Chemistry of Novel Compounds with Multifunctional Carbon Structure. 9.[1] Molecular Design, Synthetic Studies, and NMR Investigation of Several Efficient Chiral Derivatizing Reagents which Give Very Large ^{19}F NMR $\Delta\delta$ Values in Enantiomeric Excess Determination

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In order to develop efficient ee-determining reagents potentially superior to MTPA (**1**), some multifunctional compounds **2**–**5** were rationally designed. From NMR investigations of the analogous diastereomeric derivatives it was found that the chemical shift differences for each pair of diastereomers ($\Delta\delta$ values) for CFPA derivatives **5d**–**f** were approximately five times greater in ^{19}F NMR spectra and two times greater in ^{1}H NMR spectra than those of **1d**–**f**. Synthesis of the optically pure CFPA, (−)-**5a** and (+)-**5a**, was achieved by nitrosation of each diastereomer of the optically active *N*-(1-phenylethyl)amides, $\mathbf{5f_M}$ and $\mathbf{5f_L}$, followed by thermal decomposition. Various derivatives were prepared by the condensation of **5b** and **1b** with alcohol and amine nucleophiles, and both $\Delta\delta_F$ and $\Delta\delta_H$ values were obtained for each compound. The CFPA derivatives **5d**–**m** have proven to be significantly superior for ee determinations when compared to the corresponding MTPA derivatives **1d**–**m**, particularly in compounds having remotely disposed chiral centers.

Introduction

The determination of enantiomeric excess (ee) of chiral molecules is one of the most important and indeed, indispensable, processes in modern organic chemistry, especially in the theoretical and practical study of asymmetric synthesis. Many methods for ee determination[2] are known which involve NMR, GC, LC, and polarimetric techniques. Among those, the method of condensation of a sample of interest with a chiral derivatizing reagent and determination of optical purity through NMR spectroscopic quantitation of the derived two diastereomers is a very useful and practical technique.[3] Mosher's method[4] of using α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, **1a**)[5] is currently the most widely employed for alcohols and amines because of the convenience in handling **1a** and the general availability of both ^{19}F and ^{1}H NMR probes.

However, many instances have been reported where ee determination by this method failed because of insufficient reactivity[6] of MTPA chloride (MTPA-Cl, **1b**) toward some secondary alcohols due to inherent steric crowding of the MTPA structure and/or because of very small chemical shift differences between the two MTPA diastereomers ($\Delta\delta$ values),[7] even by ^{19}F NMR spectroscopy, especially for those compounds which have remotely disposed chiral centers. During the course of our studies of both theoretical molecular design and synthetic studies of new ee determining reagents,[8,9] we have recently reached the conclusion[10] that α-cyano-α-fluorophenylacetic acid (CFPA, **5a**) is much more widely applicable for ee determination than the existing reagents,[2] including **1a** and others recently reported.[11–13] Here we report the full account of the design and synthetic studies of structurally new compounds **2**–**5** and the detailed process of the development of acid **5a** as a practical ee-determining reagent by evaluation of $\Delta\delta_F$ and $\Delta\delta_H$ NMR data.

Results and Discussion

Molecular Design of Efficient Reagents for ee Determination. Two important factors for new candidate carboxylic acids to serve as efficient chiral derivatizing reagents are (1) a high ability for distinguishing the two diastereomers derived from them and (2) a high reactivity of the corresponding acid chlorides for complete conden-

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(1) Part 8: Takeuchi, Y.; Itoh, N.; Kawahara, S.; Koizumi, T. *Tetrahedron*, in press.

(2) (a) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1983; Vol. 1. (b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(3) In contrast to the direct method for ee determination, the indirect method involving derivatization of chiral samples into the two diastereomers has several merits in addition to ee determination, e.g., structural characterization, prediction of absolute configuration, purification, enantiomeric separation, etc.

(4) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(5) Although there are a few reagents reported for ee determination of carboxylic acids and aldehydes, methods for assessing the chirality of alcohol, thiol, and amine compounds, like Mosher's method, are much more widely applicable considering the variety of structures to be applied and ease of establishing the reaction conditions employed for complete derivatization.

(6) Svatos, A.; Valterova, I.; Saman, D.; Vrkoc, J. *Collect. Czech. Chem. Commun.* **1990**, *55*, 485.

(7) We ascribe the relatively small $\Delta\delta$ values for MTPA derivatives to the steric resemblance of the three substituents (Ph, OMe, and CF_3) on the chiral center of the MTPA structure.

(8) Takeuchi, Y.; Ogura, H.; Ishii, Y.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1721.

(9) Takeuchi, Y.; Ogura, H.; Ishii, Y.; Koizumi, T. *Chem. Pharm. Bull.* **1990**, *38*, 2404.

(10) Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318.

(11) Terunuma, D.; Kato, M.; Kamei, M.; Uchida, H.; Ueno, S.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3581.

(12) Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826.

(13) (a) Silks, L. A.; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979. (b) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Org. Chem.* **1991**, *56*, 6733. (c) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495.

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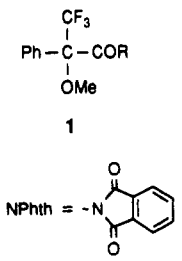

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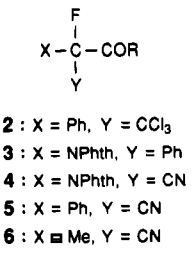


2 : X = Ph, Y = CCl_3
3 : X = NPhth, Y = Ph
4 : X = NPhth, Y = CN
5 : X = Ph, Y = CN
6 : X = Me, Y = CN

a : R = OH
b : R = Cl
c : R = OEt
d : R = OCH(Me)Et
e : R = OCH(Me)Ph
f : R = NHCH(Me)Ph

sation with various nucleophiles. Detection by ^1H NMR spectroscopy of the OMe signals of the acid part or any proton signals in the alcohol or the amine part of MTPA derivatives can be limited because of small $\Delta\delta_H$ values in general and signal-overlapping by other protons of the sample. In contrast, ^{19}F NMR detection of the two CF_3 signals in the MTPA diastereomers is more useful, especially for structurally complex molecules. The fact that the ^{19}F nucleus generally has a remarkably large range of chemical shift values and an almost 2 orders of magnitude higher relative sensitivity[14] when compared to other nuclei such as ^2H,[15,16] ^{13}C,[16,17] ^{31}P,[18] and ^{77}Se[13] became the focus of our thinking.

In designing new reagents which might exceed the capability of, but still preserve the merits of MTPA (**1a**), it was found to be significant for the molecules to have *a single fluorine atom*,[8] *as well as a phenyl group or the steric equivalent*,[9] directly attached to the chiral center. The third substituent on the α-carbon of acetates should have suitable steric and electronic characteristics, namely, the substituent should have no protons and an effective steric bulkiness *significantly different* from that of both the F and the Ph substituents, while also having *a highly electronegative character*.[19] We believed that this substitution pattern would result in a molecule sufficiently reactive to nucleophilic condensation and it would induce, after diastereomer formation, large magnetic nonequivalencies between a pair of the diastereomeric derivatives.[20] It was also noted that the reagent should preferably be crystalline for convenience in handling.

On the basis of these design considerations, we turned our attention to some unique multifunctionalized fluorides, i.e., α-fluoro-α-(trichloromethyl)phenylacetate **2**, α-fluoro-*N*-phthaloylphenylglycinate **3**, α-cyano-α-fluoro-*N*-phthaloylglycinate **4**, and α-cyano-α-fluorophenylacetate **5**. α-Cyano-α-fluoropropionate **6** was also chosen to test the soundness of our molecular design. That is, structure **6** having a Me group on the α-position was predicted to bring about both lower reactivity and smaller $\Delta\delta$ values than **2–5** due to its electron-donating character and its steric similarity to the adjacent CN group.

Synthetic Studies of Representative Diastereomers of 2, 5, and 6. We chose three kinds of representative derivatives, i.e., 2-butyl ester (**d**), 1-phenylethyl ester (**e**), and *N*-(1-phenylethyl)amide (**f**) diastereomers as indicators to ascertain a preliminary structure–$\Delta\delta$ relationship. Since the direct synthesis of the multifunctional carbon compounds **2–6** in their acid forms seemed potentially difficult, based on our long experience in the synthesis of such compounds,[21,22] we attempted to prepare derivatives **2d–f**–**6d–f** directly as a "quick and dirty" approach in order to obtain their $\Delta\delta$ values for direct comparison with those of MTPA and of our specimens previously prepared.[8,9]

We first focused on the trichloromethylated compound **2** considering the ease of preparation. The cyanohydrin derivative obtained by treatment of trichloroacetophenone with TMSCN was fluorinated with (diethylamino)sulfur trifluoride (DAST) to give **7**. Reduction of the cyano group of **7** with DIBALH followed by Jones oxidation of the resulting aldehyde **8** successfully produced the desired acid **2a** as a crystalline substance. The rather unstable acid **2a** was converted, without purification, to the chloride **2b**, which was treated with three representative nucleophiles to afford the diastereomers **2d–f**. Although the $\Delta\delta_F$ values for **2d–f** in ^{19}F NMR spectra (Table I) were, in general, greater than those for **1d–f**,[23] they were smaller than we had expected.

We next turned our attention to the phthalimidyl structure **3**. Fluorination of *N*-phthaloylphenylglycine ethyl ester (**9**) to produce **3c** was accomplished by the use of our standard method[24] using diluted perchloryl fluoride ($FClO_3$). However, neither saponification of the ester **3c** to the acid **3a** nor direct conversion of **3c** into derivatives **3d–f** was successful, probably due to the steric crowding of the two bulky groups, so further efforts using **3** to establish ee's were abandoned.

We also attempted synthesis of the analogous structure **4** which contains a CN group in place of the Ph group of **3**. In addition to the CN group's inherently greater electronegativity, we hoped that its less crowded linear shape[9] would facilitate condensation of **4c** with nucleophiles. Bromo derivative **10** seemed to be a potential precursor of **4c**. Brominations (NBS/BPO/$h\nu$/CCl_4 and Br_2/LDA/THF or $h\nu$/CCl_4) of α-fluoro-*N*-phthaloylglycine ethyl ester[22] and phthalimidation (KNPhth/DMF/90 °C) followed by cyanation (NaCN/DMF/120 °C) of ethyl dibromofluoroacetate were attempted. However, **10** could not be obtained presumably because of the instability associated with the multifunctional carbon structure[21] and/or the failure of functionalization due to some steric and/or electronic problems (Scheme I).

(14) (a) Harris, R. K.; Mann, B. E. *NMR and the Periodic Table*; Academic Press: London, 1978. (b) Lee, K.; Anderson, W. A. *A Table of Nuclear Spins, Moments, and Magnetic Resonance Frequencies*; Varian Associates: Palo Alto, 1967.

(15) (a) Schwab, J. M.; Ray, T.; Ho, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 1057. (b) Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 83. (c) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274. (d) Brosch, D.; Kirmse, W. *J. Org. Chem.* **1991**, *56*, 907.

(16) Schwab, J. M.; Li, W.-b.; Thomas, L. P. *J. Am. Chem. Soc.* **1983**, *105*, 4800.

(17) (a) Mangeney, P.; Grojean, F.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2675. (b) Mangeney, P.; Alexakis, A.; Normant, J. F. *Ibid.* **1988**, *29*, 2677.

(18) (a) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (b) Feringa, B. L.; Smaardijk, A.; Wynberg, H. *Ibid.* **1985**, *107*, 4798. (c) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304. (d) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron Asymmetry* **1990**, *1*, 437. (e) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224.

(19) Takeuchi, Y.; Itoh, N.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1514.

(20) The presence of the fluorine on the α-carbon makes it much more sensitive to diastereotopic magnetic differences in comparison to fluorine nuclei further removed as in MTPA. The presence of a third, electron-withdrawing substituent on the α-carbon enhances the reactivity in the acylation reactions, while the importance of steric differences of the α-carbon substituents may be necessary to enhance the population of a single, dominant rotamer.

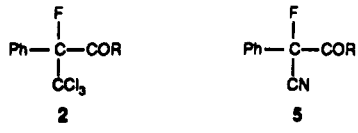
(21) (a) Takeuchi, Y.; Asahina, M.; Nagata, K.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2203. (b) Takeuchi, Y.; Asahina, M.; Hori, K.; Koizumi, T. *Ibid.* **1988**, 1149.

(22) Takeuchi, Y.; Asahina, M.; Murayama, A.; Hori, K.; Koizumi, T. *J. Org. Chem.* **1986**, *51*, 955.

(23) Since our ^{19}F NMR spectrometer JEOL GX-270 (254 MHz) and measuring conditions were different from those of Mosher, the $\Delta\delta_F$ values and signal widths we obtained for MTPA derivatives are not always consistent with his data.[4]

(24) Takeuchi, Y.; Murayama, A.; Hagi, T.; Koizumi, T. *Nippon Kagaku Kaishi* **1985**, 2029.

Table I. $\Delta\delta_F$ and $\Delta\delta_H$ Values (in ppm) of Three Diastereomers for 1, 2, 5, and 6 by 254-MHz ^{19}F and 270-MHz ^1H NMR



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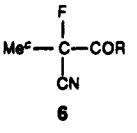

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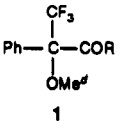

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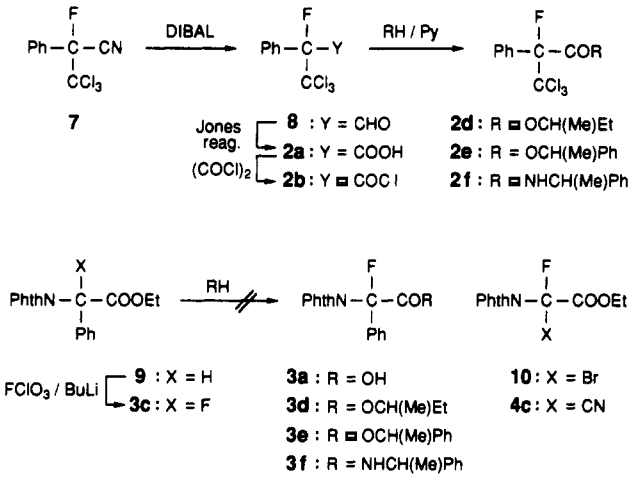
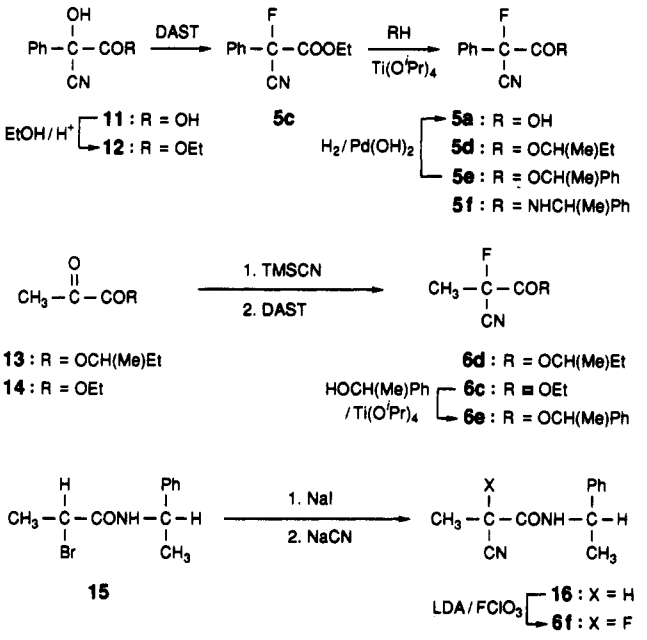
deriv R	$\Delta\delta_F$(F)	$\Delta\delta_H$(Me^a)	Me^b)	$\Delta\delta_F$(F)	$\Delta\delta$H(Me^a	Me^b)	$\Delta\delta_F$(F)	$\Delta\delta_H$(Me^a	Me^b	Me^c)	$\Delta\delta_F$(CF$_3$)	$\Delta\delta_H$(Me^a	Me^b	OMe^d)
-OCH(Me^a)CH$_2$Me^b (d)	0.188	0.094	0.124	0.241	0.146	0.232	0.159	0.014	0.014	0.003	ND^e	0.079	0.110	ND^e
-OCH(Me^a)Ph (e)	0.688	0.060		1.078	0.097		0.105	0.012		0.055	0.203	0.059		0.085
-NHCH(Me^a)Ph (f)	0.137	0.122		1.006	0.080		0.015	0.013		0.070	0.181	0.040		0.040

^{a} Me signals in chiral alcohol or amine moiety (Me^a). ^{b} Me signals of the Et groups in 2-butyl alcohol (d) moiety (Me^b). ^{c} Me signals in 6 (Me^c). ^{d} OMe signals in 1 (OMe^d). ^{e} Not detectable.

Scheme I



Scheme II



We finally focused on the CFPA structure **5**, a less hindered analogue of **4**. Condensation of benzoylformic acid with TMSCN gave **11**, which was submitted to Fischer esterification to yield **12**. The alcohol **12** was fluorinated with DAST giving CFPA ethyl ester **5c**. Conversion of **5c** into the three diastereomers **5d–f** was accomplished by transesterification using Ti(OPr^i)$_4$ as a catalyst.[25] Although attempted saponification of the ester **5c** generally degraded the CN group, catalytic hydrogenation of the 1-phenylethyl esters **5e** using Pd(OH)$_2$[26] successfully produced the acid **5a**.

The syntheses of the test derivatives **6d–f** were much more challenging owing primarily to the instability of **6**. Each compound **6d–f** required a different synthetic strategy not based on the usual analogy approach for its ultimately successful preparation. The pyruvate **13** was treated with TMSCN and then with DAST to produce the 2-butyl esters **6d**. The 1-phenylethyl esters **6e** were prepared by submitting the unstable ethyl ester **6c** derived from **14** to ester exchange reaction catalyzed by Ti(OPr^i)$_4$.[25] On the other hand, the corresponding *N*-(1-phenylethyl)-amide diastereomers **6f** were obtained by treatment of **15** with NaCN/NaI followed by the FClO$_3$ fluorination[24] of the resulting cyano compounds **16**, as shown in Scheme II.

The $\Delta\delta$ Value Measurement in ^{19}F and ^1H NMR for the Diastereomers 1d–f, 2d–f, 5d–f, and 6d–f. The ^{19}F and ^1H $\Delta\delta$ values for the pair of diastereomers of each of the three derivatives of the **2**, **5**, **6**, and MTPA (**1**) structures are summarized in Table I. The unexpectedly smaller $\Delta\delta_F$ values for **2d–f**[27] may be ascribed to the resemblance of the Ph and the CCl$_3$ groups in their bulkiness. The much larger $\Delta\delta_F$ values for CFPA derivatives **5d–f**, when compared to those of MTPA derivatives **1d–f** and even those for previous derivatizing agents,[8,9] clearly indicate the soundness of our molecular design; namely, the three substituents (Ph, CN, and F) on the chiral center of **5** are sufficiently differentiated from each other in their bulkiness.[7] The small $\Delta\delta_F$ values in general for **6d–f** can be explained in terms of the steric resemblance of the Me and CN groups in **6**.[28]

The $\Delta\delta_H$ values of the Me groups in the alcohol or the amine part, and the Me and the OMe groups in the acid part in case of **6** and **1**, respectively, for each pair of diastereomers (**d–f**), were also obtained. The relative magnitudes of $\Delta\delta_H$ values for all compounds generally parallel those of the $\Delta\delta_F$ values for the corresponding derivatives. The $\Delta\delta_H$ values for **5d–f** are approximately two times greater than those for **1d–f**, and therefore, they are not so dramatically different when compared to the corresponding $\Delta\delta_F$ values. However, detection of the Me signals in **5d–f** is substantially more useful than that of the OMe signals in **1d–f**, considering that, in addition to the smaller $\Delta\delta_H$ values of the diastereomeric OMe signals,

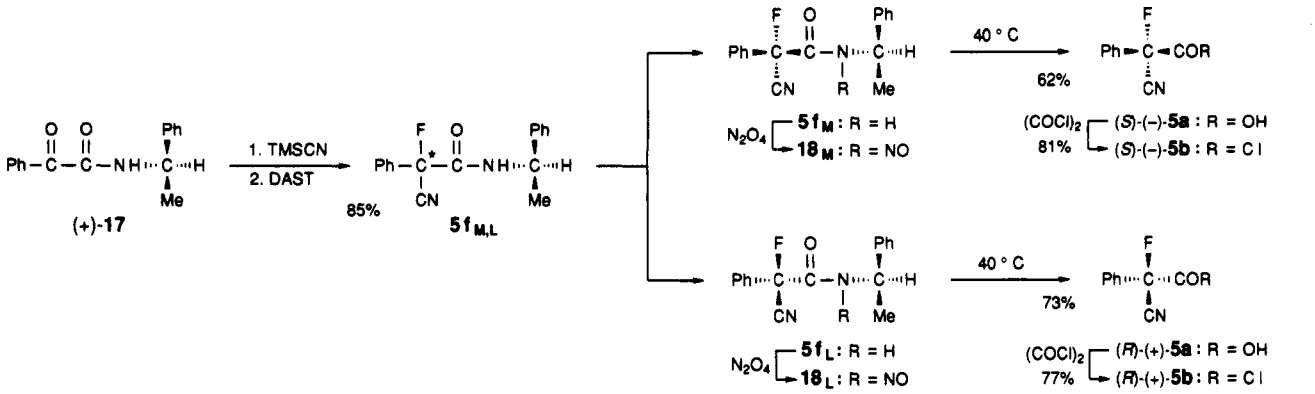
(25) (a) Schnurrenberger, P.; Zuger, M. F.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1197. (b) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138. (c) Rehwinkle, H.; Steglich, W. *Ibid.* **1982**, 826.

(26) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396.

(27) The fluorine signal for **2f** appears as doublet (J = 5.5 Hz) presumably due to the coupling with the amide proton.

(28) The greater $\Delta\delta$ values observed for **5d–f** compared **6d–f** would appear to be primarily a result of the magnetic anisotropy of the Ph ring relative to a Me group; for a similar effect, see: (a) Pirkle, W. H.; Simmons, K. A.; Boeder, C. W. *J. Org. Chem.* **1979**, *44*, 4891. (b) Pirkle, W. H.; Simmons, K. A. *Ibid.* **1981**, *46*, 3239.

Scheme III



they are being broadened due to long-range coupling[4] with the CF_3 group.

The surprisingly large $\Delta\delta$ values originating from the novel CFPA structure **5** in both ^{19}F and ^{1}H NMR spectra prompted us to prepare optically active CFPA (**5a**) in order to investigate its practical use as a new reagent alternative to MTPA (**1a**).

Synthesis of Optically Active CFPA (5a). Acid (±)-**5a** was unfortunately difficult to crystallize, and further attempts at the resolution by fractional recrystallization of the diastereomeric mixture of (±)-**5a** as its salts with chiral amines were unsuccessful. Since the separation of the two diastereomeric esters **5e** by conventional methods was found to be tedious due to their unexpectedly nonpolar character, a method using the readily crystallizable amide diastereomers **5f** was employed.

Thus, benzoylformic acid was condensed with (*R*)-(+)-1-phenylethylamine by DCC (CH_2Cl_2, room temperature, 2 h, 92%) to give (+)-**17**, which was subjected to hydrocyanation (TMSCN/THF, reflux, 8 h) followed by fluorination (DAST/CH_2Cl_2, −78 °C, 2 h) to afford the diastereomeric amides $\mathbf{5f_{M,L}}$ in 85% yield from **17**. Each diastereomer was obtained by fractional recrystallization thus providing the more polar amide $\mathbf{5f_M}$ and the less polar isomer $\mathbf{5f_L}$ in 45% and 33% yields, respectively. Both isomers were separately treated with N_2O_4 (NaOAc/CCl_4, 0 °C, 2 h) to produce the *N*-nitroso derivatives, $\mathbf{18_M}$ and $\mathbf{18_L}$, which were then submitted, without isolation, to thermal decomposition (40 °C, 0.5 h)[29] to produce (*S*)-(−)-CFPA (**5a**) and (*R*)-(+)-CFPA (**5a**) in ca. 70% yields, respectively. Although acid **5a** is a liquid, it was fortunately found to be a stable substance in spite of its multifunctional carbon structure.[21,22] Both acids, (−)-**5a** and (+)-**5a**, were converted, in the usual manner [$(COCl)_2$/cat. DMF/CH_2Cl_2], into the corresponding chlorides (−)-**5b** and (+)-**5b** in ca. 80% yields after distillation, as shown in Scheme III.

The absolute configuration of $\mathbf{5f_M}$ was determined through X-ray crystallographic analysis.[30] The optical purity of (−)-**5b** thus prepared was determined to be greater than 99.5% by application of the Eu(hfc)$_3$ method[31] to the (−)- and (±)-**5** methyl esters and also through both NMR[32] and HPLC analyses of the diastereomeric mixtures obtained by reaction of (−)-**5b** with (±)- and (−)-1-phenylethyl alcohols.

Preparation and $\Delta\delta$ Values of Various CFPA and MTPA Derivatives. Condensation of **5b** with various alcohols and amines was achieved according to the general procedure described in the Experimental Section. Both $\Delta\delta_F$ and $\Delta\delta_H$ values for each of pair of diastereomers were obtained from ^{19}F and ^{1}H NMR spectra of the crude CFPA derivatives. The corresponding $\Delta\delta$ values for MTPA derivatives were also obtained, for reference, by our standard measuring conditions.[23] These results are summarized in Table II.

The $\Delta\delta_F$ values for CFPA derivatives of some alcohols and amines are, in general, several times greater than those of the corresponding MTPA derivatives. Furthermore, the ^{19}F signals of the CF_3 groups in the MTPA diastereomers were somewhat broad, with signal widths ($w_{1/2}$) of 5.0–6.5 Hz due to coupling with the OMe groups. In contrast, the ^{19}F signals of CFPA derivatives appeared as sharper singlets ($w_{1/2}$ = 3.5–5.0 Hz), which is an additional merit of the CFPA method.[33] The ratios of the $\Delta\delta_F$ values of CFPA derivatives to those of MTPA derivatives, for all compounds shown in Tables I and II, are almost the same. Therefore, our selection of which three kinds of diastereomers (**d–f**) as indicators to examine structure–$\Delta\delta$ relationships has been shown to be reasonable.

These very large $\Delta\delta_F$ values for CFPA derivatives prompted us to investigate ee detection of some compounds having remote chiral centers (entries 4–7). The MTPA method is not useful for ee determination for those alcohols and amines *having chiral centers more than two bonds remotely disposed from the acyl functionalities.* In contrast, ee determination by the CFPA method is in many cases possible for such compounds, although some CFPA derivatives do give $\Delta\delta_F$ values comparable to corresponding MTPA derivatives.

The $\Delta\delta_H$ values for the characteristic Me and OMe signals in these diastereomers were also obtained. It is apparent that the CFPA method is also superior to the MTPA method for secondary alcohols and some amines, even if ^{1}H NMR spectroscopy is used for detection. However, both CFPA and MTPA derivatives of those nucleophiles having remotely disposed chiral center failed to produce sufficiently large $\Delta\delta_H$ values for ee determination. Therefore, only the CFPA method by ^{19}F NMR detection can be used for ee determination of some

(29) (a) White, E. H. *J. Am. Chem. Soc.* **1954**, *76*, 4497. (b) White, E. H. *Ibid.* **1955**, *77*, 6008. (c) White, E. H. *Ibid.* **1955**, *77*, 6011. (d) White, E. H. *Ibid.* **1955**, *77*, 6014.

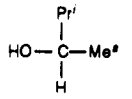
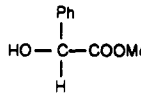
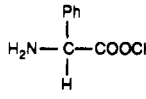
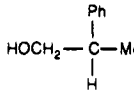
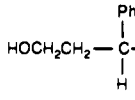
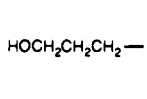
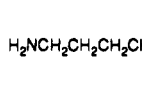
(30) For X-ray crystallographic data for $\mathbf{5f_M}$, see Experimental Section.

(31) Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) [Eu(hfc)$_3$] was used as a chiral shift reagent.

(32) The ^{19}F NMR of the esters obtained by reaction of (−)-**5b** with (±)-1-phenethyl alcohol and (*S*)-(−)-1-phenethyl alcohol revealed two singlets at −145.91 and −146.99 ppm ($\Delta\delta_F$ = 1.080 ppm) in a ratio of 1:1 for the former and one singlet at −145.95 ppm for the latter.

(33) The $\Delta\delta/w_{1/2}$ ratio of ca. 2–7 reported in the recent methods using ^{1}H,[11] ^{13}C,[17] ^{31}P,[18] and ^{77}Se[13] nuclei are much smaller compared to those (ca. 7–50) of the CFPA method using the ^{19}F nucleus.

Table II. $\Delta\delta_F$ and $\Delta\delta_H$ Values (in ppm) of Some CFPA and MTPA Derivatives by 254 MHz ^{19}F and 270 MHz ^1H NMR

entry	deriv alcohol or amine (HR)	compd	$\Delta\delta_F$(F)	$\Delta\delta_H$(Me[a])	compd	$\Delta\delta_F$(CF_3)	$\Delta\delta_H$(Me[a])	$\Delta\delta_H$(OMe[b])
1		5g	0.752 (191.2)[d]	0.162 (43.7)	1g	0.029 (7.3)	0.077 (20.8)	0.029 (7.8)
2		5h	0.274 (69.6)	0.097 (26.1)	1h	0.296 (75.3)	0.029 (7.8)	0.145 (39.1)
3		5i	0.245 (316.2)	0.053 (14.2)	1i	0.260 (66.1)	0.018 (4.9)	0.191 (51.5)
4		5j	0.623 (158.2)	ND[c]	1j	0.051 (12.9)	ND[c]	0.029 (7.9)
5		5k	0.224 (57.0)	0.019 (5.1)	1k	ND[c]	0.006 (1.7)	0.004 (1.0)
6		5l	0.014 (3.6)	ND[c]	1l	ND[c]	ND[c]	ND[c]
7		5m	0.094 (23.9)	0.011 (2.9)	1m	ND[c]	0.006 (1.5)	ND[c]

[a] Me signals in chiral alcohol or amine moiety (Me[a]). [b] OMe signals in 1 (OMe[b]). [c] Not detectable. [d] Values in Hz are given in parentheses.

compounds having remote chiral centers, and our initial insight of using ^{19}F NMR for this purpose has been justified.

Conclusions

In the course of our molecular design and synthetic studies of efficient molecules for ee determination surpassing the capability of the currently much-used MTPA (**1a**), CFPA molecule (**5**) was chosen as the ultimate structure for this purpose. Optically active CFPA (**5a**) was prepared through diastereomeric separation of the amides, $\mathbf{5f_M}$ and $\mathbf{5f_L}$, followed by conversion into the acids (−)-**5a** and (+)-**5a** respectively. The $\Delta\delta$ values for CFPA diastereomers were, in general, much greater than those for the corresponding MTPA derivatives in both ^{19}F and ^1H NMR spectra. The CFPA method with ^{19}F NMR analysis has proven to be an excellent means for ee determination of various nucleophiles having both proximate and remotely disposed chiral centers from the derivatizing functionality.

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were measured in $CDCl_3$ at 270 MHz, unless specified otherwise. ^{13}C NMR spectra were measured in $CDCl_3$ at 50 MHz. ^{19}F NMR spectra were measured in $CDCl_3$ at 254 MHz with $CFCl_3$ as internal standard. Upfield shifts are quoted as negative δ values. All $\Delta\delta$ values in parentheses are given in ppm.

α-Fluoro-α-(trichloromethyl)phenylacetonitrile (7). A solution of trichloroacetophenone (4.5 g, 20.3 mmol) and TMSCN (5.6 mL, 42 mmol) in dry THF (20 mL) was heated at reflux under Ar for 12 h, quenched with 1 N HCl (20 mL), extracted with Et_2O (20 mL × 4), and dried over $MgSO_4$. Evaporation of the solvent gave crude cyanohydrin, which was dissolved in dry CH_2Cl_2 (80 mL). To the solution was added dropwise a solution of DAST (2.7 mL, 20.4 mmol) in CH_2Cl_2 (5 mL) at −78 °C under a N_2 stream, and the reaction mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction mixture was poured into water (50 mL), extracted with CH_2Cl_2 (50 mL × 3), and dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel chromatography (hexane–EtOAc (7:1) as eluent) to give 1.96 g (57%) of the fluoride **7** as a pale yellow oil: IR (neat) 2240 (CN) cm^{-1}; ^1H NMR δ 7.47–8.12 (5 H, m, Ph); ^{19}F NMR δ −139.99 (s); MS (EI) m/z 251 (M^+, ^{35}Cl); HRMS calcd for $C_9H_5{}^{35}Cl_3FN$ (M^+) m/z 250.9771, found 250.9520.

α-Fluoro-α-(trichloromethyl)phenylacetaldehyde (8). To a solution of **7** (50 mg, 0.2 mmol) in hexane (2 mL) was added dropwise a solution of 0.94 M DIBALH in hexane (0.43 mL, 0.4 mmol) at −78 °C and stirred for 30 min. The reaction mixture was allowed to warm to rt and stirred at rt for 1 h. MeOH (0.1 mL) was added, and the whole mixture was poured into saturated NH_4Cl (1 mL). After stirring for 20 min, 1 N HCl (2 mL) was added and the mixture was extracted with Et_2O (2 mL × 3). The ethereal layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by preparative TLC (hexane–EtOAc (7:1) as solvent) to afford 32 mg (62%) of the aldehyde **8** as a colorless oil: IR (neat) 3064, 2855 (CH), 1751 (CO) cm^{-1}; ^1H NMR δ 7.35–7.85 (5 H, m, Ph), 10.02 (1 H, d, J_{HF} = 7.1 Hz, CHO); ^{19}F NMR δ −155.16 (d, J_{HF} = 7.4 Hz); MS m/z 254 (M^+, ^{35}Cl); HRMS calcd for $C_9H_6{}^{35}Cl_3FO$ (M^+) m/z 253.9469, found 253.9470.

α-Fluoro-α-(trichloromethyl)phenylacetic Acid (2a). Jones reagent was added dropwise to a solution of **8** (1.3 g, 5.0 mmol) in Me_2CO (30 mL) at 0 °C until the orange color persisted. One drop of 2-propanol and a small amount of water were added, and the solution was concentrated under reduced pressure. The residue was saturated with NaCl and extracted with EtOAc (10 mL × 3). The extract was washed with brine, dried over $MgSO_4$, and concentrated to give 1.3 g (99%) of the acid **2a** as a white amorphous solid: mp 110–120 °C; IR (KBr) 2985 (CH), 1725 (CO) cm^{-1}; ^1H NMR δ 5.83 (1 H, br s, OH), 7.40–7.95 (5 H, m,

Ph); ^{19}F NMR δ −148.48 (s); MS m/z 270 (M^+, ^{35}Cl), 153 ($M^+ - CCl_3$); HRMS calcd for $C_9H_6{}^{35}Cl_3FO_2$ (M^+) m/z 269.9417, found 269.9417.

General Procedure for Preparation of α-Fluoro-α-(trichloromethyl)phenylacetic Acid Derivatives 2d–f. To a solution of **2a** (46 mg, 0.17 mmol) and DMF (7.3 mg, 0.1 mmol) in PhH (3 mL) was added oxalyl chloride (0.05 mL, 0.6 mmol) at 0 °C by means of a syringe. The solution was stirred at rt for 2 h and concentrated in vacuo to give crude acid chloride **2b**. 2-Butyl alcohol, 1-phenylethyl alcohol, or 1-phenylethylamine (0.5 mmol) was added to a solution of **2b** (0.5 mmol) and pyridine (0.04 mL, 0.5 mmol) in Et_2O (3 mL), and the mixture was stirred at rt for 30 min. To the mixture was added 1 N HCl (3 mL), and the whole mixture was extracted with EtOAc (3 mL × 3). The organic layer was washed successively with saturated Na_2CO_3 (1 mL) and water (1 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by silica gel preparative TLC (hexane–EtOAc (4:1) as solvent) to afford the diastereomeric derivatives **2d–f**.

2-Butyl α-fluoro-α-(trichloromethyl)phenylacetates (2d): colorless oil; 37 mg (66% yield); IR (neat) 2976 (CH), 1750 (CO) cm^{-1}; ^1H NMR δ 0.84 and 0.97 ($\Delta\delta$ = 0.124), (3 H, t, J = 7.6 Hz, CH_2Me), 1.25 and 1.35 ($\Delta\delta$ = 0.094), (3 H, d, J = 6.4 Hz, $CHMe$), 1.55–1.85 (2 H, m, CH_2), 5.08 (1 H, sextet, J = 6.3 Hz, CH), 7.39–7.90 (10 H, m, Ph × 2); ^{19}F NMR ($CDCl_3$) δ −149.07 and −148.88 ($\Delta\delta$ = 0.188), (s); MS m/z 328 (M^+, $C_{13}H_{14}{}^{35}Cl_2{}^{37}ClFO_2$), 209 ($M^+ - CCl_3$); HRMS calcd for $C_{13}H_{14}{}^{35}Cl_3FO_2$ (M^+) m/z 326.0043, found 326.0053.

1-Phenylethyl α-fluoro-α-(trichloromethyl)phenylacetates (2e): colorless oil; 51 mg (80% yield); IR (neat) 2984 (CH), 1752 (CO) cm^{-1}; ^1H NMR δ 1.60 and 1.66 ($\Delta\delta$ = 0.060), (3 H, d, J = 6.59 Hz, $CHMe$), 6.08 (1 H, q, J = 6.6 Hz, CH), 7.21–7.88 (10 H, m, Ph × 2); ^{19}F NMR δ −149.57 and −148.88 ($\Delta\delta$ = 0.688), (s); MS m/z 374 (M^+, ^{35}Cl), 257 ($M^+ - CCl_3$); HRMS calcd for $C_{17}H_{14}O_2{}^{35}Cl_3F$ (M^+) m/z 374.0042, found 374.0042.

α-Fluoro-N-(1-phenylethyl)-α-(trichloromethyl)phenylacetamides (2f): colorless solid; 53 mg (83% yield); mp 104–108 °C; IR (KBr) 3351, 3308 (NH), 1672 (CO) cm^{-1}; ^1H NMR δ 1.44 and 1.57 ($\Delta\delta$ = 0.122), (3 H, d, J = 6.8 Hz, $CHMe$), 5.15 (1H, quintet, J = 7.3 Hz, CH), 6.85 (1 H, br s, NH), 7.11–8.04 (10 H, m, Ph x 2); ^{19}F NMR δ −148.81 and −148.67 ($\Delta\delta$ = 0.137), (d, J_{HF} = 5.5 Hz); MS m/z 373 (M^+, ^{35}Cl), 256 ($M^+ - CCl_3$); HRMS calcd for $C_{17}H_{15}{}^{35}Cl^{37}Cl_2FNO$ (M^+) m/z 377.0144, found 377.0149.

α-Fluoro-N-phthaloylphenylglycine Ethyl Ester (3c). To a chilled solution of *N*-phthaloylphenylglycine ethyl ester (**9**) (1.08 g, 3.5 mmol) in THF (60 mL) was added dropwise 1.55 M BuLi in hexane (2.16 mL, 3.5 mmol) at −78 °C under Ar, and the solution was stirred for 30 min. To the solution was introduced diluted $FClO_3$ gas[24] at −78 °C for 1 h, and the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc (7:1) as eluent) to afford 357 mg (32%) of the fluoro ester **3c** as a colorless solid. Recrystallization from $CHCl_3$–hexane gave colorless needles; mp 141–142 °C; IR (KBr) 1751 (COO), 1734 (CON) cm^{-1}; ^1H NMR δ 1.30 (3 H, t, J = 7.1 Hz, Me), 4.25–4.39 (2 H, m, CH_2), 7.42–7.69 (5 H, m, Ph), 7.76–7.89 (4 H, m, NPhth); ^{19}F NMR δ −128.60 (s); MS m/z 327 (M^+), 308 ($M^+ - F$) 254 ($M^+ - COOEt$). Anal. Calcd for $C_{18}H_{14}FNO_4$: C, 66.05; H, 4.31; N, 4.28. Found: C, 65.86; H, 4.25; N, 4.35.

α-Cyano-α-hydroxyphenylacetic Acid Monohydrate (11). A solution of benzoylformic acid (555 mg, 3.70 mmol) in dry THF (1.2 mL) was stirred under Ar at rt as TMSCN (1.21 mL, 9.1 mmol) was added by means of a syringe. After 1 h the solution was concentrated in vacuo. To the residue were added EtOAc (10 mL) and then 1 N HCl (10 mL) slowly. The organic layer was separated, and aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a colorless solid which was purified by recrystallization from $CHCl_3$ to afford 524 mg (73%) of the acid **11** (monohydrate) as colorless prisms: mp 63 °C; IR (neat) 3370 (OH), 2250 (CN), 1730 (CO) cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 6.34 (2 H, br s, OH × 2), 6.95 (2 H, br s, OH × 2), 7.35–7.85 (5 H, m, Ph); MS m/z 177 (M^+), 151 ($M^+ - CN$), 132 ($M^+ - COOH$). Anal. Calcd for $C_9H_7NO_3 \cdot H_2O$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.70; H, 4.36; N, 7.08.

Ethyl α-Cyano-α-hydroxyphenylacetate (12). A solution of **11** (419 mg, 2.15 mmol) and concd H_2SO_4 (10 mg) in dry EtOH (15 mL) was heated at reflux for 3 h. After removal of the solvent in vacuo, Et_2O (10 mL) was added to the residue and the mixture was successively washed with water (5 mL), saturated $NaHCO_3$ (5 mL), and water (5 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 210 mg (48%) of the ester **12** as a colorless oil: IR (neat) 3400 (OH), 2240 (CN), 1750 (CO) cm^{-1}; ^1H NMR (60 MHz) δ 1.23 (3 H, t, J = 7.1 Hz, CH_3), 4.28 (2 H, q, J = 7.1 Hz, CH_2), 4.76 (1 H, br s, OH), 7.30–7.73 (5 H, m, Ph); MS m/z 206 ($M^+ + 1$), 188 ($M^+ - OH$), 179 ($M^+ - CN$); HRMS calcd for $C_{11}H_{11}NO_3$ (M^+) m/z 205.0738, found 205.0750.

Ethyl α-Cyano-α-fluorophenylacetate (5c). In a 10-mL plastic vessel were placed **12** (209 mg, 1.02 mmol) and dry CH_2Cl_2 (2 mL), and the solution was chilled at −78 °C. To the stirred solution was added dropwise a solution of DAST (0.6 mL, 5 mmol) in dry CH_2Cl_2 (0.5 mL) for a period of 2 min under Ar, and the mixture was allowed to warm to rt and stirred at rt for 2 h. Water (3 mL) was added at 0 °C, and the mixture was stirred at rt for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residual mixture was chromatographed on silica gel (hexane–Et_2O (7:1) as eluent) to afford 167 mg (79%) of the fluoro ester **5c** as a colorless oil: IR (neat) 2240 (CN), 1770 (CO), 1595 (Ph) cm^{-1}; ^1H NMR δ 1.31 (3 H, t, J = 7.1 Hz, CH_3), 4.25–4.45 (2 H, m, CH_2), 7.45–7.70 (5 H, m, Ph); ^{19}F NMR δ −146.59 (s); MS m/z 207 (M^+), 188 ($M^+ - F$), 181 ($M^+ - CN$); HRMS calcd for $C_{11}H_{10}FNO_2$ (M^+) m/z 207.0695, found 207.0718.

General Procedure for Preparation of α-Cyano-α-fluorophenylacetic Acid Derivatives 5d–f. A solution of **5c** (31 mg, 0.15 mmol) in 2-butyl alcohol (1 mL) or 1-phenylethyl alcohol (0.9 mL) was heated at 90 °C for 2 h with a catalytic amount of $Ti(OPr^i)_4$. A solution of **5c** (31 mg, 0.15 mmol) in 1-phenylethylamine (0.6 mL) was heated at 100 °C for 5 h. Evaporation of excess of the alcohol or the amine under reduced pressure gave a residual oil, which was purified by silica gel preparative TLC (hexane–Et_2O as solvent) to afford the diastereomeric esters **5d** or **5e** or amides **5f**.

2-Butyl α-cyano-α-fluorophenylacetates (5d): colorless oil; 24 mg (68% yield); IR (neat) 2250 (CN), 1750 (CO), 1600 (Ph) cm^{-1}; ^1H NMR δ 0.68 and 0.92 ($\Delta\delta$ = 0.232), (3 H, t, J = 7.3 Hz, CH_2Me), 1.16 and 1.13 ($\Delta\delta$ = 0.146), (3 H, d, J = 6.4 Hz, $CHMe$), 1.58 (2 H, m, CH_2), 4.98 (1 H, sextet, J = 6.3 Hz, CH), 7.35–7.78 (5 H, m, Ph); ^{19}F NMR δ −146.88 and −146.64 ($\Delta\delta$ = 0.241), (s); MS m/z 235 (M^+), 209 ($M^+ - CN$); HRMS calcd for $C_{13}H_{14}FNO_2$ (M^+) m/z 235.1008, found 235.0968.

1-Phenylethyl α-cyano-α-fluorophenylacetates (5e): colorless oil; 30 mg (71% yield); IR (neat) 2250 (CN), 1775 (CO), 1595 (Ph) cm^{-1}; ^1H NMR δ 1.52 and 1.62 ($\Delta\delta$ = 0.097), (3 H, d, J = 6.6 Hz, $CHMe$), 5.97 (1 H, q, J = 6.6 Hz, CH), 7.21–7.60 (10 H, m, Ph × 2); ^{19}F NMR δ −147.16 and −146.11 ($\Delta\delta$ = 1.078), (s); MS m/z 283 (M^+), 134 ($PhC^+(F)CN$); HRMS calcd for $C_{17}H_{14}FNO_2$ (M^+) m/z 283.1008, found 283.0982.

***N*-(1-Phenylethyl)-α-cyano-α-fluorophenylacetamides (5f)**: colorless solid; 13 mg (31% yield); IR (KBr) 3350 (NH), 2240 (CN), 1675 (CO), 1600 (Ph) cm^{-1}; ^1H NMR δ 1.54 and 1.61 ($\Delta\delta$ = 0.080), (3 H, d, J = 7.1 Hz, $CHMe$), 5.15 (1 H, quint, J = 6.8 Hz, CH), 6.71 (1 H, br s, NH), 7.22–7.65 (10 H, m, Ph × 2); ^{19}F NMR δ −144.65 and −143.65 ($\Delta\delta$ = 1.006), (s); MS m/z 282 (M^+), 134 ($PhC^+(F)CN$); HRMS calcd for $C_{17}H_{15}FN_2O$ (M^+) m/z 282.1168, found 282.1144.

2-Butyl Pyruvate (13). To a solution of pyruvic acid (8.3 mL, 125 mmol), 2-butyl alcohol (12 mL, 130 mmol), and *p*-toluenesulfonic acid (100 mg) in pyridine (100 mL) was added in portions DCC (28.8 g, 140 mmol) at 0 °C over a period of 20 min, and the mixture was allowed to warm to rt and stirred at rt for 24 h. To the cooled reaction mixture at 0 °C was added AcOH (10 mL), and the mixture was stirred at 0 °C for 10 h. The insoluble materials were removed by filtration. To the filtrate were added $CHCl_3$ (100 mL) and water (100 mL), and pH of the aqueous layer was adjusted at 2 by adding 5 N HCl. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (60 mL × 3), and the combined organic layer was washed successively with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (10 mL) and dried over $MgSO_4$. Evaporation of the

solvent gave an oil which was distilled (bp 62 °C/11 Torr) to afford 7.49 g (42%) of 2-butyl pyruvate (**13**) as a colorless oil: IR (neat) 2976 (CH), 1726 (CO) cm^{-1}; ^1H NMR δ 0.94 (3 H, t, J = 7.5 Hz, CH_2Me), 1.31 (3 H, d, J = 6.4 Hz, $CHMe$), 1.51–1.83 (2 H, m, CH_2), 2.47 (3 H, s, CH_3CO), 4.97 (1 H, sextet, J = 6.4 Hz, CH); MS m/z 144 (M^+), 101 ($M^+ - CH_3CO$); HRMS calcd for $C_7H_{12}O_3$ (M^+) m/z 144.0787, found 144.0822.

2-Butyl 2-Cyano-2-fluoropropionates (6d). A solution of **13** (4.0 g, 27 mmol) and TMSCN (5.3 mL, 40 mmol) in dry THF (20 mL) was heated at reflux under Ar for 5 h. Evaporation of the solvent gave a residual oil which was transferred into a plastic vessel with dry CH_2Cl_2 (20 mL), and the solution was chilled at −78 °C. To the stirred solution was added dropwise a solution of DAST (5.3 mL, 40 mmol) in dry CH_2Cl_2 (10 mL) over a period 5 min under a N_2 stream, and the mixture was allowed to warm to rt and stirred at rt for 2 h. Water (20 mL) was added, and the mixture was stirred at rt for 1 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residual mixture was chromatographed on silica gel (hexane–Et_2O (9:1) as eluent) to afford 4.1 g (88%) of the 2-butyl esters **6d** as a colorless oil: IR (neat) 2978 (CH), 2253 (CN), 1774 (CO) cm^{-1}; ^1H NMR δ 0.94 and 0.96 ($\Delta\delta$ = 0.014), (3 H, t, J = 7.5 Hz, CH_2Me), 1.32 and 1.33 ($\Delta\delta$ = 0.014), (3 H, d, J = 6.4 and 6.1 Hz, $CHMe$), 1.52–1.84 (2 H, m, CH_2), 1.954 and 1.957 ($\Delta\delta$ = 0.003), (3 H, d, J_{HF} = 21.2 and 21.0 Hz, CFMe), 5.02 (1 H, sextet, J = 6.4 Hz, CH); ^{19}F NMR δ −151.89 and −151.73 ($\Delta\delta$ = 0.159), (q, J_{HF} = 20.2 Hz); MS m/z 173 (M^+), 100 ($CH_3CF(CN)C^+O$); HRMS calcd for $C_8H_{12}FNO_2$ (M^+) m/z 173.0851, found 173.0826.

Ethyl 2-Cyano-2-fluoropropionate (6c). A solution of ethyl pyruvate **14** (4.1 g, 40 mmol) and TMSCN (10.2 mL, 80 mmol) in dry THF (45 mL) was heated at reflux for 8 h. Concentration of the mixture gave a residual oil which was transferred into a plastic vessel with dry CH_2Cl_2 (50 mL) and chilled at −78 °C. To the stirred solution was added dropwise a solution of DAST (8.0 mL, 61 mmol) in dry CH_2Cl_2 (10 mL) over a period of 5 min under a N_2 stream, and the mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was quenched by adding water (30 mL), and the whole mixture was stirred at rt for 10 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residual mixture was chromatographed on silica gel (hexane–EtOAc (2:1) as eluent) to afford 5.1 g (89%) of the fluoro ester **6c** as a colorless oil: IR (neat) 2989 (CH), 2253 (CN), 1776 (CO) cm^{-1}; ^1H NMR δ 1.38 (3 H, t, J = 7.1 Hz, CH_3), 1.97 (3 H, d, J_{HF} = 21.0 Hz, CFMe), 4.39 (2 H, q, J = 7.1 Hz, CH_2); ^{19}F NMR δ −151.86 (q, J_{HF} = 20.3 Hz); MS m/z 145 (M^+), 126 ($M^+ - F$), 119 ($M^+ - CN$); HRMS calcd for $C_6H_9FNO_2$ ($M^+ + 1$) m/z 146.0617, found 146.0612.

1-Phenylethyl 2-Cyano-2-fluoropropionates (6e). A solution of **6c** (355 mg, 2.5 mmol) and a catalytic amount of $Ti(OPr^i)_4$ in 1-phenylethyl alcohol (11.3 mL) was heated at 100 °C for 5 h. Evaporation of excess of the alcohol under reduced pressure gave a residual oil, which was purified by silica gel column chromatography (hexane–EtOAc (7:1) as eluent) to afford 93 mg (17%) of the 1-phenylethyl esters **6e** as a colorless oil: IR (neat) 2987 (CH), 2253 (CN), 1773 (CO) cm^{-1}; ^1H NMR δ 1.65 and 1.66 ($\Delta\delta$ = 0.012), (3 H, t, J = 6.8 and 6.6 Hz, $CHMe$), 1.89 and 1.95 ($\Delta\delta$ = 0.055), (3 H, d, J_{HF} = 21.0 Hz, CFMe), 6.00 (1 H, q, J = 6.6 Hz, CH), 7.24–7.40 (5 H, m, Ph); ^{19}F NMR δ −152.02 and −151.92 ($\Delta\delta$ = 0.105), (q, J_{HF} = 20.2 Hz); MS m/z 221 (M^+), 176 ($M^+ - CN - F$); HRMS calcd for $C_8H_{12}FNO_2$ (M^+) m/z 221.0851, found 221.0818.

2-Bromo-*N*-(1-phenylethyl)propionamides (15). To a solution of 2-bromopropionic acid (0.9 mL, 10 mmol) in Et_2O (40 mL) were added dropwise oxalyl chloride (1.3 mL, 15 mmol) and then DMF (10 mg) at 0 °C, and the mixture was stirred at 0 °C for 2 h and concentrated. To a solution of the residue in Et_2O (100 mL) were added 1-phenylethylamine (1.2 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) at 0 °C, and the resulting solution was stirred at rt for 15 min. Water (100 mL) was added, and the whole mixture was transferred into a separatory funnel and separated. The organic layer was washed successively with 1 N HCl, saturated Na_2CO_3, and water and dried over $MgSO_4$. Evaporation of the solvent gave a colorless solid, which was recrystallized from hexane–EtOAc to afford 2.1 g (81%) of the amides **15** as colorless needles: mp 122–124 °C; IR (KBr) 3264 (NH), 3061, 3032 (CH), 1657 (CO) cm^{-1}; ^1H NMR δ 1.51 (3 H, d, J = 6.8 Hz, $CHMe$), 1.85 and 1.87 ($\Delta\delta$ = 0.025), (3 H, d, J = 7.1 and 6.8 Hz, $CHBrMe$), 4.38 and 4.42 ($\Delta\delta$ = 0.037), (1 H, q, J = 6.8 and 7.1 Hz, CHBr), 5.07 (1 H, quintet, J = 7.3 Hz, $CHPh$), 6.66 (1 H, br s, NH), 7.24–7.40 (5 H, m, Ph); MS m/z 258, 256 ($M^+ + 1$), 257, 255 (M^+), 242, 240 ($M^+ - Me$); HRMS calcd for $C_{11}H_{15}{}^{81}BrNO$ ($M^+ + 1$) m/z 258.0317, found 258.0289, calcd for $C_{10}H_{11}{}^{81}BrNO$ ($M^+ - Me$) m/z 242.0003, found 241.9992.

2-Cyano-*N*-(1-phenylethyl)propionamides (16). A mixture of **15** (1.28 g, 5.0 mmol) and NaI (900 mg, 6.0 mmol) in Me_2CO (30 mL) was stirred at rt for 12 h. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. To a solution of the residue in DMF (40 mL) was added NaCN (294 mg, 6.0 mmol), and the mixture was stirred at rt for 12 h. After removal of the solvent under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with EtOAc (50 mL × 3) and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was purified by silica gel column chromatography (hexane–EtOAc (2:1) as eluent) to afford 949 mg (94%) of the amides **16** as a colorless solid: mp 106–114 °C; IR (KBr) 3313 (NH), 3066, 2984, 2937 (CH), 2254 (CN), 1656 (CO) cm^{-1}; ^1H NMR δ 1.49 (3 H, d, J = 7.1 Hz, $CH(Ph)Me$), 1.50 (3 H, d, J = 7.3 Hz, $CH(CN)Me$), 3.35 and 3.39 ($\Delta\delta$ = 0.034), (1 H, q, J = 7.3 Hz, $CH(CN)Me$), 5.03 (1 H, quint, J = 7.1 Hz, $CHPh$), 6.77 (1 H, br s, NH), 7.22–7.40 (5 H, m, Ph); MS m/z 202 (M^+), 187 ($M^+ - Me$); HRMS calcd for $C_{12}H_{14}N_2O$ (M^+) m/z 202.1104, found 202.1056.

2-Cyano-2-fluoro-*N*-(1-phenylethyl)propionamides (6f). To a solution of LDA (1.1 mmol) in THF (20 mL) was added dropwise a solution of **16** (202 mg, 1 mmol) in THF (3 mL) at −78 °C, and the mixture was stirred for 30 min. Into the reaction mixture was introduced $FClO_3$ gas[24] at −78 °C until a dark reddish color persisted. Evaporation of the solvent gave an oil, which was purified by silica gel column chromatography (hexane–EtOAc (4:1) as eluent) to afford 169 mg (77%) of the fluorides **6f** as a pale yellow oil: IR (neat) 3329 (NH), 2980 (CH), 2252 (CN), 1684 (CO) cm^{-1}; ^1H NMR δ 1.54 and 1.56 ($\Delta\delta$ = 0.013), (3 H, d, J = 7.1 and 6.8 Hz, $CHMe$), 1.89 and 1.96 ($\Delta\delta$ = 0.070), (3 H, d, J_{HF} = 22.2 Hz, CF(CN)Me), 5.00–5.20 (1 H, m, CH), 6.74 and 6.85 (1 H, br s, NH), 7.22–7.42 (5 H, m, Ph); ^{19}F NMR δ −151.46 and −151.45 ($\Delta\delta$ = 0.015), (q, J_{HF} = 22.1 Hz); MS m/z 220 (M^+), 205 ($M^+ - Me$), 201 ($M - F$); HRMS calcd for $C_{12}H_{13}FN_2O$ (M^+) m/z 220.1012, found 220.1029.

***N*-[(*R*)-1-Phenylethyl]benzoylformamide (17).** A solution of benzoylformic acid (150 mg, 1.0 mmol), (*R*)-(+)-1-phenylethylamine (0.13 mL, 1.0 mmol), and DCC (206 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was stirred at −20 °C for 2 h and then at rt for 6 h. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc (4:1) as eluent) to afford 233 mg (92%) of the amide **17** as a colorless solid. Recrystallization from hexane–EtOAc gave colorless needles: mp 113–114 °C; $[\alpha]^{25}_D$ +108.9° (*c* 1.00, $CHCl_3$); IR (KBr) 3270 (NH), 1685 (COC), 1655 (CON), 1595 (Ph) cm^{-1}; ^1H NMR δ 1.59 (3 H, d, J = 6.8 Hz, Me), 5.18 (1 H, dq, J = 7.1, 6.8 Hz, $CH(Me)Ph$), 7.36 (5 H, s, $PhCH$), 7.41–8.34 (6 H, m, PhCO and NH); MS m/z 253 (M^+), 120 ($M^+ - PhCOCO$). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.78; H, 5.96; N, 5.51.

α-Cyano-α-fluoro-*N*-[(*R*)-1-phenylethyl]phenylacetamides ($5f_{M,L}$). A solution of **17** (5.1 g, 20 mmol) and TMSCN (5.3 mL, 40 mmol) in dry THF (20 mL) was heated at reflux under Ar for 8 h. Concentration of the solution gave a residual oil, which was transferred into a plastic vessel with dry CH_2Cl_2 (20 mL), and the solution was chilled at −78 °C. To the stirred solution was added dropwise a solution of DAST (5.3 mL, 40 mmol) in dry CH_2Cl_2 (10 mL) over a period of 5 min, and the mixture was allowed to warm to rt and stirred at rt for 2 h. Water (10 mL) was added, and the mixture was stirred at rt for 1 h. The combined organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL × 3). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and concentrated. The residual pale yellow solid was chromatographed on silica gel (hexane–EtOAc (4:1) as eluent) to afford the diastereomeric mixture $5f_{M,L}$. Repeated recrystallization of the mixture from

hexane–EtOAc gave the more polar isomer **5f$_M$** and the less polar isomer **5f$_L$** as colorless needles in 45% (2.15 g) and 33% (1.58 g) yields, respectively.

(*S*)-α-Cyano-α-fluoro-*N*-[(*R*)-1-phenylethyl]phenylacetamide (5f$_M$): colorless needles; mp 174 °C; $[\alpha]^{24}_D$ +109.0° (*c* 1.03, $CHCl_3$); IR (KBr) 3350 (NH), 2250 (CN), 1670 (CO), 1600 (Ph) cm^{-1}; ^1H NMR δ 1.53 (3 H, d, *J* = 6.8 Hz, Me), 5.14 (1 H, quint, *J* = 6.8 Hz, C*H*(Me)Ph), 6.72 (1 H, br s, NH), 7.31–7.63 (10 H, m, Ph × 2); ^{19}F NMR δ −144.64 (s); MS *m/z* 282 (M^+), 134 (M^+ − COOEt). Anal. Calcd for $C_{17}H_{15}FN_2O$: C, 72.33; H, 5.36; N, 9.92. Found: C, 72.20; H, 5.46; N, 10.07. **X-ray crystallographic data for compound 5f$_M$**: $C_{17}H_{15}FN_2O$, M_r = 282.32, monoclinic, $P2_1$, *a* = 8.367(1) Å, *b* = 17.006(1) Å, *c* = 5.253(1) Å, β = 105.3(1)°, *V* = 720.9(2) Å^3, *Z* = 2, D_x = 1.3000 M g^{-3}, λ(Cu Kα$_1$) = 1.540 50 Å, μ = 0.761 mm^{-1}, *F*(000) = 296, *T* = 295 K. Crystallographic data were collected on a Rigaku AFC-5 diffractometer. The structures were solved by the direct method and refined by full-matrix least-squares calculations assuming anisotropic temperature factors for nonhydrogen atoms and isotropic ones for hydrogen atom. *R* = 0.049, R_w = 0.048 for 1096 reflections above 3σ(*F*). For further X-ray crystallographic data for **5f$_M$**, see supplementary material. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(*R*)-α-Cyano-α-fluoro-*N*-[(*R*)-1-phenylethyl]phenylacetamide (5f$_L$): colorless needles; mp 101 °C; $[\alpha]^{24}_D$ +106.3° (*c* 1.00, $CHCl_3$); IR (KBr) 3362 (NH), 2251 (CN), 1677 (CO), 1600 (Ph) cm^{-1}; ^1H NMR δ 1.61 (3 H, d, *J* = 7.1 Hz, Me), 5.15 (1 H, quint, *J* = 7.1 Hz, C*H*(Me)Ph), 6.73 (1 H, br s, NH), 7.22–7.55 (10 H, m, Ph × 2); ^{19}F NMR δ −143.78 (s); MS *m/z* 282 (M^+), 134 (M^+ − COOEt). Anal. Calcd for $C_{17}H_{15}FN_2O$: C, 72.33; H, 5.36; N, 9.92. Found: C, 72.39; H, 5.06; N, 9.90.

(*S*)-(−)-α-Cyano-α-fluorophenylacetic Acid (5a). Into a mixture of **5f$_M$** (1.41 g, 5.0 mmol) and anhyd NaOAc (25 g) in CCl_4 (150 mL) was slowly introduced N_2O_4 gas below 0 °C. The mixture was stirred at 0 °C while additional N_2O_4 gas was introduced until the starting material was no longer detected on the TLC plate (usually 2 or 3 h are required). The mixture was heated at 40 °C with a water bath and stirred at 40 °C for 1 h. Water (100 mL) was added over a period of 3 min, and the mixture was stirred at 40 °C for 15 min. The aqueous layer was separated, cooled below 0 °C, made slightly acidic (pH ca. 4.5) with 1 N HCl, and washed with Et_2O (200 mL × 2). The aqueous layer was made strongly acidic (pH <1) with concd HCl and extracted with EtOAc (200 mL × 3). The extract was dried over $MgSO_4$ and concentrated in vacuo to afford 555 mg (62%) of (*S*)-(−)-**5a** as a colorless oil: $[\alpha]^{23}_D$ −24.5° (*c* 1.00, $CHCl_3$); IR (neat) 3503 (OH), 2255 (CN), 1766 (CO), 1595 (Ph) cm^{-1}; ^1H NMR δ 7.44–7.66 (5 H, m, Ph), 8.25 (1 H, br s, COOH); ^{19}F NMR δ −147.77 (s); MS *m/z* 179 (M^+), 134 (M^+ − COOH), 108 (M^+ − COOH − CN).

The acid (*R*)-(+)-**5a** was prepared in 73% yield in the same manner from the less polar isomer **5f$_L$**: colorless oil; $[\alpha]^{23}_D$ +24.3° (*c* 1.00, $CHCl_3$).

(*S*)-(−)-α-Cyano-α-fluorophenylacetic Acid Sodium Salt. To a solution of (*S*)-(−)-**5a** (537 mg, 3.0 mmol) in THF (30 mL) was added 60% NaH in mineral oil (120 mg, 3.0 mmol) at 0 °C, and the mixture was stirred for 10 min. The solvent was evaporated, and the residual solid was crystallized from THF to afford 207 mg (39%) of (*S*)-(−)-CFPA sodium salt as colorless prisms: mp >300 °C; IR (KBr) 2267 (CN), 1679 (CO) cm^{-1}; ^1H NMR δ 7.42–7.70 (5 H, m, Ph); ^{19}F NMR δ −136.13 (s); MS *m/z* 178 (M^+ − Na), 134 (M^+ − COONa), 108 (M^+ − COONa − CN). Anal. Calcd for $C_9H_5FNNaO_2$: C, 53.75; H, 2.51; N, 6.96. Found: C, 53.86; H, 2.45; N, 6.90.

(*S*)-(−)-α-Cyano-α-fluorophenylacetyl Chloride (5b). To a stirred solution of (*S*)-(−)-**5a** (537 mg, 3.0 mmol) and DMF (30 mg) in dry CH_2Cl_2 (30 mL) was added oxalyl chloride (0.6 mL, 7.0 mmol) at 0 °C. The solution was stirred at rt for 2 h and concentrated in vacuo. The residue was purified by distillation (bp 40–41 °C/0.4 Torr) to give 480 mg (81%) of (*S*)-(−)-**5b** as a colorless oil: $[\alpha]^{24}_D$ −23.5° (*c* 1.13, $CHCl_3$); IR (neat) 2255 (CN), 1796 (CO), 1599 (Ph) cm^{-1}; ^1H NMR δ 7.27–7.70 (5 H, m, Ph); ^{13}C NMR δ 91.55 (d, *J* = 208.6 Hz, CF), 112.44 (d, *J* = 32.9 Hz, CN), 125–134 (Ph), 165.88 (d, *J* = 36.6 Hz, COCl); ^{19}F NMR δ −133.66 (s); MS *m/z* 199, 198, 197 (M^+), 134 (M^+ − COCl), 108 (M^+ − COCl − CN). Anal. Calcd for C_9H_5ClFNO: C, 54.71; H, 2.55; N, 7.09. Found: C, 54.38; H, 2.51; N, 6.96.

The chloride (*R*)-(+)-**5b** was prepared in 77% yield in the same manner from (*R*)-(+)-CFPA **5a** as a colorless oil: $[\alpha]^{23}_D$ + 23.4° (*c* 1.00, $CHCl_3$).

General Procedure for Preparation of CFPA and MTPA Derivatives 5g–5m and 1d–1m. A chiral alcohol or amine (1.0 mmol) was added to a solution of distilled (−)-**5b** or (−)-**1b** (1.1 mmol) and pyridine (1.2–1.5 mmol) in CCl_4 (5 mL), and the solution was stirred at rt for 5 min–24 h. Water (5 mL) was added, and the reaction mixture was transferred into a separatory funnel with CH_2Cl_2 (2 mL). The solution was washed successively with 1 N HCl, saturated Na_2CO_3, and water and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography, preparative TLC, or recrystallization to afford diastereomeric esters or amides **5g–5m** and **1d–1m**. The Δδ values were directly obtained, before purification, from ^{19}F and ^1H NMR spectra of crude derivatives.

3-Methylbut-2-yl α-cyano-α-fluorophenylacetates (5g): colorless oil; IR (neat) 2252 (CN), 1771 (CO) cm^{-1}; ^1H NMR δ 0.72 and 0.92 (Δδ = 0.197), (6 H, d, *J* = 6.8 Hz, CH*Me*$_2$), 1.10 and 1.26 (Δδ = 0.162), (3 H, d, *J* = 6.3 Hz, Pr^{i}CHMe), 1.80–1.95 (1 H, m, C*H*Me$_2$), 4.85 and 4.88 (Δδ = 0.024), (1 H, quintet, *J* = 6.4 Hz, Pr^{i}CHMe), 7.25–7.66 (5 H, m, Ph); ^{19}F NMR δ −147.10 and −146.35 (Δδ = 0.752), (s); MS *m/z* 250 (M^+ + 1), 223 (M^+ − CN); HRMS calcd for $C_{14}H_{17}FNO_2$ (M^+ + 1) *m/z* 250.1242, found 250.1242, calcd for $C_{14}H_{16}FNO_2$ (M^+) *m/z* 249.1164, found 249.1214.

(Methoxycarbonyl)phenylmethyl α-cyano-α-fluorophenylacetates (5h): colorless oil; IR (neat) 2254 (CN), 1745 (CO) cm^{-1}; ^1H NMR δ 3.63 and 3.72 (Δδ = 0.097), (3 H, s, Me), 6.01 and 6.06 (Δδ = 0.044), (1 H, s, CH), 7.30–7.80 (10 H, m, Ph × 2); ^{19}F NMR δ −145.94 and −145.66 (Δδ = 0.274), (s); MS *m/z* 327 (M^+), 149 ($PhC^+HCOOMe$); HRMS calcd for $C_{18}H_{14}FNO_4$ (M^+) *m/z* 327.0908, found 327.0956.

α-Cyano-*N*-[(ethoxycarbonyl)phenylmethyl]-α-fluorophenylacetamides (5i): colorless solid; mp 74–76 °C; IR (KBr) 3300 (NY), 3050, 3000 (CH), 2250 (CN), 1750 (COO), 1680 (CON) cm^{-1}; ^1H NMR δ 1.18 and 1.24 (Δδ = 0.053), (3 H, t, *J* = 7.1 Hz, Me), 4.10–4.25 (2 H, m, CH_2), 5.52 and 5.55 (Δδ = 0.027), (1 H, d, *J* = 7.3 and 7.1 Hz, CH), 7.20–7.75 (10 H, m, Ph × 2 and NH); ^{19}F NMR δ −144.68 and −143.48 (Δδ = 0.245), (s); MS *m/z* 340 (M^+), 321 (M^+ − F), 267 (M^+ − COOEt); HRMS calcd for $C_{19}H_{17}FN_2O_3$ (M^+) *m/z* 340.1223, found 340.1233.

2-Phenylprop-1-yl α-cyano-α-fluorophenylacetates (5j): colorless oil; IR (neat) 2253 (CN), 1776 (CO), 1603 (Ph) cm^{-1}; ^1H NMR δ 1.25 (3 H, d, *J* = 7.1 Hz, Me), 3.12 (1 H, sextet, *J* = 7.1 Hz, CH), 4.25–4.44 (2 H, m, CH_2), 7.08–7.54 (10H, m, Ph × 2); ^{19}F NMR δ −147.52 and −146.89 (Δδ = 0.623), (s); MS *m/z* 297 (M^+), 134 ($PhC^+(F)CN$); HRMS calcd for $C_{18}H_{16}FNO_2$ (M^+) *m/z* 297.1165, found 297.1130.

3-Phenylbut-1-yl α-cyano-α-fluorophenylacetates (5k): colorless oil; IR (neat) 2253 (CN), 1774 (CO) cm^{-1}; ^1H NMR δ 1.21 and 1.23 (Δδ = 0.019), (3 H, d, *J* = 6.8 Hz, Me), 1.91 (2 H, m, OCH_2CH_2), 2.68 (1 H, sextet, *J* = 6.8 Hz, CH), 3.96–4.26 (2 H, m, OCH_2), 6.96–7.66 (10 H, m, Ph × 2); ^{19}F NMR δ −146.63 and −146.41 (Δδ = 0.224), (s); MS *m/z* 311 (M^+), 105 (PhC^+-HMe); HRMS calcd for $C_{19}H_{18}FNO_2$ (M^+) *m/z* 311.1320, found 311.1294.

4-Methylhex-1-yl α-cyano-α-fluorophenylacetates (5l): colorless oil; IR (neat) 2252 (CN), 1776 (CO) cm^{-1}; ^1H NMR δ 0.78–0.85 (6 H, m, CH(*Me*)CH_2*Me*), 1.00–1.80 (7 H, m, CH_2CH_2CH(Me)CH_2Me), 4.27 (2 H, t, *J* = 6.8 Hz, OCH_2), 7.26–7.68 (5 H, m, Ph); ^{19}F NMR δ −146.89 and −146.88 (Δδ = 0.014), (s); MS *m/z* 278 (M^+ + 1), 277 (M^+), 251 (M^+ − CN); HRMS calcd for $C_{16}H_{20}FNO_2$ (M^+) *m/z* 277.1478, found 277.1506.

α-Cyano-*N*-(5-ethoxyhex-1-yl)-α-fluorophenylacetamides (5m): colorless oil; IR (neat) 3330 (NH), 2252 (CN), 1686 (CO) cm^{-1}; ^1H NMR δ 1.108 and 1.115 (Δδ = 0.011), (3 H, d, *J* = 6.1 Hz, CH*Me*), 1.17 and 1.18 (Δδ = 0.006), (3 H, t, *J* = 7.1 Hz, CH_2Me), 1.20–1.80 (6 H, m, $NHCH_2(CH_2)_3$), 3.37 (4 H, m, $NHCH_2$ and OCH_2) 3.54 (1 H, m, CH), 6.62 (1 H, br s, NH), 7.40–7.70 (5 H, m, Ph); ^{19}F NMR δ −145.04 and −144.95 (Δδ = 0.094), (s); MS *m/z* 307 (M^+ + 1), 261 (M^+ − OEt); HRMS calcd for $C_{17}H_{23}FN_2O_2$ (M^+) *m/z* 306.1742, found 306.1702.

2-Butyl α-methoxy-α-(trifluoromethyl)phenylacetates (1d): colorless oil; IR (neat) 2978 (CH), 1744 (CO) cm^{-1}; ^1H NMR δ 0.83 and 0.94 (Δδ = 0.110), (3 H, t, J = 7.6 Hz, CH_2Me), 1.25 and 1.33 (Δδ = 0.079), (3 H, d, J = 6.4 Hz, $CHMe$), 1.55–1.80 (2 H, m, CH_2), 3.56 (3 H, q, J_{HF} = 1.2 Hz, OMe), 5.00–5.20 (1 H, m, CH), 7.30–7.60 (5 H, m, Ph); ^{19}F NMR δ −71.98 (s); MS m/z 291 (M^+ + 1), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{14}H_{18}F_3O_3$ (M^+ + 1) m/z 291.1207, found 291.1194.

1-Phenylethyl α-methoxy-α-(trifluoromethyl)phenylacetates (1e): colorless oil; IR (neat) 2956 (CH), 1753 (CO) cm^{-1}; ^1H NMR δ 1.58 and 1.64 (Δδ = 0.059), (3 H, d, J = 6.6 and 6.8 Hz, $CHMe$), 3.47 and 3.56 (Δδ = 0.085), (3 H, q, J_{HF} = 1.1 and 1.3 Hz, OMe), 6.09 and 6.13 (Δδ = 0.042), (1 H, q, J = 6.6 Hz, CH), 7.22–7.48 (10 H, m, Ph × 2); ^{19}F NMR δ −72.17 and −71.97 (Δδ = 0.203), (s); MS m/z 339 (M^+ + 1), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{18}H_{18}F_3O_3$ (M^+ + 1) m/z 339.1208, found 339.1236.

α-Methoxy-*N*-(1-phenylethyl)-α-(trifluoromethyl)-phenylacetamides (1f): colorless solid; mp 63–80 °C; IR (KBr) 3311 (NH), 2981 (CH), 1669 (CO) cm^{-1}; ^1H NMR δ 1.51 and 1.55 (Δδ = 0.040), (3 H, d, J = 7.1 and 6.8 Hz, $CHMe$), 3.37 and 3.41 (Δδ = 0.040), (3 H, q, J_{HF} = 1.5 Hz, OMe), 5.18 and 5.19 (Δδ = 0.088), (1 H, quintet, J = 7.1 and 6.8 Hz, CH), 6.97 (1 H, br s, NH), 7.21–7.60 (10 H, m, Ph × 2); ^{19}F NMR δ −69.32 and −69.14 (Δδ = 0.181), (s); MS m/z 337 (M^+), 189 ($PhC^+C(OMe)CF_3$); HRMS calcd for $C_{18}H_{19}F_3NO_2$ (M^+ + 1) m/z 338.1366, found 338.1338.

3-Methylbut-2-yl α-methoxy-α-(trifluoromethyl)phenylacetates (1g): colorless oil; IR (neat) 2969 (CH), 1744 (CO) cm^{-1}; ^1H NMR δ 0.846 and 0.857 (Δδ = 0.011), (3 H, d, J = 6.8 Hz, $CH(Me)Me$), 0.921 and 0.927 (Δδ = 0.006), (3 H, d, J = 6.6 and 7.1 Hz, $CH(Me)Me$), 1.215 and 1.292 (Δδ = 0.077), (3 H, d, J = 6.3 Hz, Pr^iCHMe), 1.72–1.96 (1 H, m, $CHMe_2$), 3.540 and 3.568 (Δδ = 0.029), (3 H, q, J_{HF} = 1.0 Hz, OMe), 4.91–5.04 (1 H, m, Pr^iCHMe), 7.33–7.60 (5 H, m, Ph); ^{19}F NMR δ −71.91 and −71.88 (Δδ = 0.029), (s); MS m/z 305 (M^+ + 1), 335 ($M^+ - CF_3$); HRMS calcd for $C_{15}H_{19}F_3O_3$ (M^+) m/z 304.1285, found 304.1280.

(Methoxycarbonyl)phenylmethyl α-methoxy-α-(trifluoromethyl)phenylacetates (1h): colorless oil; IR (neat) 2956 (CH), 1753 (CO) cm^{-1}; ^1H NMR δ 3.548 and 3.692 (Δδ = 0.145), (3 H, q, J = 1.0 Hz, OMe), 3.74 and 3.77 (Δδ = 0.029), (3 H, s, COOMe), 6.09 and 6.11 (Δδ = 0.022), (1 H, s, CH), 7.34–7.65 (10 H, m, Ph × 2); ^{19}F NMR δ −72.43 and −72.14 (Δδ = 0.296), (s); MS m/z 382 (M^+), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{19}H_{17}F_3O_5$ (M^+) m/z 382.1028, found 382.1034.

***N*-[(Ethoxycarbonyl)phenylmethyl]-α-methoxy-α-(trifluoromethyl)phenylacetamides (1i)**: colorless oil; IR (neat) 3412 (NH), 2985 (CH), 1741 (COO), 1702 (CON) cm^{-1}; ^1H NMR δ 1.196 and 1.215 (Δδ = 0.018), (3 H, t, J = 7.1 Hz, Me), 3.35 and 3.54 (Δδ = 0.191), (3 H, q, J_{HF} = 1.2 and 1.7 Hz, OMe), 4.11–4.32 (2 H, m, CH_2), 5.57 and 5.59 (Δδ = 0.020), (1 H, d, J = 7.3 Hz, CH), 7.20–7.80 (11 H, m, Ph × 2 and NH); ^{19}F NMR δ −69.54 and −69.28 (Δδ = 0.260), (s); MS m/z 395 (M^+), 322 (M^+ − COOEt), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{20}H_{20}F_3NO_4$ (M^+) m/z 395.1342, found 395.1317.

2-Phenylprop-1-yl α-methoxy-α-(trifluoromethyl)phenylacetates (1j): colorless oil; IR (neat) 2971 (CH), 1750 (CO) cm^{-1}; ^1H NMR δ 1.28 (3 H, d, J = 6.8 Hz, Me), 3.08–3.24 (1 H, m, CH), 3.38 and 3.41 (Δδ = 0.029), (3 H, q, J_{HF} = 1.2 and 1.0 Hz, OMe), 4.24–4.57 (2 H, m, CH_2), 7.12–7.43 (10 H, m, Ph × 2); ^{19}F NMR δ −72.13 and −72.08 (Δδ = 0.051), (s); MS m/z 352 (M^+), 283 ($M^+ - CF_3$); HRMS calcd for $C_{19}H_{19}F_3N_3$ (M^+) m/z 352.1285, found 352.1283.

3-Phenylbut-1-yl α-methoxy-α-(trifluoromethyl)phenylacetates (1k): colorless oil; IR (neat) 2962 (CH), 1749 (CO) cm^{-1}; ^1H NMR δ 1.251 and 1.257 (Δδ = 0.006), (3 H, d, J = 7.1 Hz, Me), 1.90–2.09 (2 H, m, OCH_2CH_2), 2.77 (1 H, m, CH), 3.540 and 3.543 (Δδ = 0.004), (3 H, q, J_{HF} = 1.8 and 1.0 Hz, OMe), 4.06–4.37 (2 H, m, OCH_2), 7.06–7.55 (10 H, m, Ph × 2); ^{19}F NMR δ −72.04 (s); MS m/z 367 (M^+ + 1), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{20}H_{22}F_3O_3$ (M^+) m/z 367.1519, found 367.1509.

4-Methylhex-1-yl α-methoxy-α-(trifluoromethyl)phenylacetates (1l): colorless oil; IR (neat) 2961 (CN), 1750 (CO) cm^{-1}; ^1H NMR δ 0.835 (3 H, t, J = 6.8 Hz, CH_2Me), 0.838 (3 H, d, J = 6.8 Hz, $CH(Me)CH_2Me$), 1.05–1.23 (2 H, m, CH_2Me), 1.23–1.42 (3 H, m, $CH_2CH(Me)CH_2Me$), 1.60–1.80 (2 H, m, OCH_2CH_2), 3.55 (3 H, q, J = 1.2 Hz, OMe), 4.24–4.40 (2 H, m, OCH_2), 7.35–7.57 (5 H, m, Ph); ^{19}F NMR δ −72.11 (s); MS m/z 333 (M^+ + 1), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{17}H_{23}F_3O_3$ (M^+) m/z 332.1600, found 332.1641.

***N*-(5-Ethoxyhex-1-yl)-α-methoxy-α-(trifluoromethyl)-phenylacetamides (1m)**: colorless oil; IR (neat) 3336 (NH), 2973, 2939, 2865 (CH), 1680 (CO) cm^{-1}; ^1H NMR δ 1.111 and 1.116 (Δδ = 0.006), (3 H, d, J = 6.1 Hz, $CHMe$), 1.172 and 1.179 (Δδ = 0.007), (3 H, t, J = 7.1 Hz, CH_2Me), 1.25–1.65 (6 H, m, $NHCH_2(CH_2)_3$), 3.25–3.61 (5 H, m, $NHCH_2$ and $CHOCH_2$), 3.41 (3 H, q, J_{HF} = 1.5 Hz, OMe), 6.82 (1 H, br s, NH), 7.33–7.60 (5 H, m, Ph); ^{19}F NMR δ −69.38 (s); MS m/z 361 (M^+), 332 (M^+ − Et), 316 (M^+ − OEt); HRMS calcd for $C_{18}H_{26}F_3NO_3$ (M^+) m/z 361.1863, found 361.1861.

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Supplementary Material Available: Further X-ray crystallographic data including atomic coordinates and anisotropic thermal parameters for compound $\mathbf{5f_M}$ and ^1H NMR spectra for compounds **2a**, **5c**, **6c**, **7**, **8**, **12**, **13**, **15**, and **16** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.