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Chemistry of Novel Compounds with Multifunctional Carbon Structure. 8.[1]

Application of the α-Cyano-α-fluorophenylacetic Acid (CFPA) Method to the Enantiomeric Excess Determination of Some Hindered Alcohols in Asymmetric and Natural Product Syntheses†

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Abstract: The reaction of CFPA chloride (**2b**) with pinacolyl alcohol was found to proceed more than 500 times faster than that of MTPA chloride (**1b**) suggesting that the CFPA method induces potentially much less kinetic resolution than the widely used MTPA method in enantiomeric excess (ee) determination. Some applications of CFPA method were also investigated to evaluate practical use of CFPA reagent in ee determination of some hindered alcohols in asymmetric and natural product syntheses.

Indirect methods for the determination of enantiomeric excess (ee) involve the derivatization of an enantiomeric mixture with a chiral reagent, producing a pair of diastereomers. These methods offer several advantages over direct determination in that, in addition to ee analysis, they permit enantiomeric separation, structural characterization, purification, determination of absolute configuration, *etc.* Among many chiral derivatizing reagents,[2] including several recently reported,[3] Mosher acid (MTPA, **1a**)[4] is currently widely employed because of the general availability of GC and LC techniques, in addition to ^{1}H, ^{13}C, and ^{19}F NMR probes. However, instances have been reported where kinetic resolution[5] and/or incomplete derivatization[6] by this method were observed due, primarily, to the insufficient reactivity of MTPA chloride (MTPA-Cl, **1b**) towards nucleophiles. Either or both of these deficiencies will result in incorrect ee values.

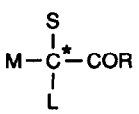
We have recently developed a new and efficient chiral derivatizing reagent, α-cyano-α-fluorophenylacetic acid (CFPA, **2a**).[7] This reagent utilizes several of the features uniquely characteristic of the element, fluorine.[8-10] It was found that ^{19}F NMR-based ee detections through diastereomeric CFPA derivatives are much more distinct than those based on MTPA derivatives, especially so in compounds which have stereogenic centers remotely disposed from fuctionalities.[1] We also found that CFPA chloride (CFPA-Cl, **2b**) reacts with hindered nucleophiles much faster than does **1b**.[11]

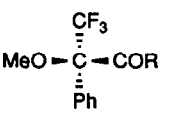
† Dedicated with all best wishes to Professor Shun-ichi Yamada on the occasion of his 77th birthday.

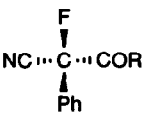
In this paper we report detailed studies both on the molecular design of CFPA structure and on the high reactivity of **2b** towards hindered nucleophiles. Further, we describe some applications of our method to hindered alcohols in studies of asymmetric and natural product syntheses.

RESULTS AND DISCUSSION

We ascribed the poor reactivity of **1b** to factors inherent in the MTPA structure. Therefore, new reagents alternative to MTPA were designed with reactivity enhanced by both steric and electronic aspects based on considerations of the multifunctionalized carbon structure.[12] Namely, the three substituents surrounding the acetate-derived chiral center (L, M, and S) should have an effective steric bulkiness significantly differentiated from each other[13] and one of them should be sterically as small as possible.[14] Also, all three should be quite electronegative,[14] and preferably have no protons.[15] After careful examination of several model candidates,[1,16,17] CFPA was chosen as the best product of these design considerations. Indeed, the very small F and CN substituents,[8,16] in combination with their strong electronegativities ($\Sigma\sigma^*$ values),[18] seemed to offer considerable advantage over the rather bulky CF_3 and OMe groups in the MTPA structure.







(*R*)-**1a** : R = OH (MTPA)
(*R*)-**1b** : R = Cl (MTPA-Cl)

(*S*)-**2a** : R = OH (CFPA)
(*S*)-**2b** : R = Cl (CFPA-Cl)

Steric Factor	$CF_3 \cong OMe < Ph$	$H \cong F \ll CN \ll Ph$
Electronic Factor ($\Sigma\sigma^*$)	1.78	2.67

We first attempted to compare the actual isolation yields in the MTPA and CFPA derivatizations (Table 1). Both (*R*)-(+)-**1b** and (*S*)-(–)-**2b** were reacted with some hindered nucleophiles under analogous conditions as Moshers' (pyridine/CCl_4, room temp).[4] Reactions were quenched *before completion* and the products were isolated by silica gel preparative TLC. In the cases of (±)-sec-phenylethyl and (±)-2-octyl alcohols (entries 3 and 4), heating for a prolonged time was not sufficient for completion of MTPA derivatization, whereas the reaction of (–)-**2b** with various nucleophiles proceeded much faster even at room temperature. Although a 1:1 ratio of diastereomers was obtained with MTPA in those cases where the yields were high, unbalanced ratios of two MTPA diastereomers were generally observed when the yields were low (entries 1–4). These results suggest that kinetic resolution occurs during the course of MTPA acylation. The higher reactivity of **2b** over **1b** was also supported by spectral data. The carbonyl absorption in IR spectra for (+)-**1b** and (–)-**2b** were 1790 and 1796 cm^{-1}. The chemical shifts in ^{13}C NMR spectra of the chiral carbon and the carbonyl carbon for (+)-**1b** and (–)-**2b** were –89.1 (s) and –91.6 (d, J = 208.6 Hz) ppm, and –171.1 (s) and –165.9 (d, J = 36.6 Hz) ppm, respectively.

Table 1. Isolated Yields by Preparative TLC of MTPA and CFPA Derivatives of Some Hindered Nucleophiles

Entry	Derivative (R)	MeO–C(CF$_3$)(Ph)–COR (1c–i)				NC–C(F)(Ph)–COR (2c–i)	
		(room temp.)		(reflux)		(room temp.)	
		t (min)	Yield(%)	*t* (min)	Yield(%)	*t* (min)	Yield(%)
1	-O-C(Bu^t)(Me)-H (c)	600	34			5	80
2	-O-C(Ph)(CF$_3$)-H (d)	300	39			5	73
3	-O-C(Ph)(Et)-H (e)	2400	57	1000	60	5	75
4	-O-C(Hex)(Me)-H (f)	2400	42	1000	61	10	72
5	-NH-C(Ph)(Me)-H (g)	30	70			10	89
6	-NH-C(Bu^t)(Me)-H (h)	30	73			10	92
7	-NH-C(Ph)(COOEt)-H (i)	10	57			5	91

Preliminary kinetic studies on the reactions of **1b** and **2b** with an appropriate hindered alcohol were also investigated in order to estimate their relative reactivities. To a solution of (±)-pinacolyl alcohol (2.5 mmol) and pyridine (5 mmol) in dry CH_2Cl_2 (50 ml) was added (+)-**1b** or (–)-**2b** (3 mmol) and the mixture was stirred at 25 °C. Periodically, 3 ml aliquots of the reaction solutions were removed and quenched with water. Each product obtained was analyzed by HPLC (stationary phase; Develosil, eluent; hexane / EtOAc = 4). The amounts of the diastereomeric esters, **1c** and **2c**, formed as a function of time are shown in Fig. 1 and 2, respectively. The reaction of (–)-**2b** with (±)-pinacolyl alcohol was almost complete within 15 min whereas the reaction of (+)-**1b** proceeded very slowly. The slopes of the graphs of the integrated second-order rate equations *vs.* time for both acid chlorides were calculated by the method of least-squares. As a result, k_{2b} (14.5 ± 0.1 $l \cdot mol^{-1} \cdot min^{-1}$) was found to be more than 500 times greater than k_{1b} (0.028 ± 0.001 $l \cdot mol^{-1} \cdot min^{-1}$).

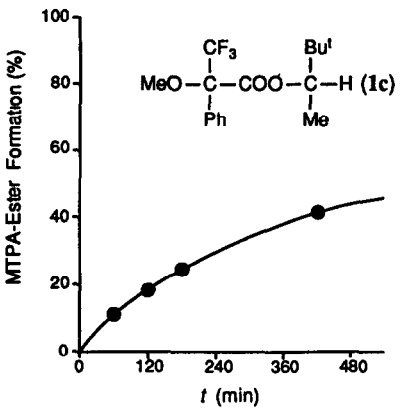


Figure 1. Formation of MTPA Ester of Pinacolyl Alcohol *vs.* Time under Standardized Conditions (Pyr / CH_2Cl_2, at 25 °C)

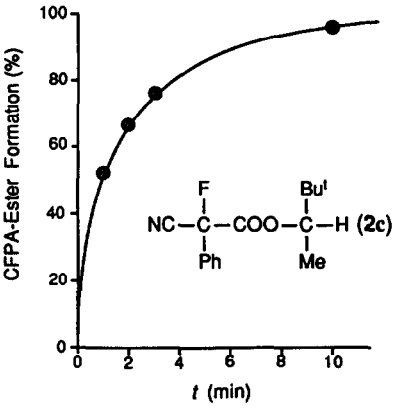
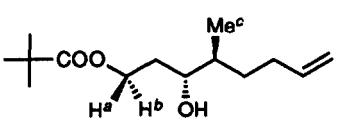
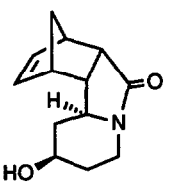


Figure 2. Formation of CFPA Ester of Pinacolyl Alcohol *vs.* Time under Standardized Conditions (Pyr / CH_2Cl_2, at 25 °C)

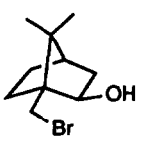
We next investigated some applications to evaluate practical use of the reagent. Two enantiomeric alcohols, (+)- and (–)-**3**, are potentially key intermediates for total syntheses of tetronomycin[19] and tetranosin,[20] respectively. Although reactions of (+)-**1b** with both enantiomers were complete within 1 h, the MTPA derivatives gave much smaller chemical shift differences ($\Delta\delta$ values) between the two diastereomers in both ^1H and ^{19}F NMR spectra than the corresponding CFPA derivatives ($\Delta\delta_H$ values for H^a, H^b, Me^c and $\Delta\delta_F$ values for the MTPA diastereomers are 53.7, 23.7, 37.8, and 22.9 Hz, and 148.5, 83.7, 70.2, and 299.7 Hz for the CFPA diastereomers). We also applied the two methods to ee detection of the more hindered alcohols, (+)-**4**[21] and (–)-**5**,[22] which are key compounds in asymmetric synthesis. Reactions of (+)-**1b** with these alcohols did not proceed even in 2 days at room temperature, apparently owing to the poor reactivity of (+)-**1b**. In contrast, reactions of (±)-**2b** with these alcohols were complete within 10 min under ambient conditions to afford the corresponding pairs of CFPA diastereomers. In both cases, fairly large chemical shift differences between the diastereomeric pairs were observed in ^{19}F NMR spectra ($\Delta\delta_F$ values for CFPA diastereomers of **4** and **5** are 36.8 and 255.6 Hz, respectively). However, ee detection of these CFPA esters by ^1H NMR failed because of insufficient magnitude of the $\Delta\delta_H$ values and/or because of overlapping of the proton signals of interest with other proton signals in the molecules. Therefore, our initial insight in using ^{19}F NMR for ee determination has been justified.



(+)-**3**



(+)-**4**



(–)-**5**

In most cases in the literature, the possibility of kinetic resolution by chiral derivatizing reagents in the course of their condensations has been neglected, in spite of its critical significance for determining exact ee values. We have demonstrated the much higher reactivity of **2b** than the widely used **1b**. We believe that the CFPA method will result in much less kinetic resolution during the course of condensation, even with hindered nucleophiles.

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EXPERIMENTAL

General. Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on JASCO A-102 or Perkin-Elmer 1600 spectrometer. ^{1}H NMR spectra were measured with Me_4Si as internal standard and were recorded on a JEOL GX-270 (270 MHz) or a JEOL PMX-60 (60 MHz) spectrometer. ^{19}F NMR spectra were measured with $CFCl_3$ as internal standard and were taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted as negative δ values. EI mass spectra including high-resolution mass spectra (HRMS) were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC were performed on Kieselgel 60 (Merck, Art. 9385 and 7748, respectively).

General Procedure for Preparation of MTPA and CFPA Derivatives, 1c—1i and 2c—i. To a solution of racemic alcohol (0.1 mmol) and pyridine (0.5 mmol) in CCl_4 (5 ml) was added distilled (*R*)-(+)-**1b** or (*S*)-(–)-**2b** (1.1 mmol). To a solution of racemic amine (0.4 mmol) and pyridine (2.0 mmol) in CCl_4 (1 ml) was added (*R*)-(+)-**1b** or (*S*)-(–)-**2b** (0.12 mmol). The solution was stirred at room temparature 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 1N HCl, saturated Na_2CO_3, and water, and dried on $MgSO_4$. Evaporation of the solvent gave a residue which was purified by silica gel preparative TLC to afford the diastereomeric (*R*)-(+)-MTPA esters and amides (**1c—1i**) or the diastereomeric (*S*)-(–)-CFPA esters and amides (**2c—2i**).

3,3-Dimethylbut-2-yl α-Methoxy-α-(trifluoromethyl)phenylacetates (1c): colorless oil; IR (neat) 2969 (CH), 1745 (CO), 1272 (C-O-C), 1169 (C-O-Me) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 and 0.91 (Δδ = 3.7 Hz), (9H, s, t-Bu), 1.20 and 1.27 (Δδ = 18.8 Hz), (3H, d, J = 6.4 Hz, CH*Me*), 3.52 and 3.57 (Δδ = 13.8 Hz), (3H, q, J_{HF} = 1.0, 1.2 Hz, OMe), 4.86 and 4.89 (Δδ = 10.0 Hz), (1H, q, J = 6.6 Hz, CH), 7.35—7.58 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ –71.78 and –71.67 (Δδ = 29.4 Hz), (s); mass spectrum (EI mode), *m/z* 318 (M^+), 189 ($PhC^+(OMe)CF_3$), 105 (PhC^+O), 77 (Ph^+), 57 (t-Bu^+); HRMS calcd for $C_{16}H_{22}F_3O_3$ ($M^+ + 1$) *m/z* 319.1519, found 319.1498.

1-Phenyl-2,2,2-trifluoroethyl α-Methoxy-α-(trifluoromethyl)phenylacetates (1d): colorless oil; IR (neat) 2954 (CH), 1767 (CO), 1271 (C-O-C), 1187 (C-O-Me) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.48 and 3.61 (Δδ = 33.7 Hz), (3H, q, J_{HF} = 1.0, 1.5 Hz, OMe), 6.26 and 6.34 (Δδ = 21.0 Hz), (1H, q, J_{HF} = 6.6 Hz, OMe), 7.23—7.51 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –72.32 and –72.28 (Δδ = 11.0 Hz), (s, C(OMe)CF_3), –76.43 and –76.19 (Δδ = 60.7 Hz), (d, J_{HF} = 7.3 Hz, CHCF_3); mass spectrum (EI mode), *m/z* 392 (M^+), 323 ($M^+ - CF_3$), 189 ($PhC^+(OMe)CF_3$), 159 (PhC^+HCF_3), 105 (PhC^+O); HRMS calcd for $C_{18}H_{14}F_6O_3$ (M^+) *m/z* 392.0847, found 392.0868.

1-Phenylprop-1-yl α-Methoxy-α-(trifluoromethyl)phenylacetates (1e): colorless oil; IR (neat) 2974 (CH), 1747 (CO), 1271 (C-O-C), 1170 (C-O-Me) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.83 and 0.93 (Δδ = 27.1 Hz), (3H, t, *J* = 7.3 Hz, Me), 1.75—2.10 (2H, m, CH_2), 3.45 and 3.54 (Δδ = 25.4 Hz), (3H, q, J_{HF} =1.2 Hz, OMe), 5.82 and 5.90 (Δδ = 20.3 Hz), (1H, ABq, $\Delta\delta_{AB}$ = 7.6, 7.7 Hz, *J* = 6.4, 6.1 Hz, CH), 7.00—7.66 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –72.1 and –71.9 (Δδ = 68.0 Hz), (s); mass spectrum (EI mode), *m/z* 352 (M^+), 189 ($PhC^+(OMe)CF_3$), 119 (PhC^+HEt); HRMS calcd for $C_{19}H_{20}F_3O_3$ ($M^+ + 1$) *m/z* 353.1363, found 353.1321.

2-Octyl α-Methoxy-α-(trifluoromethyl)phenylacetates (1f): colorless oil; IR (neat) 2933 (CH), 1745 (CO), 1271 (C-O-C), 1169 (C-O-Me) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 and 0.88 (Δδ = 5.1 Hz), (3H, t, *J* = 7.1, 6.1 Hz, $(CH_2)_5Me$), 1.25 and 1.33 (Δδ = 21.4 Hz), (3H, d, *J* = 6.1, 6.3 Hz, CH*Me*), 1.10—1.40 (8H, m, $(CH_2)_4Me$), 1.40—1.75 (2H, m, $CH_2(CH_2)_4Me$), 3.55 and 3.57 (Δδ = 4.9 Hz), (3H, q, J_{HF} = 1.2 Hz, OMe), 5.08—5.23 (1H, m, CH), 7.30—7.60 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ –72.06 and –72.01 (Δδ =12.9 Hz), (s); mass spectrum (EI mode), *m/z* 347 ($M^+ + 1$), 189 ($PhC^+(OMe)CF_3$), 113 ($Hex^{13}C^+HMe$), 105 (PhC^+O); HRMS calcd for $C_{18}H_{26}F_3O_3$ ($M^+ + 1$) *m/z* 347.1832, found 347.1804.

α-Methoxy-*N*-(1-phenylethyl)-α-(trifluoromethyl)phenylacetamides (1g): colorless solid; mp 63—80 °C; IR (KBr) 3311 (NH), 2981 (CH), 1669 (CO), 1188, 1156 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.51 and 1.55 (Δδ = 10.9 Hz), (3H, d, *J* = 7.1, 6.8 Hz, CH*Me*), 3.37 and 3.41 (Δδ = 10.9 Hz), (3H, q, J_{HF} = 1.5 Hz, OMe), 5.18 and 5.19 (Δδ = 2.2 Hz), (1H, quintet, *J* = 7.1, 6.8 Hz, CH), 6.97(1H, br s, NH), 7.21—7.60 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –69.32 and –69.14 (Δδ = 45.9 Hz); mass spectrum (EI mode), *m/z* 337 (M^+), 189 ($PhC^+C(OMe)CF_3$), 105 (PhC^+O, PhC^+HMe), 104 ($PhCHCH_2$), 77 (Ph^+); HRMS calcd for $C_{18}H_{19}F_3NO_2$ ($M^+ + 1$) *m/z* 338.1366, found 338.1338.

***N*-(3,3-Dimethylbut-2-yl)-α-methoxy-α-(trifluoromethyl)phenylacetamides (1h)**: colorless oil; IR (neat) 3422, 3345 (NH), 2967 (CH), 1700 (CO), 1165 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.86 and 0.96 (Δδ = 19.5 Hz), (9H, s, t-Bu) 1.05 and 1.11 (Δδ = 15.4 Hz), (3H, d, *J* = 6.8 Hz, CH*Me*) 3.41 (Δδ = 0.0 Hz), (3H, s, OMe), 3.89 and 3.92 (Δδ = 9.96 Hz), (1H, m, CH), 6.61 and 6.70 (Δδ = 23.9 Hz), (1H, d, *J* = 9.3 Hz, NH), 7.37—7.56 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ –69.50 and –69.11 (Δδ = 97.4 Hz), (s); mass spectrum (EI mode), *m/z* 318 ($M^+ + 1$), 317 (M^+), 302 ($M^+ - Me$), 189 ($PhC^+(OMe)CF_3$), 105 (PhC^+O), 57 (t-Bu); HRMS calcd for $C_{16}H_{22}F_3NO_2$ (M^+) *m/z* 317.1601, found 317.1600.

***N*-[(Ethoxycarbonyl)phenylmethyl]-α-methoxy-α-(trifluoromethyl)phenylacetamides (1i)**: colorless oil; IR (neat) 3412 (NH), 2985 (CH), 1741 (CO), 1702 (CO), 1267 (C-O-C), 1167 (C-O-Me) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.196 and 1.215 (Δδ = 4.9 Hz), (3H, t, *J* = 7.1 Hz, Me), 3.35 and 3.54 (Δδ = 51.5 Hz), (3H, q, J_{HF} = 1.2, 1.7 Hz, Me), 4.11—4.32 (2H, m, CH_2), 5.57 and 5.59 (Δδ = 5.4 Hz), (1H, d, *J* = 7.3 Hz, CH), 7.20—7.80 (10H, m, Ph X 2 and NH); ^{19}F NMR ($CDCl_3$) δ –69.54 and –69.28 (Δδ = 66.1 Hz), (s); mass spectrum (EI mode), *m/z* 395 (M^+), 322 (M^+ – COOEt), 189 ($PhC^+(OMe)CF_3$) 163 ($PhC^+HCOOEt$), 105 (PhC^+O), 77 (Ph^+); HRMS calcd for $C_{20}H_{20}F_3NO_4$ (M^+) *m/z* 395.1342, found 395.1317.

3,3-Dimethylbut-2-yl α-Cyano-α-fluorophenylacetates (2c): colorless oil; IR (neat) 2970 (CH), 2252 (CN), 1772 (CO), 1253 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.73 and 0.92 (Δδ = 43.5 Hz), (9H, s, t-Bu), 1.04 and 1.23 (Δδ = 51.6 Hz), (3H, d, *J* = 6.4, 6.6 Hz, CH*Me*), 4.77 and 4.82 (Δδ = 13.5 Hz), (1H, q, *J* = 6.4 Hz, CH), 7.47—7.66 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ –147.56 and –146.36 (Δδ = 305.2 Hz), (s); mass spectrum (EI mode), *m/z* 264 (M^+ + 1), 237 (M^+ – CN), 134 ($PhC^+(F)CN$), 85 ($t\text{-}BuC^+HMe$); HRMS calcd for $C_{15}H_{19}FNO_2$ (M^+ + 1) *m/z* 264.1398, found 264.1340.

1-Phenyl-2,2,2-trifluoroethyl α-Cyano-α-fluorophenylacetates (2d): colorless oil; IR (neat) 2254 (CN), 1774 (CO), 1268 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.98 (1H, q, *J* = 6.8 Hz, CH), 7.37—7.80 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –76.63 and –76.61 (Δδ = 6.4 Hz), (d, J_{HF} = 46.0, 47.8 Hz, CF_3), –147.63 and –146.48 (Δδ = 292.3 Hz), (s, C(F)CN); mass spectrum (EI mode), *m/z* 337 (M^+), 134 ($PhC^+(F)CN$), 77 (Ph^+); HRMS calcd for $C_{17}H_{11}F_4NO_4$ (M^+) *m/z* 337.0726, found 337.0728.

1-Phenylprop-1-yl α-Cyano-α-fluorophenylacetates (2e): colorless oil; IR (neat) 2252 (CN), 1774 (CO), 1248 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.68 and 0.90 (Δδ = 59.8 Hz), (3H, t, *J* = 7.6, 7.3 Hz, Me), 1.72—2.03 (2H, m, CH_2), 5.73 (1H, m, CH), 7.00—7.66 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –146.73 and –145.76 (Δδ = 248.2 Hz), (s); mass spectrum (EI mode), *m/z* 297 (M^+), 134 ($PhC^+(F)CN$), 119 (PhC^+HEt); HRMS calcd for $C_{18}H_{16}FNO_2$ (M^+) *m/z* 297.1164, found 297.1132.

2-Octyl α-Cyano-α-fluorophenylacetates (2f): colorless oil; IR (neat) 2252 (CN), 1772 (CO), 1254 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.84 and 0.87 (Δδ = 10.0 Hz), (3H, t, *J* = 7.1 Hz, $(CH_2)_5CH_3$), 1.16 and 1.31 (Δδ = 38.8 Hz), (3H, d, *J* = 6.4 Hz, CH*Me*), 0.90—1.75 (10H, m, $(CH_2)_5CH_3$), 5.03 (1H, m, CH), 7.42 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ –146.94 and –146.37 (Δδ = 143.4 Hz), (s); mass spectrum (EI mode), *m/z* 292 (M^+ + 1), 134 ($PhC^+(F)CN$), 113 ($HexC^+HMe$); HRMS calcd for $C_{17}H_{23}FNO_2$ (M^+ + 1) *m/z* 292.1713, found 292.1718.

α-Cyano-α-fluoro-*N*-(1-phenylethyl)phenylacetamides (2g): colorless solid; IR (KBr) 3350 (NH), 2240 (CN), 1675 (CO), 1600 (Ph) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 and 1.61 (Δδ = 21.0 Hz), (3H, d, *J* = 7.1 Hz, CH*Me*), 5.15 (1H, quint, *J* = 6.8 Hz, CH), 6.71(1H, br s, NH), 7.22—7.65 (10H, m, Ph X 2); ^{19}F NMR ($CDCl_3$) δ –144.65 and –143.65 (Δδ = 255.5 Hz), (s); mass spectrum (EI mode), *m/z* 282 (M^+), 134 ($PhC^+(F)CN$), 105 (PhC^+HMe), 77 (Ph^+); HRMS calcd for $C_{17}H_{15}FN_2O$ (M^+) *m/z* 282.1168, found 282.1144.

α-Cyano-*N*-(3,3-dimethylbut-2-yl)-α-fluorophenylacetamides (2h): colorless solid; mp 67—95° C; IR (KBr) 3389, 3345 (NH), 2970 (CH), 2361 (CN), 1694, 1682 (CO), 1133 (C-O-C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 and 0.94 (Δδ = 40.0 Hz), (9H, s, t-Bu), 1.07 and 1.15 (Δδ = 20.0 Hz), (3H, d, J = 6.8 Hz, CH*Me*), 3.86 and 3.92 (Δδ = 7.8 Hz), (1H, m, CH), 6.45 (Δδ = 0.0 Hz), (1H, br s, NH), 7.45—7.63 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −145.79 and −143.13 (Δδ = 676.6 Hz), (s); mass spectrum (EI mode), *m/z* 263 (M^+ + 1), 262 (M^+), 134 ($PhC^+(F)CN$), 85 (t-BuC^+HMe); HRMS calcd for $C_{15}H_{19}FN_2O$ (M^+) *m/z* 262.1480, found 262.1524.

α-Cyano-*N*-[(ethoxycarbonyl)phenylmethyl]-α-fluorophenylacetamides (2i): colorless solid; mp 74—76 °C; IR (KBr) 3300 (NH), 3050 (CH), 3000 (CH), 2250 (CN), 1750 (CO), 1680 (CO) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 and 1.24 (Δδ =14.2 Hz), (3H, t, J = 7.1 Hz, Me), 4.10—4.25 (2H, m, CH_2), 5.52 and 5.55 (Δδ = 7.2 Hz), (1H, d, J = 7.3, 7.1 Hz, CH), 7.20—7.75 (10H, m, Ph X 2 and NH); ^{19}F NMR ($CDCl_3$) δ −144.68 and −143.48 (Δδ = 316.2 Hz), (s) mass spectrum (EI mode), *m/z* 340 (M^+), 321 (M^+ − F), 267 (M^+ − COOEt), 206 (M^+ − $PhC^+(F)CN$), 178 ($N^+HCH(Ph)COOEt$), 163 ($PhC^+HCOOEt$), 134 ($PhC^+(F)CN$), 77 (Ph^+); HRMS calcd for $C_{19}H_{17}FN_2O_3$ (M^+) *m/z* 340.1223, found 340.1233.

(*R*)-MTPA Ester of (3*R*,4*S*)-4-Methyl-1-(trimethylacetoxy)-7-octen-3-ol: colorless oil; IR (neat) 1744 ($C(CF_3)COOCH_2$), 1731 (t-$BuCOOCH_2$), 1641 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (3H, d, J = 7.1Hz, CH_3), 1.21 (9H, s, t-Bu), 1.12—1.44 (2H, m, $CH_2CH_2CH{=}CH_2$), 1.39—1.44 (1H, m, MeC*H*), 1.85—1.94 (2H, m, CH_2CH_2OCOt-Bu), 1.97—2.17 (2H, m, $CH_2CH{=}CH_2$), 3.53 (3H, br s, OMe), 3.95 (1H, ddd, J = 11.0, 6.5, 3.4 Hz, CH_aH_bOCOt-Bu), 4.16 (1H, dt, J = 11.0, 5.3 Hz, CH_aH_bOCOt-Bu), 4.96 (1H, ddt, J = 10.0, 1.9, 1.5 Hz, $CH_aH_b{=}CH$), 5.00 (1H, ddt, 13.7, 1.9, 1.5 Hz, $CH_aH_b{=}CH$), 5.18 (1H, dt, J = 8.1, 4.6 Hz, $C(CF_3)COOCH$), 5.75 (ddtd, 13.7, 10.0, 6.6, 1.5 Hz, $CH{=}CH_2$), 7.26—7.53 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −71.51 (s); mass spectrum (EI mode), *m/z* 459 (M^+ + H), 357 (M^+ − t-BuCOO), 225 (M^+ − $PhC(CF_3)OMeCOO$), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{23}H_{30}O_5F_3$ (M^+ − Me) *m/z* 443.2044 found 443.2002.

(*R*)-MTPA Ester of (3*S*,4*R*)-4-Methyl-1-(trimethylacetoxy)-7-octen-3-ol: colorless oil; IR (neat) 1744 ($C(CF_3)COOCH_2$), 1731 (t-$BuCOOCH_2$), 1641 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.8Hz, CH_3), 1.21 (9H, s, t-Bu), 1.17—1.52 (2H, m, $CH_2CH_2CH{=}CH_2$), 1.42—1.52 (1H, m, MeC*H*), 1.68—1.98 (2H, m, CH_2CH_2OCOt-Bu), 2.01—2.21 (2H, m, $CH_2CH{=}CH_2$), 3.55 (3H, br s, OMe), 3.75 (1H, ddd, J = 11.2, 5.4, 3.2 Hz, CH_aH_bOCOt-Bu), 4.07 (1H, dt, J = 11.2, 5.6 Hz, CH_aH_bOCOt-Bu), 4.98 (1H, dq, J = 9.2, 1.7 Hz, $CH_aH_b{=}CH$), 5.02 (1H, ddt, 15.4, 1.7 Hz, $CH_aH_b{=}CH$), 5.22 (1H, dt, J = 8.5, 4.3 Hz, $C(CF_3)COOCH$), 7.77 (1H, ddt, J = 16.8, 10.3, 6.6 Hz, $CH{=}CH_2$), 7.00—7.53 (5H, m, Ph); ^{19}F NMR ($CDCl_3$) δ −71.60 (s); mass spectrum (EI mode), *m/z* 459 (M^+ + H), 357 (M^+ − t-BuCOO), 225 (M^+ − $PhC(CF_3)OMeCOO$), 189 ($PhC^+(OMe)CF_3$); HRMS calcd for $C_{23}H_{17}O_5F_3$ (M^+ + H − OMe) *m/z* 428.2173 found 428.2157.

(*S*)-CFPA Ester of (3*R*,4*S*)-4-Methyl-1-(trimethylacetoxy)-7-octen-3-ol: colorless oil; IR (neat) 1774 ($C(F)COOCH_2$), 1731 (t-$BuCOOCH_2$), 1641 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.8 Hz CH_3), 1.15 (9H, s, t-Bu), 1.10—1.33 (2H, m, $CH_2CH_2CH{=}CH_2$), 1.35—1.49 (1H, m, MeC*H*),

1.71—1.91 (2H, m, C*H*$_2$CH$_2$OCOt-Bu), 1.92—2.06 (1H, m C*H*$_a$H$_b$CH=CH$_2$), 2.09—2.25 (1H, m, CH$_a$*H*$_b$CH=CH$_2$), 3.41 (1H, dt, *J* = 9.5, 5.7Hz, C*H*$_a$H$_b$OCOt-Bu), 3.86 (1H, dt, *J* = 11.2, 6.4 Hz, CH$_a$*H*$_b$OCOt-Bu), 4.98 (1H, dq, *J* = 10.0, 1.7 Hz, C*H*$_a$H$_b$=CH), 5.03 (1H, ddd, *J* = 13.8, 1.7 Hz, CH$_a$*H*$_b$=CH), 5.09 (1H, dt, *J* = 8.7, 4.1 Hz, PhC(F)CNCOOC*H*), 5.75 (1H, ddt, *J* = 13.8, 10.0, 6.6 Hz, C*H*=CH$_2$), 7.26—7.66 (5H, m, Ph); ^{19}F NMR (254 MHz, CDCl$_3$) δ –145.98 (s); mass spectrum (EI mode), *m/z* 404 (M^+ + H), 320 (M^+ – CH$_2$=CHCH$_2$CH$_2$CHCH$_3$); HRMS calcd for $C_{23}H_{30}FNO_4$ (M^+) *m/z* 403.2157, found 403.2142.

(*S*)-CFPA Ester of (3*S*,4*R*)-4-Methyl-1-(trimethylacetoxy)-7-octen-3-ol: colorless oil; IR (neat) 1774 (C(F)COOCH$_2$), 1731 (t-BuCOOCH$_2$), 1641 (C=C) cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.67 (3H, d, *J* = 6.8 Hz CH$_3$), 1.19 (9H, s, t-Bu), 0.97—1.09 (1H, m, C*H*$_a$H$_b$CH$_2$CH=CH$_2$), 1.16—1.33 (1H, m, CH$_a$*H*$_b$CH$_2$CH=CH$_2$), 1.64—1,67 (1H, m, MeC*H*), 1.81—2.06 (4H, m, C*H*$_2$CH$_2$OCOt-Bu C*H*$_2$CH=CH$_2$), 2.09—2.25 (1H, m, CH$_2$=CHCH$_a$*H*$_b$), 3.96 (1H, dt, *J* = 11.2, 7.3 Hz, C*H*$_a$H$_b$OCOt-Bu), 4.17 (1H, dt, *J* = 10.7, 5.4 Hz, CH$_a$*H*$_b$OCOt-Bu), 4.92 (1H, ddt, *J* = 11.2, 2.1, 1.2 Hz, C*H*$_a$H$_b$=CH), 4.93 (1H, dq, *J* = 16.1, 2.1 Hz,CH$_a$*H*$_b$=CH), 5.05 (1H, dt, *J* = 12.5, 2.4 Hz, PhC(F)CNCOOC*H*), 5.62 (1H, ddt, *J* = 16.1, 11.2, 6.6 Hz, C*H*=CH$_2$), 7.09—7.67 (5H, m, Ph); ^{19}F NMR (CDCl$_3$) δ –147.16 (s); mass spectrum (EI mode), *m/z* 404 (M^+ + H), 320 (M^+ – CH$_2$=CHCH$_2$CH$_2$CHCH$_3$); HRMS calcd for $C_{23}H_{30}FNO_4$ (M^+) *m/z* 403.2157, found 403.2195.

(*R*,*S*)-CFPA Esters of (1*S*,2*R*,3*S*,5*R*,10*S*,11*R*)-5-Hydroxy-8-azatetracyclo[9.2.1.0^{2,10}.0^{3,8}]tetradec-12-en-9-one: colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.17—1.58 (4H, m, H^{4a}, H^{6a}, H^{14} X 2), 1.94—2.28 (2H, m, H^{4b}, H^{6b}), 2.43—2.64 (2H, m, H^2, H^{7a}), 2.91—3.39 (4H, m, H^1, H^3, H^{10}, H^{11}) 4.04 and 4.06 (1H, t, *J* = 12.4 Hz, H^5 X 2), (Δδ = 5.4 Hz), 4.91 (1H, m, H^{7b}) 6.07—6.14 (2H, m, *H*$^{12, 13}$) 7.26—7.69 (5H, m, Ph); ^{19}F NMR (CDCl$_3$) δ –147.13 and –146.99 (Δδ = 36.8 Hz); mass spectrum (EI mode), *m/z* 380 (M^+), 134 (PhC$^+$(F)CN); HRMS calcd for $C_{22}H_{21}FN_2O_3$ (M^+) *m/z* 380.1537, found 380.1573.

(*R*,*S*)-CFPA Esters of 10-Bromo-isoborneol: colorlessoil; IR (neat) 2253 (CN), 1774 (CO); ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.81 (3H X 2, s, CH$_3$), 0.88 (3H, s, CH$_3$), 0.89 (3H, s, CH$_3$), 1.08—1.98 (7H, m), 3.09 (2H, ABq, Δδ = 10.8 Hz, *J* = 10.0, 9.8 Hz, CH$_2$Br), 3.44 (2H, ABq, Δδ = 81.0 Hz, *J* = 10.0 Hz, CH$_2$Br), 4.91—5.02 (1H X 2, m, PhC(F)CNCOOC*H*), 7.48—7.64 (5H, m, Ph); ^{19}F NMR (CDCl$_3$) δ –147.0 and –146.0 (Δδ = 255.6 Hz), (s);mass spectrum (EI mode), *m/z* 396, 394 (M^+ + 1), 315 (M^+ + 1 – Br); HRMS calcd for $C_{19}H_{22}Br^*FNO_2$ *m/z* 396.0798 (M^+ + H), found 396.0858, $C_{19}H_{22}BrFNO_2$ *m/z* 394.0819 (M^+ + H), found 394.0845.

REFERENCES AND NOTES

1 Part 7, see Takeuchi, Y.; Ogura, H.; Kanada, A.; Koizumi, T. *J. Org. Chem.* **1992**, *57*, 2196.

2 Yamaguchi, S.: Nuclear Magnetic Resonance Analysis Using Chiral Derivatives. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. I, pp. 125–152.

3 (a) Terunuma, D.; Kato, M.; Kamei, M.; Uchida, H.; Ueno, S.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3581. (b) Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826. (c) Silks, L. A.; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979. (d) Trost, B. M.; Belletire, J. L.; Godleski, S.; Mc Doughs, P. G.; Balkove, J. M. *J. Org. Chem.* **1986**, *51*, 2370. (e) Hamman, S.; Barrelle, M.; Tetaz, F.; Beguin, C. G. *J. Fluorine Chem.* **1987**, *37*, 85.

4 (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

5 (a) Hietaniemi, L.; Pohjala, E.; Malkonen, P.; Riekkola, M. *Finn Chem. Lett.* **1989**, *16*, 67. (b) J. S. I.; Saman, D.; Vrkoc, J. *Collect. Czech. Chem. Commun.* **1990**, *55*, 485.

6 Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170.

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

8 Only hydrogen is sterically smaller than fluorine.

9 The fluorine substituent has a highly electronegative character.

10 The method using a ^{19}F NMR probe has a great advantage both because of the very large chemical shift range of the ^{19}F nucleus, and a relative sensitivity almost two orders of magnitide higher than those of ^{1}H, ^{2}H, ^{13}C, ^{31}P, and ^{77}Se NMR probes.

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

12 (a) Takeuchi, Y.; Asahina, M.; Nagata, K.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2203. (b) Takeuchi, Y.; Asahina, M.; Murayama, A.; Hori, K.; Koizumi, T. *J. Org. Chem.* **1986**, *51*, 955.

13 The importance of steric differences of the three substituents on a chiral center may be necessary to enhance the population of a single, dominant rotamer.

14 We believed that diminution of the total steric bulk surrounding the acyl functionality and the presences of strong electron-withdrawing groups near the carbonyl would enhance the reactivity in acylation reactions.

15 The ^{19}F signals of MTPA derivatives appear as broader peaks than those of CFPA derivatives due to the long-range coupling between CF_3 and OMe groups.[4]

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

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

18 (a) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205. (b) Taft, Jr., R. W.: Separation of Polar, Steric, and Resonance Effects in Reactivity. In *Steric Effects in Organic Chemistry;* Newman, M. S., Ed.; John Wiley & Sons: New York, 1956; pp. 556–675.

19 Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888.

20 (a) Davies, D. H.; Snape, E. W.; Suter, P. J.; King, T. J.; Falshaw, C. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1073. (b) Bulsing, J. M.; Laue, E. D.; Leeper, F. J.; Staunton, J.; Davies, D. H.; Richie, G. A. F.; Davies, A. B.; Mabelis, R. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1301.

21 Arai, Y.; Kontani, T.; Koizumi, T. *Chem. Lett.* **1991**, 2135.

22 Kawanami, S.; Itoh, N.; Koizumi, T. unpublished data.