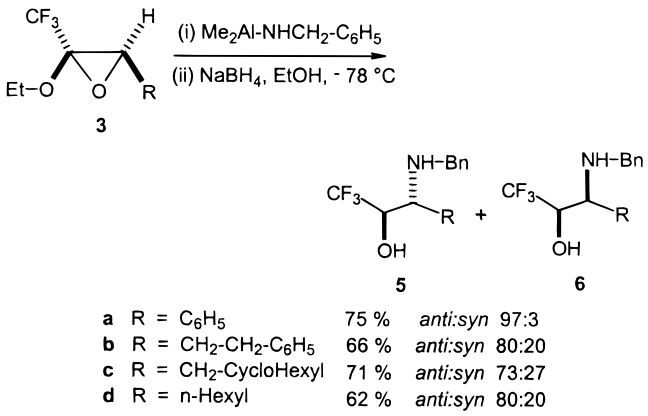
In this paper, we report the reaction of epoxy ethers **3** with aluminum amides as a new and efficient preparation of anti amino alcohols **2** and the enantioselective preparation of these latter through the reaction of chiral epoxy ethers, prepared by asymmetric epoxidation of enol ethers **4** (Figure 1).

Results and Discussion

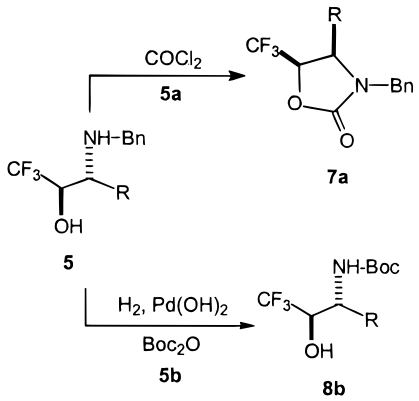
Epoxy ethers were prepared by *m*-chloroperbenzoic acid (*m*-CPBA) epoxidation of enol ethers **4**, obtained in good yields through the Wittig olefination of ethyl trifluoroacetate.[17,18] Dimethylaluminum amides[19] were prepared in dichloromethane at 0 °C from trimethylaluminum (Me_3Al) and a primary amine, used in a strictly stoechiometric proportion.

The epoxy ethers **3** reacted slowly at room temperature with 2 equiv of the dimethylaluminum benzylamide. The reaction with **3a** was monitored by ^{19}F NMR: signal of starting epoxy ether at −78 ppm slowly disappeared (in ∼16 h) with the appearance of a signal at −74.8 ppm. The reduction step was then performed in situ at −78 °C with $NaBH_4$ in the presence of ethanol. The use of ethanol as solvent is very important since, in methanol, the reaction failed, leading to an inseparable mixture. In ethanol, the N-monosubstituted amino alcohols *anti*-**5** and *syn*-**6** were obtained in good yields (Scheme 1). No trace of products resulting from ring opening by a methyl group, as previously observed with Me_3Al,[20] could be detected. Furthermore, nucleophilic substitution occurred at C_β, whatever the R group is, unlike reactions with $EtAlCl_2$ and Me_3Al, which most often occurred with a Cα−O bond cleavage.[20] As expected, the anti/syn diastereoselectivity is high, ranging from 97/3 (R = C_6H_5) to 73/27 (R = $CH_2C_6H_{13}$). The anti configuration of the major isomer has been determined by NMR data of the corresponding oxazolidinone **7a** (^3J = 9 Hz) according to the literature[15,21] and then by comparison of ^{19}F NMR chemical shifts (Scheme 2).

Scheme 1



Scheme 2



The selective formation of anti diastereoisomers confirms that the aluminum atom allows a chelation control in the reduction reaction. Surprisingly, the ^{13}C NMR spectrum of this chelated intermediate, before addition of $NaBH_4$/ethanol, exhibited no signal corresponding to a ketonic group but a quadruplet at 88 ppm ($^2J_{CF}$ = 26 Hz), indicating a hemiketal that was supposed to be the intermediate **A** (Figure 2). However, since the addition of hydride must involve a ketonic function, the reactive intermediate is likely the complex **B**, produced immediately on addition of ethanol. Hydride addition takes place on the less hindered face leading to anti amino alcohols **5** (Figure 2).

We have shown, as an example, that the *N*-benzylamino alcohol **5b** could be converted to *N*-Boc amino alcohol **8b** through catalytic hydrogenation promoted by palladium hydroxide in the presence of Boc_2O (Scheme 2).

Chiral *anti*-Trifluoromethyl *β*-Amino Alcohols. Two approaches have been investigated to obtain chiral anti amino alcohols: first we performed the reaction of epoxy ethers **3a**,**b** with the chiral dimethylaluminum amide, prepared from the (*R*)-phenethylamine and Me_3Al (Scheme 3). From **3a**, the reaction was effective, leading, after reduction, to a 50:50 mixture of the anti diastereoisomers **9a** and **10a** (anti/syn 98:2) (Scheme 3). Here again, the selectivity anti/syn is poorer (70:30) when

(17) Bégué, J. P.; Benayoud, F.; Bonnet-Delpon, D.; Fischer-Durand, N.; Sdassi, H. *Synthesis* **1993**, 1083−1085.

(18) Bégué, J. P.; Mesureur, D. *J. Fluorine Chem.* **1988**, *39*, 271. Bégué, J. P.; Bonnet-Delpon, D.; Née, G.; Wu, S. W. *J. Org. Chem.* **1992**, *57*, 3807. Bégué, J. P.; Bonnet-Delpon, D.; Kornilov, A. *Organic Synthesis*, in press.

(19) (a) Levin, J. I.; Turos, S. M.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195−198.

(20) Bégué, J. P.; Bonnet-Delpon, D.; Benayoud, F. *J. Org. Chem.* **1995**, *60*, 5029−5036.

(21) Sham, H. L.; Trempel, C. A.; Stein, H.; Cohen, J. J. *J. Chem. Soc., Chem. Commun.* **1990**, 904−905.

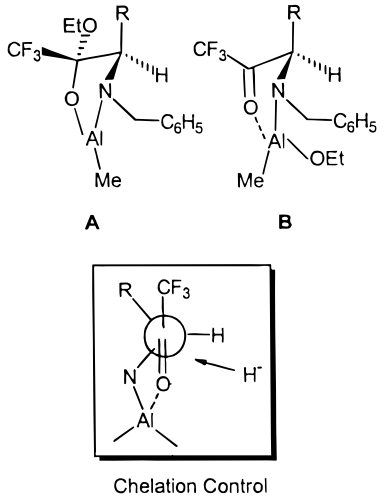
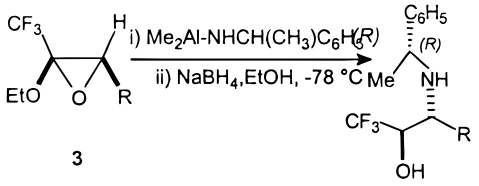


Figure 2.

Scheme 3



a R = C_6H_5 70% d.e. = 50:50

b R = CH_2-CH_2-C_6H_5 60% d.e. = 50:50

the R group is different from phenyl (R = $CH_2CH_2C_6H_5$). Separation of the anti diastereoisomers **9b** was efficient by crystallization of the mandelate salts.

A second approach, based on the ring opening of chiral epoxy ethers **11** and **12**, has been investigated. Since the preparation of chiral epoxy ethers from enol ethers bearing a chiral auxiliary was disappointing,[22] we turned to the SALEN-mediated asymmetric epoxidation, largely developed by Jacobsen[23] and by Katsuki.[24] The reaction of the enol ether **4a** with the (*R*,*R*) Mn-salen **13**, bleach, and 4-phenylpyridine *N*-oxide as co-oxidant, under the accurate conditions of pH reported by Jacobsen,[23] has been monitored by GC with an internal standard. The reaction was very slow compared to that of nonfluorinated enol ethers.[24] However, the epoxy ether **11a** was relatively stable in the reaction medium in contrast to nonfluorinated epoxy ethers, which could not be isolated in this reaction.[25,26] We noticed that efficiency of the catalyst decreased with the reaction time and that reaction rate slowed after some hours. Thus, despite the relative stability of epoxy ether **11a**, degradation partially occurred (Figure 3). The best compromise reaction time was 16 h, with about 50−60% of conversion. The ee (≥80%) of the resulting epoxy ether **11a** could be determined by ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$. Despite the weakly basic character of epoxy ether **11a**, an interaction with Eu(hfc)$_3$ occurred, allowing a shift of the *β*-proton (Figure 4). The same reaction performed with the (*S*,*S*) Mn-salen catalyst **14** led to the epoxy ether **12a** (Scheme 4). Enol ether **4b** has also been studied under the same conditions. With **4b**, degradation of the produced epoxy ether was faster than the disappearance of starting material (Figure 3).

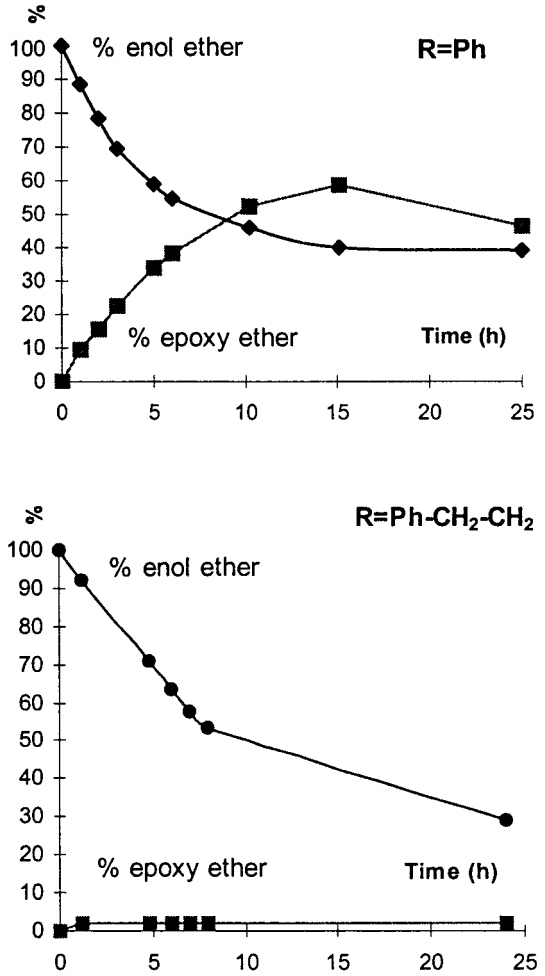


Figure 3. Mn-salen asymmetric epoxidation of enol ethers **4a** and **4b**.

As separation of epoxy ethers **11a** or **12a** from starting enol ether **4a** was difficult, the crude mixture resulting from the asymmetric epoxidation was directly used for the preparation of amino alcohols **9a** and **10a**. Reaction of **11a** and **12a** with the aluminum amide prepared from Me_3Al and the (*R*)-phenethylamine and subsequent reduction step occurred with the same excellent anti/syn diastereoselection (95:5) as before and led, respectively, to anti amino alcohols **9a** and **10a**. These amino alcohols are obtained with excellent purity (**9a**/**10a** = 93/7; **10a**/**9a** = 90/10). The stereoisomeric excess is the same as the enantiomeric excess of starting epoxy ethers. No racemization occurred in the reaction: ring opening does not involve a carbenium ion, and no enolization occurs from intermediate **A** or **B**. Unfortunately, we have not been able to assign the absolute configuration of the asymmetric carbons of **9a** and **10a**. Debenzylation with palladium hydroxide led to homochiral amino alcohols **15a** and **16a** (Scheme 5).

(22) (a) Bégué, J. P.; Bonnet-Delpon, D.; Kornilov, A. Unpublished results. (b) Bégué, J. P.; Rollin, P.; Richard, C. Unpublished results.
(23) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064. Brandies, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380.
(24) Katsuki, T. *J. Synth. Org. Chem. Jpn* **1995**, *53*, 940−951.
(25) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4389−4392.
(26) Adam, W.; Fell, R. T.; Mock-Knoblauch, C.; Saha-Möller, C. *Tetrahedron Lett.* **1996**, *37*, 4389−4392.

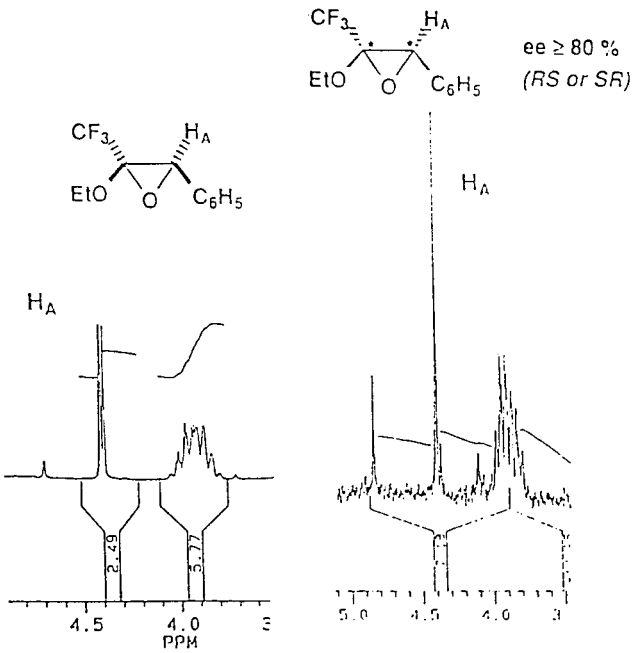


Figure 4. ^{1}H NMR (400 MHz) determination of the ee of epoxy ethers **11a** and **12a** in the presence of Eu(hfc)$_3$.

In conclusion, these results have highlighted the usefulness of aluminum amide as nucleophilic amination reagent in the epoxy ether ring opening to prepare fluoroalkyl aminoalcohols. Ring opening is stereoselective. Chelation control in the reduction is efficient. Stabilization by complexation of the unstable intermediate α-amino ketone is essential for the chiral approach to fluoroalkyl amino alcohols. Both homochiral epoxy ethers (*R*,*R*) and (*S*,*S*) could be obtained by asymmetric epoxidation with Mn-salen with an 80% ee, whereas nonfluorinated epoxy ethers cannot be isolated in a such reaction. From these chiral epoxy ethers, homochiral trifluoromethyl *β*-amino alcohols could be prepared. Studies are in progress for new applications of these valuable synthons, which can be obtained in enantiomerically pure form.

Experimental Section

NMR spectra have been performed in $CDCl_3$ solution on a Varian EM, FH dual probehead and/or Bruker AC 200 and ARX 400 (^{1}H: 90, 200, or 400 MHz; ^{19}F: 84, 188, or 376 MHz; ^{13}C: 50, 75, or 100 MHz). Chemical shifts are reported in ppm relative to Me_3Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C−F coupling. For the determination of fine coupling constants, an acquisition of 16K data points, a Lorenz-Gauss transformation of the FID, and a zero filling to 64K were performed in order to obtain a minimum of resolution of 0.2 Hz/pt (^{1}H and ^{19}F) or 0.5 Hz/pt (^{13}C). COSY, HMQC, and HMBC experiments were performed on a multinuclear probehead equipped with a Z-gradient coil. GC analysis was performed on a capillary column SE30, 10 or 25 m.

General Procedure for *anti*-Amino Alcohol 5: Reaction of Epoxy Ether 3 with Aluminum Amide. Trimethylaluminum (1.65 mL of a solution 2 M in hexanes, 2 equiv) was slowly added via syringe at 0 °C under Ar to a stirred solution of the primary amine (3.3 mmol, 2 equiv) in CH_2Cl_2 (8 mL). After 1 h, the solution of 1-CF_3 epoxy ether (1.65 mmol, 1 equiv) in CH_2Cl_2 (8 mL) was added. After 1 h at 0 °C, the reaction mixture was stirred 24 h at 25 °C and then cooled to −78 °C. EtOH (5 mL) and $NaBH_4$ (124 mg, 3.3 mmol, 2 equiv) were added. After 1 h at this temperature, the reaction mixture was stirred for 1 h at room temperature. Water (2 mL) and Et_2O (30 mL) were added. The resulting mixture was directly dried with $MgSO_4$ and concentrated. The residue was purified by SiO_2 column chromatography, leading to the pure anti amino alcohol **5**.

***anti*-3-(*N*−Benzylamino)-1,1,1-trifluoro-2-hydroxy-3-phenylpropane (5a).** From epoxy ether **3a** (200 mg, 0.85 mmol), Me_3Al (0.85 mL of a solution 2 M in hexanes), and benzylamine (185 mg, 1.7 mmol), after reaction, reduction step, and workup and purification, amino alcohols **5a** and **6a** were obtained as a (97:3) mixture (190 mg, 75%). After chromatography (petroleum ether/Et_2O 80:20), pure *anti*-**5a** was obtained: mp 103 °C; NMR ^{19}F δ −73.9 (d, $^3J_{HF}$ = 7.6 Hz); NMR ^{1}H δ 3.76 (q_{AB}, δ_A = 3.69, δ_B 3.82, ^2J = 13 Hz, CH_2−N), 3.9 (d, ^3J = 4.7 Hz, 1 H, H-3), 4.2 (qd, $^3J_{HF}$ = 7.4 Hz, ^3J = 4.7 Hz, 1 H, H-2), 7.2 (m, 10 H); NMR ^{13}C δ 51.0, 61.3, 72.0 (q, $^2J_{CF}$ = 28.6 Hz), 124.7 (q, $^1J_{CF}$ = 283.4 Hz), 127.6, 128.4, 128.6, 128.7, 136.5, 138.8. Anal. Calcd for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74. Found: C, 64.72; H, 5.58; N, 4.74.

***anti*-3-(*N*-Benzylamino)-1,1,1-trifluoro-2-hydroxy-5-phenylpentane (5b).** From epoxy ether **3b** (200 mg, 0.77 mmol), Me_3Al (0.8 mL of a solution 2 M in hexanes), and benzylamine (170 mg, 1.6 mmol), after reaction, reduction step, workup, and purification, amino alcohols **5b** and **6b** were obtained in a 80:20 mixture (164 mg, 66%). After chromatography (petroleum ether/Et_2O 80:20), pure *anti*-**5b** was obtained: NMR ^{19}F δ −73.7 (d, $^3J_{HF}$ = 7.6 Hz); NMR ^{1}H δ 1.8 (m, 2 H), 2.6 (t, ^3J = 7 Hz, 2 H), 2.8 (bs, 1 H, NH), 2.9 (m, 1 H, H-2), 3.1 (bs, 1 H, OH), 3.8 (q, $^3J_{AB}$ = 12.8 Hz), 4.1 (qd, $^3J_{FH}$ = 7.5 Hz, ^3J = 6.4 Hz, 1 H, H-2), 6.8−7.3 (m, 10 H); NMR ^{13}C δ 30.9, 32.3, 51.7, 56.8, 69.1 (q, $^2J_{CF}$ = 28.8 Hz), 126.3 (q, $^1J_{CF}$ = 280 Hz), 127.4, 128.2, 128.3, 128.5, 128.6, 138.9, 141.0. Anal. Calcd for $C_{18}H_{20}F_3NO$: C, 66.86; H, 6.23; N, 4.33. Found: C, 66.57; H, 6.39; N, 4.25.

***anti*-3-(N-Benzylamino)-1,1,1-trifluoro-2-hydroxy-4-cyclohexylbutane (5c).** From epoxy ether **3c** (3 g, 12 mmol), Me_3Al (12 mL of a solution 2 M in hexanes), and benzylamine (2.55 g, 24 mmol) after reaction, reduction step, and workup, amino alcohols **5c** and **6c** were obtained in a 73:27 mixture (2.67 g, 71%) and have been separated by a chromatography on SiO_2.

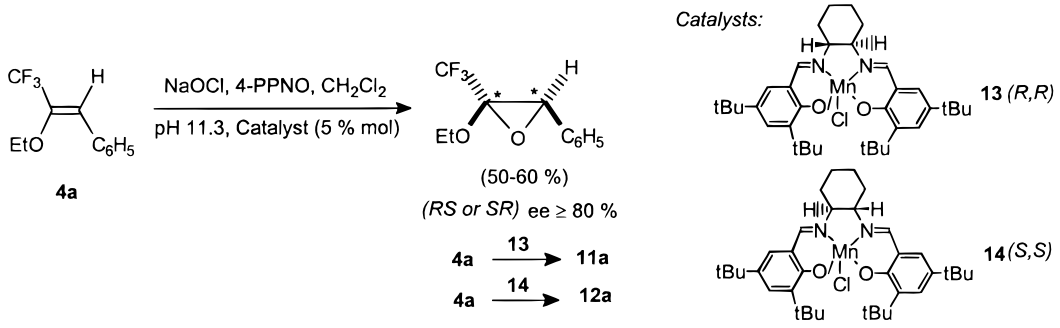
syn-Amino alcohol **6c** (petroleum ether/AcOEt, 90/10): mp 69 °C; NMR ^{19}F δ −78.0 (d, $^3J_{HF}$ = 8.2 Hz); NMR ^{1}H δ 0.8−1.8 (m, 13 H), 2.75 (m, 1 H, OH), 3.04 (td, ^3J = 7.4, 2.34 Hz, 1 H, H-3), 3.55 (qd, $^3J_{HF}$ = 8.2 Hz, ^3J = 2.3 Hz, 1 H, H-2), 3.80 (q_{AB}, δ_A = 3.73, δ_B 3.86, ^2J = 12.9 Hz, CH_2N), 7.30 (m, 5 H); NMR ^{13}C δ 26.0, 26.2, 26.3, 32.8, 33.5, 34.1, 42.8, 52.0, 52.74, 71.15 (q, $^2J_{CF}$ = 29.7 Hz), 125.5 (q, $^1J_{CF}$ = 288.7 Hz), 127.6, 127.9, 128.4, 128.7, 128.8, 139.1. Anal. Calcd for $C_{17}H_{22}F_3NO$: C, 64.74; H, 7.1; N, 4.44. Found: C, 64.8; H, 7.09; N, 4.45.

anti-Amino alcohol **5c** (petroleum ether/AcOEt, 85/15): mp 65 °C; NMR ^{19}F δ −73.4 (d, $^3J_{HF}$ = 8.2 Hz); NMR ^{1}H δ 0.8−1.6 (m, 13 H), 2.94 (m, ^3J = 7.7, 4.2 Hz, ^4J = 1 Hz, 1 H, H-3), 3.76 (q_{AB}, δ_A = 3.69, δ_B 3.82, ^2J = 13 Hz, CH_2N), 3.94 (qd, $^3J_{HF}$ = 8.2 Hz, ^3J = 4.2 Hz, 1 H, H-2), 7.28 (m, 5 H); NMR ^{13}C δ 26.1, 26.2, 26.3, 33.1, 33.8, 34.2, 37.1, 52.2, 69.0 (q, $^2J_{CF}$ = 28.6 Hz), 125.0 (q, $^1J_{CF}$ = 283.8 Hz), 127.7, 128.3, 128.5, 128.7, 128.8, 139.4. Anal. Calcd for $C_{17}H_{22}F_3NO$: C, 64.74; H, 7.1; N, 4.44. Found: C, 64.97; H, 7.28; N, 4.40.

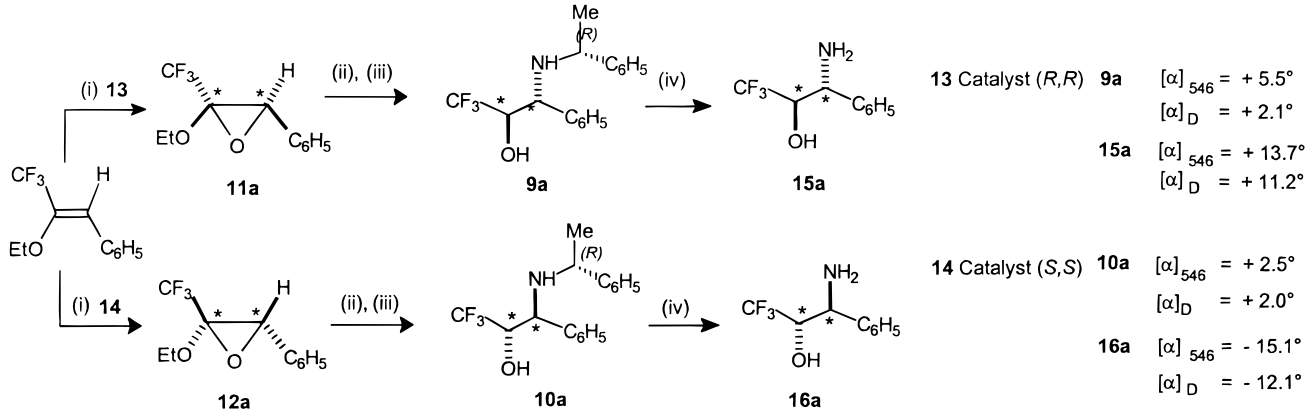
***anti*-3-(*N*-Benzylamino)-1,1,1-trifluoro-2-hydroxy-4-nonane (5d).** From epoxy ether **3d** (700 mg, 2.9 mmol), Me_3Al (2.9 mL of a solution 2 M in hexanes), and benzylamine (625 mg, 5.8 mmol), after reaction, reduction step, workup, and purification, amino alcohols **5d** and **6d** were obtained in a 80:20 mixture (540 mg, 62%), leading after chromatography to pure **5d** as an oil (280 mg): NMR ^{19}F δ −73.6 (d, $^3J_{HF}$ = 7.3 Hz); NMR ^{1}H δ 0.8 (t, 3 H), 1.23 (m, 8 H), 1.55 (m, 2 H), 2.4 (brs, 2 H, NH, OH), 2.80 (m, 1 H)), 3.80 (q, ^3J = 12.8 Hz, δ_A 3.92 δ_B 3.92), 3.96 (dq, $^3J_{FH}$ = 7.9 Hz, ^3J = 4.4 Hz, 1 H, H-2), 7.25 (m, 5 H); NMR ^{13}C δ 14.1, 22.6, 26.3, 29.4, 29.6, 31.7, 52.4, 58.0, 68.9 (q, $^2J_{CF}$ = 29 Hz), 120.0 (q, $^1J_{CF}$ = 278 Hz), 127.6, 128.3, 128.8, 139.3. Anal. Calcd for $C_{16}H_{24}F_3NO$: C, 64.34; H, 7.97; N, 4.62. Found: C, 64.11; H, 8.18; N, 4.50.

5-Benzyl-3-(trifluoromethyl)-4-phenyloxazolidin-2-one (7a). A solution of amino alcohol **5a** (139 mg, 0.47 mmol)

Scheme 4



Scheme 5[a]



[a] Key: (i) NaOCl, 4-PPNO, CH_2Cl_2, 0 °C, catalyst (5% mol), 18 h; (ii) $Me_2Al-NHCH(CH_3)-C_6H_5$ (*R*); (iii) BH_4Na; (iv) $Pd(OH)_2/C$; H_2.

and triethylamine (0.2 mL, 1.2 mmol, 2.5 equiv) in toluene (7 mL) was cooled to 0 °C, treated with a 20% solution of phosgene in toluene (4.7 mL, 0.95 mmol, 2 equiv), and stirred for 30 min (the reaction was monitored by TLC). After complete reaction, methanol (3.5 mL) was added, and the mixture was washed with an aqueous saturated solution of $NaHCO_3$ (10 mL). The aqueous layers were extracted with CH_2Cl_2 several times, and the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the crude oxazolidinone **7a** (130 mg, 86%): NMR ^{19}F δ −73.0 (d, $^3J_{HF}$ = 6.6 Hz); NMR ^1H δ 4.1 (d, J = 14 Hz, 1 H), 4.59 (d, ^3J = 9 Hz, 1 H, H-4), 4.76 (d, ^3J = 14 Hz, 1 H), 4.82 (dq, ^3J = 9 Hz, $^3J_{FH}$ = 6.6 Hz, H-3), 4.92 (d, ^3J = 9 Hz, H_β), 7.3 (m, 10 H); NMR ^{13}C δ 46.8, 60.9, 73.9, 121.9 ($^1J_{CF}$ = 274 Hz), 127, 127.3, 128.6, 128.9, 135.4, 139.8, 155.4.

***anti*-3-(Tert-Butylcarboxyamino)-1,1,1-trifluoro-2-hydroxy-5-phenylpentane (8b).** A solution of amino alcohol **5b** (100 mg, 0.3 mmol) in AcOEt (4 mL) was stirred with Boc_2O (97 mg, 0.44 mmol, 1.5 equiv) and $Pd(OH)_2$ (20 mg) under H_2 during 24 h at room temperature. After filtration of the catalyst, the filtrate was concentrated. The crude *N*-Boc amino alcohol **8b** was purified by SiO_2 chromatography (petroleum ether/AcOEt, 80:20) to give the pure compound **8b** (61 mg, 62%): NMR ^{19}F δ −74.7 (d, $^3J_{HF}$ = 7.6 Hz); NMR ^1H δ 1.45 (s, 9 H), 1.85 (m, 2 H), 2.66 (m, 2 H), 3.70 (m, 1 H, C-3), 3.94 (qd, $^3J_{HF}$ = 8.2 Hz, ^3J = 4.2 Hz, 1 H, H-2), 4.3 (bd, 1 H), 4.6 (bd, 1 H), 7.15 (m, 5 H); NMR ^{13}C δ 28.2, 31.6, 32.6, 45.5, 52.3, 74.8 (q, $^2J_{CF}$ = 28.6 Hz), 127.8 (q, $^1J_{CF}$ = 288 Hz), 127.3, 128.9, 129.3, 176.7. Anal. Calcd for $C_{16}H_{24}F_3NO$: C, 57.30; H, 7.21; N, 4.17. Found: C, 57.09; H, 7.00; N, 3.95.

(2*S,3*R**)-*anti*-3-((*R*)-Phenethylamino)-1,1,1-trifluoro-2-hydroxy-5-phenylpropane (9a and 10a).** From epoxy ether **3a** (200 mg, 0.85 mmol), Me_3Al (0.85 mL of a solution 2 M in hexanes), and (*R*)-phenethylamine (207 mg, 1.7 mmol), after reaction, workup, and purification, a 98:2 anti/syn mixture of the anti amino alcohols **9a** and **10a**, in a ratio 50:50, was obtained (184 mg, 69%): NMR ^{19}F δ −73.5 (d, $^3J_{HF}$ = 7.4 Hz) (**9a**) and −73.8 (d, $^3J_{HF}$ = 7.3 Hz) (**10a**) (description below); amino alcohols syn: NMR ^{19}F δ 77.4 (d, $^3J_{FH}$ = 7.3 Hz).

(2*S,3*R**)-*anti*-3-(*R*)-(Phenethylamino)-1,1,1-trifluoro-2-hydroxy-5-phenylpentane (9b and 10b).** From epoxy ether **3b** (3.402 g, 13 mmol), Me_3Al (13.08 mL of a solution 2 M in hexanes), and (*R*)-phenethylamine (3.171 g, 26 mmol), after reaction and workup, amino alcohols were obtained after purification as a 70:30 mixture of anti and syn isomers (2.706 g, 61%): ^{19}F δ −73.2 (d, $^3J_{FH}$ = 8.5 Hz) (37%) (anti), −73.7 (d, $^3J_{HF}$ = 7.6 Hz) (33%) (anti), −77.5 (d, $^3J_{HF}$ = 7.6 Hz) (13%) (syn), −77.9 (d, $^3J_{FH}$ = 7.6 Hz) (17%) (syn).

After chromatography on SiO_2 (petroleum ether/AcOEt, 65/35), formation of the (*S*) mandelate salt, and further liberation, one pure anti isomer could be isolated as an oil: $[\alpha]_D$ = −31.8°, $[\alpha]_{546}$ = −36.4°, $[\alpha]_{495}$ = −41.54° (MeOH, *c* = 1.95); NMR ^{19}F δ −73.7 (d, $^3J_{HF}$ = 7.8 Hz); NMR ^1H δ 1.30 (d, ^3J = 6.5 Hz, 3 H), 1.75 (q, ^3J = 7.3 Hz, 2 H), 2.6 (m, 2 H), 2.8 (m, 1 H, H-3), 3.7 (q, ^3J = 6.5 Hz), 4.1 (qd, $^3J_{HF}$ = 7.8 Hz, ^3J = 4.0 Hz, 1 H, H-2), 7.2 (m, 10 H); NMR ^{13}C δ 23.9, 31.8, 32.5, 55.3, 56.1, 68.4 (q, $^2J_{CF}$ = 28.8 Hz), 125.5 (q, $^1J_{CF}$ = 283.8 Hz), 126.3, 126.7, 127.8, 128.4, 128.7, 141.4, 145.0. Anal. Calcd for $C_{19}H_{22}F_3NO$: C, 67.67; H, 6.57; N, 4.15. Found: C, 67.24; H, 6.65; N, 4.08.

Chiral Epoxidation of 1-CF_3 Enol Ether: General Procedure. A round-bottom flask equipped with magnetic bar was charged with a solution of commercial bleach (2.3 mL, 1.5 mmol, ACROS, 13% of active chlorine) and a 0.05 M aqueous solution of Na_2PO_4 (13.3 mL) buffered to pH = 11.3 with 1 M NaOH aqueous solution. To this precooled solution at 0 °C were added a solution of enol ether **4** (200 mg, 0.98 mmol) in CH_2Cl_2 (2.5 mL), (*R*,*R*)- or (*S*,*S*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (31 mg, 0.05 mmol) **13** or **14**, and 4-phenylpyridine *N*-oxide (4-PPNO) (103 mg, 0.6 mmol). The course of the reaction was monitored by GC against internal quantitative standard (undecane or dodecane). The reaction was stirred at 0−2 °C for 15−24 h. The reaction mixture was poured into petroleum ether. The aqueous layer was separated and washed several times with petroleum ether. The combined organic phases were washed with water, separated, dried over $MgSO_4$, filtered through a Celite column, and concentrated. The crude product

was usually used without purification for the reaction with the reaction with aluminum amide.

Asymmetric Epoxidation of Enol Ether 4a with (*R*,*R*)-Salen 13. The epoxidation reaction from enol ether **4a** (600 mg, 2.9 mmol) and (*R*,*R*)-Salen-Mn complex **13** (94 mg, 0.15 mmol) and internal standard (undecane) was monitored by GC. After 15−17 h, the conversion ratio was about 50−60%. When the reaction time was prolonged, the slow disappearance of the epoxy ether was observed. After workup and filtration on SiO_2, the crude mixture of epoxy ether **11a** and enol ether **4a** was isolated (382 mg, 60:40). The ee (determined by NMR in the presence of Eu(hfc)$_3$ at 400 MHz) was 80−90%.

Asymmetric Epoxidation of Enol Ether 4a with (*S*,*S*)-Salen 14. The epoxidation reaction (15−17 h) from enol ether **4a** (600 mg, 2.9 mmol) and (*S*,*S*)-salen-Mn complex **14** (94 mg, 0.15 mmol) led after the workup to a crude mixture of epoxy ether **12a**, and enol ether **4a** was isolated (314 mg, 61:39).

Asymmetric Epoxidation of Enol Ether 4b. The epoxidation reaction from enol ether **4b** (200 mg, 0.82 mmol) and (*R*,*R*)-salen-Mn complex **13** (26 mg) was monitored by GC in the presence of an internal standard (dodecane). The disappearance of enol ether **4b** was observed (60% after 16 h), but the epoxy ether **11b** was not detected at any time. After 24 h, the reaction was treated, and enol ether **4b** was partially recovered (40 mg, 20%).

3-(*S)-((*R*)-Phenethylamino)-1,1,1-trifluoro-2(*R**)-hydroxy-5-phenylpropane (9a).** From crude epoxy ether **11a** (788 mg of a mixture of **11a**/**4a** 52:48), Me_3Al (1.75 mL of a 2 M solution in hexanes), and (*R*)-phenethylamine (408 mg, 3.5 mmol), after reaction and reduction, amino alcohol **9a** was obtained (390 mg, 71% (yield calculated from epoxy ether **11a**) (de 90%, anti/syn 95:5). Pure **9a** (247 mg) was obtained after chromatography (petroleum ether/AcOEt, 90/10): $[\alpha]_D$ = +118.4°, $[\alpha]_{546}$ = +140.5° (MeOH, c = 1.85); NMR ^{19}F δ −73.5 (d, $^3J_{FH}$ = 7.4 Hz); NMR ^{1}H δ 1.30 (d, ^3J = 6.5 Hz, 3 H), 3.67 (q, ^3J = 6.5 Hz, 1 H), 4.05 (d, ^3J = 4.4 Hz, 1 H, H-3), 4.18 (qd, $^3J_{FH}$ = 7.4 Hz, ^3J = 4.4 Hz, 1 H, H-2), 7.2 (m, 10 H); NMR ^{13}C δ 22.3, 54.7, 59.5, 71.6 (q, $^2J_{CF}$ = 28.9 Hz), 124.7 (q, $^1J_{CF}$ = 283 Hz), 126.3, 127.4, 127.8, 128.1, 128.7, 141.4, 145.0. Anal. Calcd for $C_{17}H_{18}F_3NO$: C, 65.96; H, 5.82; N, 4.52. Found: C, 66.22; H, 5.75; N, 4.38.

3(*R)-((*R*)-Phenethylamino)-1,1,1-trifluoro-2(*S**)-hydroxy-5-phenylpropane (10a).** From crude epoxy ether **12a** (400 mg of a mixture **12a**/**4a** 54:46), Me_3Al (1.2 mL of a 2 M solution in hexanes), and (*R*)-phenethylamine (288 mg, 2.4 mmol), after reaction and reduction step, amino alcohol **10a** was obtained (216 mg, 75%, calculated from epoxy ether **12a**) (de 90%, anti/syn 95:5). Pure **10a** (168 mg) was obtained after chromatography (petroleum ether/AcOEt, 90/10): $[\alpha]_D$ = +1.85°, $[\alpha]_{546}$ = +2.44° (MeOH, c = 3.25); NMR ^{19}F δ −73.7 (d, $^3J_{FH}$ = 7.3 Hz); NMR ^{1}H δ 1.30 (d, ^3J = 6.5 Hz, 3 H), 3.67 (q, ^3J = 6.5 Hz, 1 H), 4.05 (d, ^3J = 4.4 Hz, 1 H, H-3), 4.18 (qd, $^3J_{FH}$ = 7.4 Hz, ^3J = 4.4 Hz, 1 H, H-2), 7.2 (m, 10 H); NMR ^{13}C δ 22.3, 54.7, 59.5, 71.6 (q, $^2J_{CF}$ = 28.9 Hz), 124.7 (q, $^1J_{CF}$ = 283 Hz), 126.4, 127.4, 127.7, 128.1, 128.6, 141.4, 145.0. Anal. Calcd for $C_{17}H_{18}F_3NO$: C, 65.96; H, 5.82; N, 4.52. Found: C, 66.24; H, 5.68; N, 4.34.

***anti*-3(*S**)-Amino-1,1,1-trifluoro-2(*R**)-hydroxy-5-phenylpropane (15a).** A solution of amino alcohol **9a** (124 mg, 0.4 mmol) in AcOEt (4 mL) was stirred with $Pd(OH)_2$/C 20% (50 mg) under H_2 during 24 h at room temperature. After filtration of the catalyst, the filtrate was concentrated, and the crude amino alcohol **15a** was purified by SiO_2 chromatography (petroleum ether/AcOEt, 60:40) to give the pure compound **15a** (77 mg, 94%): mp 142 °C; $[\alpha]_D$ = +10.5°, $[\alpha]_{546}$ = 12.7° (MeOH, c = 2.4); NMR ^{19}F δ −74.4 (d, $^3J_{HF}$ = 7.5 Hz); NMR ^{1}H δ 2.4 (m, 3 H, OH and NH_2), 4.15 (qd, $^3J_{HF}$ = 6.9 Hz, ^3J = 6.2 Hz, 1 H, H-2), 4.27 (d, ^3J = 5.7 Hz, 1 H), 7.38 (m, 5 H); NMR ^{13}C δ 55.7, 72.7 (q, $^2J_{CF}$ = 27 Hz), 125.4 (q, $^1J_{CF}$ = 247 Hz), 126.9, 127.7, 127.9, 142.8. Anal. Calcd for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.53; H, 5.08; N, 6.74.

***anti*-3-(*R**)-Amino-1,1,1-trifluoro-2(*S**)-hydroxy-5-phenylpropane (16a).** A solution of amino alcohol **10a** (89 mg, 0.29 mmol) in AcOEt (4 mL) was stirred with $Pd(OH)_2$/C 20% (36 mg) under H_2 during 24 h at room temperature. After filtration of the catalyst, fitrate was concentrated, and the crude amino alcohol **16a** was purified by SiO_2 chromatography (petroleum ether/AcOEt, 60:40) to give the pure compound **16a** (56 mg, 95%): mp 142 °C; $[\alpha]_D$ = −10.5°, $[\alpha]_{546}$ = 12.7 (MeOH, c = 2.4); NMR ^{19}F δ −74.4 (d, $^3J_{HF}$ = 7.5 Hz); NMR ^{1}H δ 2.4 (m, 3 H, OH and NH_2), 4.15 (qd, $^3J_{HF}$ = 6.9 Hz, ^3J = 6.2 Hz, 1 H, H-2), 4.27 (d, ^3J = 5.7 Hz, 1 H), 7.38 (m, 5 H); NMR ^{13}C δ 55.7, 72.7 (q, $^2J_{CF}$ = 27 Hz), 125.4 (q, $^1J_{CF}$ = 247 Hz), 126.9, 127.7, 127.9, 142.8. Anal. Calcd for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.48; H, 5.05; N, 6.69.

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