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Nonenzymatic kinetic resolution of racemic 2,2,2-trifluoro-1-aryl ethanol via enantioselective acylation

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ABSTRACT

Kinetic resolution of a series of 2,2,2-trifluoro-1-aryl ethanol with (*R*)-benzotetramisole as the catalyst has been investigated. The result showed that when the aryl group in the substrate was a phenyl (or a phenyl substituted by an electron-donating group) or a naphthyl (an extended phenyl) group, the system could give an *s* value higher than 20. Preparative KR examples demonstrated the applicability of this method in the preparation of some of enantiomerically pure 2,2,2-trifluoro-1-aryl ethanol or 2,2,2-trifluoro-1-aryl-ethyl *iso*-butyrate.

1. Introduction

Organic fluorine chemistry is a rapid growing field of organic chemistry.[1] Chiral fluoroorganic compounds are important in the synthesis of biologically active molecules. The methodology of asymmetric fluorination, trifluoromethylation, and perfluoroalkylation has recently been reviewed.[2] Among the huge number of fluoroorganic compounds, chiral 1-substituted 2,2,2-trifluoro-ethanols are of great importance and being used as intermediates for the transformation of introducing a chiral CF_3 group into molecules.

For stereoselective preparation of enantiopure 2,2,2-trifluoro-1-alkyl(or aryl)-ethanol, methods have been reported, which include (1) asymmetric reduction of trifluoromethyl ketones;[3] (2) enantioselective trifluoromethylation of aldehydes;[4] and (3) lipase-catalyzed kinetic resolution of racemic 2,2,2-trifluoro-1-aryl ethanols.[5]

Recently, nonenzymatic kinetic resolution of racemic non-fluorinated secondary alcohols has been an active research topic. Small molecules of organocatalysts have been designed and synthesized for this purpose, some of which showed high efficiency.[6] We extended the application of organocatalyst to fluorinated secondary alcohols and reported the kinetic resolution of 2,2-difluoro-3-hydroxy-3-aryl-propionates.[7] Here we report our kinetic resolution results of 2,2,2-trifluoro-1-aryl ethanols.

2. Results and discussion

2.1. Optimization of reaction conditions

2.1.1. Variation of catalyst

Among a number of the reported organocatalysts in the literatures,[6] we chose 6-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridine (CF_3-PIP) (**I**), benzotetramisole (BTM) (**II**), and 5,6-dibromo-2,3-dihydroimidazo[1,2-*a*]pyridine (5,6-Br_2-PIP) (**III**), which were developed by Birman and co-workers,[6j,k] due to their high efficiency in the kinetic resolution of non-fluorinated secondary alcohols and good accessibility. Screening using 2,2,2-trifluoro-1-phenyl ethanol as a model compound showed that BTM (**II**) was the best one of the three. Table 1 summarizes the results.

2.1.2. Variation of acylating reagent

Different anhydrides were tested and isobutylic anhydride gave the best *s* value (Table 2). The low *s* value given by benzoic anhydride could probably be attributed to the competitive interaction of the benzene ring in benzoic anhydride molecule with the aryl group in BTM molecule.

2.1.3. Variation of solvent

As shown in Table 3, diisopropyl ether gave the best *s* value (entries 8–11). The reason could be its proper polarity. Increasing catalyst load did not give better selectivity (entries 1 vs 3). Higher reactant concentration did not make significant improvement (entries 1 vs 2). The results showed that slow addition of the

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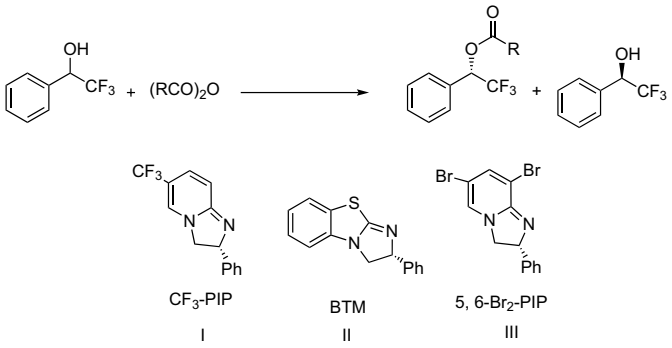
Table 1
Variation of catalyst



Entry	Catalyst	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*s*
1	**I**	1	64.7	37.1	37	7
2	**II**	1	66.6	73.1	52	11
3	**III**	1	36	3.8	10	2

Reaction conditions: 0.3 mmol substrate, 20 mol% catalyst, 100 mol% $(i\text{-PrCO})_2O$, 1 ml $CHCl_3$, 14 °C. ee_E and ee_A were established by CSP-HPLC. Enantioselectivity factor (*s*) is defined as $s=\ln[(1-C_{HPLC})(1-ee_A)]/\ln[(1-C_{HPLC})(1+ee_A)]$, where $C_{HPLC}=100\times ee_A/(ee_E+ee_A)$ (Ref. 8).

Table 2
Variation of acylating reagent

Entry	Anhydride	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*s*
1	$(EtCO)_2O$	4	75.3	30.9	29	10
2	$(i\text{-PrCO})_2O$	1.5	66.6	73.1	52	11
3	Bz_2O	2	25.7	3	9	2

Reaction conditions: 0.3 mmol substrate, 20 mol% (*R*)-BTM as catalyst, 75 mol% anhydride, 1 ml $CHCl_3$, 28 °C.

anhydride to the reaction could give a little higher enantioselectivity and reaction rate (entries 10 vs 11). At lower reaction temperature (−40 °C), the selectivity factor (*s*) was almost the same as that at 0 °C, but the reaction time was much longer (entries 8 vs 9). By comparison of entry 8 with entry 10, 0 °C appeared to be the most proper reaction temperature.

In summary, through the above-mentioned optimization, we could establish our reaction conditions: racemic substrate (0.3 mmol), BTM (4 mol%) as the catalyst, isopropyl ether (1 ml) as the solvent, isobutylic anhydride (0.3 mmol) as the acylating reagent, and 0 °C as the reaction temperature.

2.2. Kinetic resolution of 2,2,2-trifluoro-1-aryl ethanol

Under the above optimized reaction conditions, sixteen racemic substrates were subjected to the kinetic resolution. Results are summarized in Table 4.

According to the transition state model proposed by Birman,[6j] the enantioselectivity depended on how strong the π–π and the cation–π interactions were between the aromatic ring of the substrate and the aromatic system of the catalyst (Fig. 1). These interactions were a sum of electronic and steric ones in nature. Electron-donating substituent (entries 2–5) favored the interactions electronically, while such favorable effect might, to some extent, be compromised by their bulky volume. In the case of electron-withdrawing substituent (entries 6–12), the interactions were diminished both electronically and sterically.

Specifically, in the case of the electron-donating substituent (entries 2–5), 2-Me, 4-Me, 4-MeO–, and 4-MeS– groups on the phenyl ring gave higher *s* values due to their electron-donating and conjugate effects to the aromatic system. However, 4-MeS–

Table 3
Variation of solvent

Entry	Solvent	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*s*
1	$CHCl_3$	1.5	60.9	72	54	9
2[a]	$CHCl_3$	3.5	52.2	84.5	62	8
3[b]	$CHCl_3$	4	55.1	85.0	61	9
4	CH_2Cl_2	10	19.1	1.2	6	2
5	Et_2O	24	78.6	42.3	35	13
6	Toluene	5	78.1	13.2	15	9
7	CCl_4	2	63.9	63	50	9
8[c,e]	$i\text{-Pr}_2O$	2.5	84.0	67.7	45	23
9[d,e]	$i\text{-Pr}_2O$	4.5	86.1	59.9	41	25
10	$i\text{-Pr}_2O$	2	76.2	77.8	51	17
11[e]	$i\text{-Pr}_2O$	1.5	64.7	96.6	60	18
12	Ethylene glycol Dimethyl ether	9	76.2	59.6	44	13

Reaction conditions: 0.3 mmol substrate, 4 mol% (*R*)-BTM as catalyst, 100 mol% $(i\text{-PrCO})_2O$, 1 ml solvent, 28 °C.
[a] 5 ml of solvent.
[b] 20 mol% of catalyst.
[c] 0 °C.
[d] −40 °C.
[e] By slow addition of $(i\text{-PrCO})_2O$ over a period of 0.5 h.

substitution (entry 5) led to the decrease of *s* value probably because the larger steric hindrance of MeS– than that of MeO– and Me– made the *s* value of entry 5 lower than that of entries 2, 3, and 4. Meanwhile, in the case of electron-withdrawing substituent, with the increasing electronegativity of the substituent (–Cl, 3.0; –CN, 3.208; $–NO_2$, 3.421; and –F, 4.0[9]), the *s* values dropped down gradually (20, 16, 13, and 13, entries 9, 12, 11, and 8). Both of 1-naphthyl and 2-naphthyl (entries 13 and 14) were enlarged aromatic system of the phenyl and produced stronger interaction with the catalyst, therefore, gave much higher *s* values.

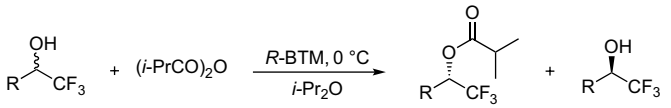
2.3. Configuration of the fast reacting enantiomer and the slow reacting enantiomer

According to the transition state model proposed by Birman[6j] (Fig. 1), the (*S*)-enantiomer was favorable to interact with the catalyst leading to the acylated product. Therefore, the (*S*)-enantiomer was the fast reacting enantiomer, which was isolated from the reaction mixture as the acylated product, while the (*R*)-enantiomer was the slow reacting one, remaining in the reaction system as the unacylated alcohol. Configuration of some of the acylated products and the unreacted alcohols (**3a**,[4c] **3b**,[3a] **3c**,[4c] **3d**,[4c] **3h**,[4c] **3i**,[4c] **3m**,[3a] **3n**[4c]) is further proved by comparison of the observed optical rotations of the obtained products with those reported in the literatures. However, in the case of thienyl compound **1o** (entry 16), the slow reacting enantiomer was assigned to (*S*)-configuration by comparison of the observed optical rotation with the reported literature,[3b] while the fast reacting one to (*R*)-configuration due to the Cahn–Ingold–Prolog rule.

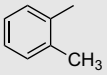
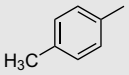
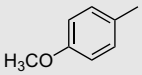
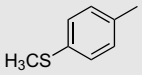
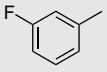
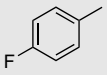
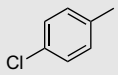
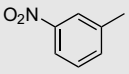
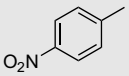
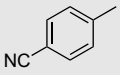
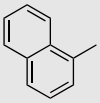
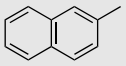
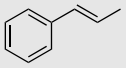
2.4. KR examples in preparative scale

We have chosen 2,2,2-trifluoro-1-(1-naphthyl)ethanol (**1m**) and 2,2,2-trifluoro-1-(2-naphthyl)ethanol (**1n**) to carry out the preparative kinetic resolution to demonstrate the applicability of this method. In the case of **1m**, we obtained the (*S*)-acylated product (**2m**) with 86.2% ee (266.6 mg, 30% yield) and the (*R*)-unreacted alcohol (**3m**) with 92% ee (257.8 mg, 38% yield); while in the case of (**1n**), the (*S*)-acylated product (**2n**) with 77% ee (222.2 mg, 25% yield) and the (*R*)-unreacted alcohol (**3n**) with >99% ee (284.9 mg, 42% yield) were obtained. The results showed that by adjusting the reaction time (i.e., the % conversion), this method could be used to obtain each of the enantiomers for some of the ethyl 2,2,2-trifluoro-1-aryl ethanol with high ee in reasonable yield.

Table 4
Kinetic resolution of 2,2,2-trifluoro-1-aryl ethanol



***rac* 1(a-p)** **2(a-p)** **3(a-p)**

Entry	R	Reaction time (h)	% ee_E	% ee_A	% C_{HPLC}	*s*
1	 **1a**	2.5	83.5 (**2a**)	68.1 (**3a**)	45	23
2	 **1b**	2.0	87.1 (**2b**)	65.1 (**3b**)	43	28
3	 **1c**	1.0	87.4 (**2c**)	70.3 (**3c**)	45	31
4	 **1d**	2.5	89.0 (**2d**)	68.5 (**3d**)	43	35
5	 **1e**	1.0	81.9 (**2e**)	82.2 (**3e**)	50	25
6	 **1f**	2.0	61.3 (**2f**)	85.4 (**3f**)	58	11
7	 **1g**	1.0	45.5 (**2g**)	47.3 (**3g**)	51	4
8	 **1h**	6.0	71.2 (**2h**)	72.5 (**3h**)	50	13
9	 **1i**	0.5	76 (**2i**)	86.2 (**3i**)	53	20
10	 **1j**	1.0	69.0 (**2j**)	91.1 (**3j**)	57	17
11	 **1k**	0.5	49.6 (**2k**)	98.3 (**3k**)	66	13
12	 **1l**	0.5	73.1 (**2l**)	83 (**3l**)	53	16
13	 **1m**	2.0	86.2 (**2m**)	92 (**3m**)	52	44
14	 **1n**	0.5	89.7 (**2n**)	95.7 (**3n**)	52	71
15	 **1o**	1.5	45.1 (**2o**)	56.5 (**3o**)	56	5
16	 **1p**	0.5	69.5 (**2p**)	70.8 (**3p**)	50	12

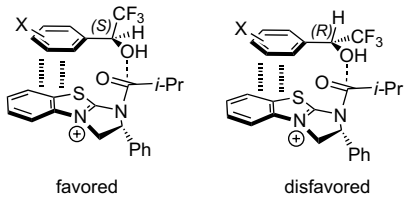


Figure 1. A schematic presentation of the proposed transition state model, adapted from Birman et al.[6j]

3. Conclusion

In this work, we have investigated the kinetic resolution of a series of 2,2,2-trifluoro-1-aryl ethanol with (*R*)-benzotetramisole as the catalyst. The result showed that when the aryl group in the substrate was a phenyl (or a phenyl substituted by an electron-donating group) or a naphthyl (an extended phenyl) group, the system could give an *s* value higher than 20. Preparative KR examples demonstrated the applicability of this method in the preparation of some of enantiomerically pure 2,2,2-trifluoro-1-aryl ethanol or 2,2,2-trifluoro-1-aryl-ethyl *iso*-butyrate.

4. Experimental section

4.1. Methods and materials

^{1}H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as an external standard; downfield shifts being designated as positive, all chemical shifts (δ) were expressed in parts per million and coupling constants (*J*) are in hertz. Mass spectra were recorded on a Finnigan MAT 8430 instrument using EI ionization at 70 eV. IR spectra were recorded on a Nicolet 380 spectrometer. High resolution mass spectral analyses were performed on a Finnigan MAT 8430 spectrometer. Optical rotations were measured by WZZ-2 polarimeter. Melting points were measured on a WRS-2A melting point apparatus. Enantiomeric excess (ee) values were determined by a Breeze LC system (Waters Corporation) on a Chiralcel OJ-H or OD-H column using *iso*-propanol/hexanes as mobile phase. All solvents used in the reaction were purified by re-distillation. Anhydrides were purified by re-distillation over P_2O_5. Other reagents were used as purchased from commercial suppliers without further purification.

Catalysts 6-trifluoromethyl-2,3-dihydroimidazo-[1,2-*a*]pyridine (CF_3-PIP) (**I**), (*R*)-benzotetramisole (BTM) (**II**), and 5,6-dibromo-2,

3-dihydroimidazo[1,2-*a*]pyridine (5,6-Br_2-PIP) (**III**) were synthesized according to known procedures[6j,k] and confirmed by comparison of the melting point, mass and ^{1}H NMR spectra, and specific optical rotation with the reported data. Racemic 2,2,2-trifluoro-1-aryl ethanols were prepared from various aldehydes and (trifluoromethyl)trimethylsilane and the acylated derivatives were prepared according to known methods,[4g] except racemic 2,2,2-trifluoro-1-phenyl ethanol was purchased from Aldrich Company and purified as necessary.

4.2. General kinetic resolution experiment

A 5 ml vial charged with catalyst (4 mol %) was flushed with nitrogen for several times. To the vial was added racemic 2,2,2-trifluoro-1-aryl ethanol (0.3 mmol) in *i*-Pr_2O (0.5 ml) and to the solution isobutylic anhydride (0.3 mmol) in *i*-Pr_2O (0.5 ml) was added in a period of 0.5 h (at which point timing was started). The content was stirred at 0 °C and monitored by HPLC (C_{18} column, MeOH/H_2O=80:20, 254 nm). The reaction was stopped when the conversion reached ca. 50% and purified by HPTLC to separate the ester and the unreacted alcohol. Enantiomeric excess was determined for the obtained acylated products and the unreacted alcohols, respectively, on a Chiralcel OJ-H or OD-H column monitored at 220 nm or 254 nm using hexanes/*i*-propyl alcohol as the mobile phase. The absolute configuration of the resolution compounds was obtained by comparison of the observed optical rotation with the literature data.

4.2.1. (*S*)-2,2,2-Trifluoro-1-phenylethyl iso-butyrate (**2a**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.47–7.39 (m, 5H), 6.14 (dd, *J*=6.8, 13.8 Hz, 1H), 2.62–2.68 (m, 1H), 1.23 (q, *J*=7.2 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.07 (d, *J*=6.8 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 246 (M^+, 2), 226 (32), 159 (20), 109 (19), 107 (4), 71 (100), 72 (6), 43 (74); HR-EI calcd for $C_{12}H_{13}O_2F_3$: 246.0868, found: 246.0862; IR (film, cm^{-1}): 3070, 3039, 2979, 2939, 2880, 1757, 1498, 1470, 1267, 1181, 1132, 1025, 933, 758, 702, 635; ee=83.5%, $[\alpha]_D^{25.5}$ −17.7 (*c* 0.71, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 0.4 ml/min, 254 nm) $t_{major(S)}$=14.04 min, $t_{minor(R)}$=15.97 min.

4.2.2. (*R*)-2,2,2-Trifluoro-1-phenyl ethanol (**3a**)

ee=96.6%, $[\alpha]_D^{25.2}$ −20.41 (*c* 0.48, $CHCl_3$) {lit.[4e] 56% ee, $[\alpha]_D^{20}$ −12.5 (*c* 0.4, CH_2Cl_2) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 254 nm) $t_{major(R)}$=21.02 min, $t_{minor(S)}$=29.04 min.

4.2.3. (*S*)-2,2,2-Trifluoro-1-(2′-methyl-phenyl)ethyl iso-butyrate (**2b**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=7.6 Hz, 1H), 7.30–7.19 (m, 3H), 6.42 (dd, *J*=6.8, 13.6 Hz, 1H), 2.69 (m, 1H), 2.48 (s, 3H), 1.24–1.18 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −75.75 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 260 (M, 5), 172 (100), 173 (19), 171 (14), 91 (12), 71 (22), 59 (20), 43 (50), 41 (16); IR (film, cm^{-1}): 3033, 2981, 2881, 1756, 1467, 1273, 1183, 1140, 913, 693; ee=87.1%, $[\alpha]_D^{25}$ 29.6 (*c* 1.0, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=100:0, 1.0 ml/min, 220 nm) t_{major}=4.81 min, t_{minor}=5.66 min.

4.2.4. (*R*)-2,2,2-Trifluoro-1-(2′-methyl-phenyl)ethanol (**3b**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, *J*=8.00 Hz, 1H), 7.30–7.24 (m, 2H), 7.21–7.18 (m, 1H), 5.30 (dd, *J*=6.56, 13.16 Hz, 1H), 2.37 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): −77.68 (d, *J*=5.26 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 190 (M^+, 37), 172 (28), 121 (100), 91 (92), 93 (82), 77 (51), 69 (14); IR (film, cm^{-1}): 3394, 3032, 2961, 1607, 1492, 1463, 1266, 1171, 1133, 760, 728, 1270, 1170, 1128, 806, 775, 722, 694; ee=65.0%, $[\alpha]_D^{16}$ −28.2 (*c* 1.0, $CHCl_3$) {lit.[3a] 74.0% ee, $[\alpha]_D^{25}$ −26.0 (*c* 0.66, $CHCl_3$) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm) t_{major}=15.94 min, t_{minor}=12.53 min.

4.2.5. (*S*)-2,2,2-Trifluoro-1-(4-methyl-phenyl)ethyl iso-butyrate (**2c**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.27 (d, *J*=8.04 Hz, 2H), 7.13 (d, *J*=7.96 Hz, 2H), 6.02 (dd, *J*=6.96, 13.92 Hz, 1H), 2.61–2.63 (m, 1H), 2.28 (s, 3H), 1.18–1.11 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.15 (d, *J*=6.76 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 260 (M^+, 13), 71 (100), 43 (75), 240 (41), 173 (36), 123 (17), 43 (98), 41 (7), 170 (7); HR-EI calcd for $C_{13}H_{15}O_2F_3$: 260.1024, found: 260.1030; IR (film, cm^{-1}): 2925, 2851, 1756, 1617, 1519, 1462, 1266, 1176, 1135, 913, 804, 744; ee=66.5%, $[\alpha]_D^{25.6}$ 29.12 (*c* 1.87, EtOH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(S)}$=4.78 min, $t_{minor(R)}$=5.71 min.

4.2.6. (*R*)-2,2,2-Trifluoro-1-(4-methyl-phenyl)ethanol (**3c**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (d, *J*=8.00 Hz, 2H), 7.12 (d, *J*=8.00 Hz, 2H), 4.86 (dd, *J*=6.70, 13.42 Hz, 1H), 2.63 (s, 1H), 2.28 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.34 (d, *J*=6.39 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 190 (M^+, 19), 173 (8), 121 (100), 91 (45), 77 (29), 69 (36); IR (film, cm^{-1}): 3406, 3031, 2921, 2868, 1617, 1519, 1417, 1270, 1170, 1128, 806, 775, 722, 694; ee=75.7%, $[\alpha]_D^{26.4}$ −9.8 (*c* 0.08, CH_2Cl_2) {lit.[4c] $[\alpha]_D^{20}$ −18.4 (*c* 0.43, CH_2Cl_2)}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 0.8 ml/min, 220 nm) $t_{major(R)}$=6.71 min, $t_{minor(S)}$=7.69 min.

4.2.7. (*S*)-2,2,2-Trifluoro-1-(4-methoxy-phenyl)ethyl iso-butyrate (**2d**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (d, *J*=8.71 Hz, 2H), 6.86–6.82 (m, 2H), 6.01 (dd, *J*=6.95, 13.90 Hz, 1H), 3.74 (s, 3H), 2.61–2.63 (m, 1H), 1.16–1.11 (q, *J*=6.98 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.25 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 276 (M^+, 48), 137 (61), 139 (22), 189 (75), 186 (31), 71 (100), 43 (98), 41 (10); HR-EI calcd for $C_{13}H_{15}O_3F_3$: 276.0973, found: 276.0985; IR (film, cm^{-1}): 2977, 2938, 2843, 1755, 1615, 1516, 1466, 1355, 1253, 1181, 1136, 1036, 933, 835, 689, 583; ee=89%, $[\alpha]_D^{24.6}$ 41.7 (*c* 1.49, CH_2Cl_2); HPLC: (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(S)}$=6.54 min, $t_{minor(R)}$=8.18 min.

4.2.8. (*R*)-2,2,2-Trifluoro-1-(4-methoxy-phenyl)ethanol (**3d**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.32 (d, *J*=8.70 Hz, 2H), 6.87–6.83 (m, 2H), 4.89 (q, 1H), 3.74 (s, 3H), 2.47 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.50 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 206 (M^+, 8), 121 (100), 137 (34), 109 (12), 189 (3), 93 (39), 77 (23), 91 (22), 69 (13); IR (film, cm^{-1}): 3443, 2920, 2845, 1614, 1517, 1463, 1252, 1172, 1126, 818, 695; ee=68.5%, $[\alpha]_D^{24.6}$ −12.55 (*c* 0.4, CH_2Cl_2) {lit.[4c] 41% ee, $[\alpha]_D^{20}$ −8.9 (*c* 1.0, CH_2Cl_2)}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 254 nm) $t_{major(R)}$=26.09 min, $t_{minor(S)}$=28.65 min.

4.2.9. (*S*)-2,2,2-Trifluoro-1-(4-methylsulfanyl-phenyl)ethyl iso-butyrate (**2e**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (d, *J*=8.00 Hz, 2H), 7.27–7.25 (m, 2H), 6.08 (dd, *J*=6.87, 13.76 Hz, 1H), 2.74–2.64 (m, 1H), 2.48 (s, 3H), 1.22–1.25 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.11 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 292 (M^+, 98), 205 (100), 43 (92), 71 (78), 153 (31), 293 (24), 155 (21), 202 (16); HR-EI calcd for $C_{13}H_{15}O_2F_3S$: 292.0743, found: 292.0745; IR (film, cm^{-1}): 2978, 2926, 1755, 1602, 1496, 1470, 1353, 1277, 1181, 1135, 829, 804; ee=73.9%, $[\alpha]_D^{24.2}$ 25.0 (*c* 1.78, acetone); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 254 nm) $t_{major(S)}$=7.63 min, $t_{minor(R)}$=11.89 min.

4.2.10. (*R*)-2,2,2-Trifluoro-1-(4-methylsulfanyl-phenyl)ethanol (**3e**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (d, *J*=8.32 Hz, 2H), 7.27 (d, *J*=8.6 Hz, 2H), 4.97 (dd, *J*=6.68, 13.36 Hz, 1H), 2.48 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.38 (d, *J*=6.76 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 222 (M^+, 44), 153 (100), 109 (50), 77 (18), 78 (13), 69 (12); IR (film, cm^{-1}): 3423, 2986, 2925, 1601, 1497, 1437, 1407, 1267, 1170, 1128, 1093, 913, 807, 742, 677; ee=96.4%, $[\alpha]_D^{24.3}$ −20.3 (*c* 0.22, acetone);

HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(R)}$=23.34 min, $t_{minor(S)}$=25.43 min.

4.2.11. (S)-2,2,2-Trifluoro-1-(2-fluoro-phenyl)ethyl iso-butyrate (**2f**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (t, *J*=7.20 Hz, 1H), 7.38–7.42 (m, 1H), 7.22–7.18 (m, 1H), 7.11 (td, *J*=0.80, 9.52 Hz, 1H), 6.52 (dd, *J*=6.80, 13.60 Hz, 1H), 2.70 (m, 1H), 1.25–1.19 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.36 (m, 3F), −116.48 (m, 1F); MS *m*/*z*: 264 (M^+, 1), 57 (100), 43 (76), 71 (72), 73 (69), 60 (57), 85 (45), 55 (40), 41 (38); HR-EI calcd for $C_{12}H_{12}O_2F_4$: 264.0773, found: 264.0775; IR (film, cm^{-1}): 2963, 2928, 2856, 1762, 1620, 1592, 1494, 1464, 1358, 1263, 1187, 1096, 801, 756, 691; ee=61.3%, $[\alpha]_D^{23.2}$ 19.1 (*c* 1.03, acetone); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=100:0, 1.0 ml/min, 254 nm) $t_{major(S)}$=5.59 min, $t_{minor(R)}$=6.11 min.

4.2.12. (R)-2,2,2-Trifluoro-1-(2-fluoro-phenyl)ethanol (**3f**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (t, *J*=7.2 Hz, 1H), 7.42–7.36 (m, 1H), 7.22 (td, *J*=1.2, 7.6 Hz, 1H), 7.12–7.07 (m, 1H), 5.41 (dd, *J*=6.52, 13.04 Hz, 1H), 2.62 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.59 (m, 3F), −117.92 (m, 1F); MS (EI, 70 eV) *m*/*z*: 194 (M^+, 16), 177 (6), 125 (100), 97 (48), 77 (33), 69 (11); IR (film, cm^{-1}): 3435, 2922, 2851, 1638, 1462, 1127, 1090, 913, 744; ee=85.4%, $[\alpha]_D^{26.4}$ −30.74 (*c* 0.43, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=98:2, 1.0 ml/min, 254 nm) $t_{minor(S)}$=23.83 min, $t_{major(R)}$=27.60 min.

4.2.13. (S)-2,2,2-Trifluoro-1-(3-fluoro-phenyl)ethyl iso-butyrate (**2g**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.35 (m, 1H), 7.25–7.09 (m, 3H), 6.12 (dd, *J*=6.78, 13.54 Hz, 1H), 2.71–2.78 (m, 1H), 1.25–1.20 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.04 (d, *J*=7.52 Hz, 3F), −111.79 to −111.85 (m, 1F); MS *m*/*z*: 264 (M^+, 2), 43 (100), 71 (93), 177 (20), 127 (17), 41 (11), 244 (8), 72 (4), 44 (3); HR-EI calcd for $C_{12}H_{12}O_2F_4$: 264.0773, found: 264.0779; IR (film, cm^{-1}): 2979, 2931, 1759, 1596, 1492, 1354, 1271, 1187, 1137, 927, 781, 711; ee=45.5%, $[\alpha]_D^{23.8}$ 42.5 (*c* 1.76, acetone); HPLC (Chiralcel OD-H, hexane/*i*-PrOH=100:0, 1.0 ml/min, 254 nm) $t_{major(S)}$=5.27 min, $t_{minor(R)}$=5.68 min.

4.2.14. (R)-2,2,2-Trifluoro-1-(3-fluoro-phenyl)ethanol (**3g**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.35 (m, 1H), 7.25–7.21 (m, 2H), 7.12–7.07 (m, 1H), 5.03 (dd, *J*=6.56, 13.12 Hz, 1H), 2.89 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.34 (d, *J*=3.76 Hz, 3F), −112.23 (t, *J*=7.52 Hz, 1F); MS (EI, 70 eV) *m*/*z*: 193 (M^+, 49), 177 (15), 157 (6), 123 (100), 95 (30), 69 (28); IR (film, cm^{-1}): 3418, 2923, 2851, 1617, 1596, 1490, 1258, 1178, 1128, 841, 788, 711; ee=47.3%, $[\alpha]_D^{26.6}$ −18.6 (*c* 0.5, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 254 nm) $t_{minor(S)}$=15.5 min, $t_{major(R)}$=16.79 min.

4.2.15. (S)-2,2,2-Trifluoro-1-(4-fluoro-phenyl)ethyl iso-butyrate (**2h**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.46–7.43 (m, 2H), 7.12–7.07 (m, 2H), 6.11 (dd, *J*=6.15, 13.00 Hz, 1H), 2.62–2.68 (m, 1H), 1.22–1.24 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.24 (d, *J*=3.87 Hz, 3F), −110.97 to −111.05 (m, 1F); MS *m*/*z*: 264 (M^+, 3), 71 (100), 43 (85), 244 (26), 177 (26), 127 (18), 41 (9), 240 (8), 173 (5); HR-EI calcd for $C_{12}H_{12}O_2F_4$: 264.0773, found: 264.0768; IR (film, cm^{-1}): 2979, 2931, 1759, 1596, 1492, 1354, 1271, 1187, 1137, 927, 781, 711; ee=71.2%, $[\alpha]_D^{24.3}$ 11.7 (*c* 1.31, CH_2Cl_2); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm) $t_{major(S)}$=5.09 min, $t_{minor(R)}$=5.59 min.

4.2.16. (R)-2,2,2-Trifluoro-1-(4-fluoro-phenyl)ethanol (**3h**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.42 (m, 2H), 7.03 (t, *J*=8.80 Hz, 2H), 4.95 (dd, *J*=6.57, 13.24 Hz, 1H), 2.72 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): −78.60 (d, *J*=3.76 Hz, 3F), −111.81 (m, 1F); MS (EI, 70 eV) *m*/*z*: 194 (M^+, 23), 125 (100), 97 (63), 77 (27), 95 (21), 75 (10), 126 (10), 69 (8); IR (film, cm^{-1}): 3420, 2922, 2852, 1608, 1514, 1232, 1173, 1129, 913, 743, 575; ee=72.5%, $[\alpha]_D^{24.6}$ −16.3 (*c* 0.246, CH_2Cl_2) {lit.[4c] 57% ee, $[\alpha]_D^{20}$ −20 (*c* 0.02, CH_2Cl_2)}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min, 220 nm) $t_{major(R)}$=5.38 min, $t_{minor(S)}$=5.77 min.

4.2.17. (S)-2,2,2-Trifluoro-1-(4-chloro-phenyl)ethyl iso-butyrate (**2i**)

^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.37 (m, 4H), 6.10 (q, *J*=6.84 Hz, 1H), 2.75–2.65 (m, 1H), 1.25–1.20 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): −76.12 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 279 (M^+, 2), 43 (100), 71 (80), 41 (46), 57 (87), 97 (42), 55 (56), 69 (52); HR-EI calcd for $C_{12}H_{12}O_2F_3Cl$: 280.0478, found: 280.0479; IR (film, cm^{-1}): 3094, 2980, 1760, 1601, 1494, 1471, 1389, 1354, 1270, 1183, 1016, 931, 873, 833, 730, 682; ee=76%; $[\alpha]_D^{26.1}$ 51.6 (*c* 3.61, EtOH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(S)}$=4.81 min, $t_{minor(R)}$=5.19 min.

4.2.18. (R)-2,2,2-Trifluoro-1-(4-chloro-phenyl)ethanol (**3i**)

^{1}H NMR (400 MHz, $CDCl_3$): 2.94 (s, 1H), 5.02 (q, *J*=6.6 Hz, 1H), 7.44–7.37 (m, 4H); ^{19}F NMR (376 MHz): −78.47 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 210 (M^+, 23), 141 (100), 77 (83), 143 (39), 113 (23), 139 (14), 111 (12); IR (film, cm^{-1}): 3398, 2924, 1600, 1496, 1411, 1268, 1173, 1129, 1091, 811, 731, 529; ee=86.2%, $[\alpha]_D^{26.1}$ −71.2 (*c* 0.43, EtOH) {lit.[4c] 45% ee, $[\alpha]_D^{20}$ −1.1.4 (*c* 0.1, CH_2Cl_2) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(R)}$=9.47 min, $t_{minor(S)}$=11.31 min.

4.2.19. (S)-2,2,2-Trifluoro-1-(3-nitro-phenyl)ethyl iso-butyrate (**2j**)

^{1}H NMR (400 MHz, $CDCl_3$): 8.35–8.28 (m, 2H), 7.79 (d, *J*=7.72 Hz, 1H), 7.62 (t, *J*=8.04 Hz, 1H), 6.22 (dd, *J*=6.88, 13.52 Hz, 1H), 2.70–2.80 (m, 1H), 1.25 (q, *J*=7.00 Hz, 6H); ^{19}F NMR (376 MHz): −75.91 (d, *J*=6.77 Hz, 3F); MS *m*/*z*: 292 (M^+, 4), 71 (100), 43 (94), 204 (13), 203 (11), 154 (4), 158 (4), 72 (5), 41 (11); HR-EI calcd for $C_{12}H_{12}NO_4F_3$: 291.0718, found: 291.0716; IR (film, cm^{-1}): 3094, 2980, 1760, 1537, 1471, 1353, 1267, 1187, 1139, 880, 712, 688; ee=69%, $[\alpha]_D^{24.8}$ 24.14 (*c* 2.42, EtOH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=100:0, 1.0 ml/min, 220 nm) $t_{minor(R)}$=23.56 min, $t_{major(S)}$=26.20 min.

4.2.20. (R)-2,2,2-Trifluoro-1-(3-nitro-phenyl)ethanol (**3j**)

Mp 50.6–52.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.27 (s, 1H), 5.12–5.22 (m, 1H), 7.61 (t, *J*=8.00 Hz, 1H), 7.85 (d, *J*=8.00 Hz, 1H), 8.26–8.28 (m, 1H), 8.39 (s, 1H); ^{19}F NMR (376 MHz): −81.60 (d, *J*=8.00 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 221 (M^+, 7), 152 (100), 105 (22), 77 (22), 78 (14), 106 (11), 153 (9); IR (KBr): 3479, 3092, 2917, 2843, 1619, 1586, 1537, 1474, 1357, 1266, 1178, 1131, 807, 713, 684; ee=91.1%, $[\alpha]_D^{25.4}$ −14.8 (*c* 0.58, EtOH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(R)}$=17.36 min, $t_{minor(S)}$=20.47 min.

4.2.21. (S)-2,2,2-Trifluoro-1-(4-nitro-phenyl)ethyl iso-butyrate (**2k**)

^{1}H NMR (400 MHz, $CDCl_3$): 8.30–8.27 (dt, *J*=2.36, 4.32 Hz, 2H), 7.66 (d, *J*=8.75 Hz, 2H), 6.22 (q, *J*=6.66 Hz, 1H), 2.78–2.71 (m, 1H), 1.26–1.23 (m, 6H); ^{19}F NMR (376 MHz): −75.68 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 291 (M^+, 2), 292 (3), 71 (100), 43 (73), 204 (4), 41 (12), 72 (5), 158 (6), 157 (8); HR-EI calcd for $C_{12}H_{12}NO_4F_3$: 291.0718, found: 291.0728; IR (film, cm^{-1}): 3084, 2978, 1759, 1605, 1530, 1351, 1267, 1187, 1139, 849, 712; ee=49.6%, $[\alpha]_D^{25.7}$ 22.8 (*c* 6.75, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=98:02, 1.0 ml/min, 254 nm) $t_{minor(R)}$=11.98 min, $t_{major(S)}$=17.16 min.

4.2.22. (R)-2,2,2-Trifluoro-1-(4-nitro-phenyl)ethanol (**3k**)

Mp 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.08 (s, 1H), 5.19 (q, *J*=6.0 Hz, 1H), 7.70 (d, *J*=8.4 Hz, 2H), 8.26–8.30 (m, 2H); ^{19}F NMR (376 MHz): −78.14 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 221 (M^+, 9), 152 (100), 77 (17), 122 (9), 105 (13), 106 (10), 153 (9); IR (KBr): 3413, 2972, 1607, 1531, 1347, 1262, 1160, 1129, 820, 712; ee=98.3%, $[\alpha]_D^{26.0}$

−11.2 (*c* 1.9, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 254 nm) $t_{major(R)}$=19.61 min, $t_{minor(S)}$=22.35 min.

*4.2.23. (S)-2,2,2-Trifluoro-1-(4-cyano-phenyl)ethyl iso-butyrate (**2l**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.74–7.71 (dt, *J*=8.4, 1.6 Hz, 2H), 7.58 (d, *J*=8.8 Hz, 2H), 6.16 (q, *J*=6.69 Hz, 1H), 2.77–2.70 (m, 1H), 1.26–1.23 (m, 6H); ^{19}F NMR (376 MHz): −75.76 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 271 (M^+, 2), 71 (100), 43 (78), 41 (20), 134 (20), 67 (18), 57 (17), 55 (16), 69 (14); HR-EI calcd for $C_{13}H_{12}NO_2F_3$: 271.0830, found: 271.0820; IR (film, cm^{-1}): 2977, 2919, 2232, 1758, 1537, 1467, 1354, 1265, 1187, 1137, 932, 841, 688; ee=73.1%, $[\alpha]_D^{25.7}$ 38.2 (*c* 3.01, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=98:02, 1.0 m/min, 220 nm) $t_{minor(R)}$=12.25 min, $t_{major(S)}$=13.03 min.

*4.2.24. (R)-2,2,2-Trifluoro-1-(4-cyano-phenyl)ethanol (**3l**)*

Mp 88.5–89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.15 (d, *J*=4.46 Hz, 1H), 5.10–5.14 (m, 1H), 7.63 (d, *J*=8.00 Hz, 2H), 7.71 (d, *J*=8.00 Hz, 2H); ^{19}F NMR (376 MHz): −78.17 (d, *J*=6.77 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 201 (M^+, 18), 132 (100), 104 (51), 77 (26), 102 (10), 133 (10), 134 (7), 69 (6); IR (KBr): 3388, 3064, 2974, 2918, 2240, 1611, 1505, 1411, 1350, 1265, 1162, 1128, 816, 690; ee=83%, $[\alpha]_D^{25.8}$ −12.4 (*c* 1.4, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min, 220 nm) $t_{major(R)}$=19.06 min, $t_{minor(S)}$=22.73 min.

*4.2.25. (S)-2,2,2-Trifluoro-1-(1-naphthyl)ethyl iso-butyrate (**2m**)*

^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (d, *J*=8.56 Hz, 1H), 7.92–7.88 (m, 2H), 7.74 (d, *J*=7.24 Hz, 1H), 7.62–7.49 (m, 3H), 7.02 (dd, *J*=6.80, 13.32 Hz, 1H), 2.71–2.75 (m, 1H), 1.21–1.25 (m, 6H); ^{19}F NMR (376 MHz): −75.01 (d, *J*=6.77 Hz, 3F); MS *m*/*z*: 296 (M^+, 48), 71 (100), 43 (87), 41 (9), 290 (28), 157 (13), 189 (11), 159 (9); HR-EI calcd for $C_{16}H_{15}O_2F_3$: 296.1024, found: 296.1026; IR (film, cm^{-1}): 3056, 2979, 1755, 1470, 1270, 1184, 1135, 799, 777, 698; ee=79.5%, $[\alpha]_D^{26.5}$ −29.1 (*c* 0.5, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 0.2 ml/min, 254 nm) $t_{minor(R)}$=33.55 min, $t_{major(S)}$=36.24 min.

*4.2.26. (R)-2,2,2-Trifluoro-1-(1-naphthyl)ethanol (**3m**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (d, *J*=8.00 Hz, 1H), 7.87–7.77 (m, 3H), 7.54–7.46 (m, 3H), 5.81 (q, *J*=8.00 Hz, 1H), 2.84 (s, 1H); ^{19}F NMR (376 MHz): −76.76 (d, *J*=7.52 Hz); MS (EI, 70 eV) *m*/*z*: 226 (M^+, 86), 157 (100), 129 (88), 128 (52), 127 (31), 158 (13), 227 (12), 77 (6); IR (film, cm^{-1}): 3423, 3047, 2921, 1593, 1515, 1264, 1167, 1125, 800, 781, 698, 632; ee=96.4%, $[\alpha]_D^{25.7}$ −12.4 (*c* 0.56, EtOH) {lit.[3a] 97% ee, $[\alpha]_D^{24}$ −21.1 (*c* 1.0, EtOH) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min, 220 nm) $t_{major(R)}$=8.41 min, $t_{minor(S)}$=9.46 min.

*4.2.27. (S)-2,2,2-Trifluoro-1-(2-naphthyl)ethyl iso-butyrate (**2n**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.94–7.86 (m, 4H), 7.56–7.51 (m, 3H), 6.30 (dd, *J*=7.2, 13.96 Hz, 1H), 2.72–2.74 (m, 1H), 1.22–1.26 (m, 6H); ^{19}F NMR (376 MHz): −75.70 (d, *J*=6.77 Hz); MS *m*/*z*: 296 (M^+, 24), 71 (100), 43 (72), 209 (12), 226 (8.6), 159 (7), 206 (6), 129 (5); HR-EI calcd for $C_{16}H_{15}O_2F_3$: 296.1024, found: 296.1031; IR (film, cm^{-1}): 3062, 2982, 2941, 1753, 1600, 1468, 1352, 1269, 1188, 1134, 932, 823, 745, 700; ee=89.7%, $[\alpha]_D^{25.3}$ 25.2 (*c* 5.12, $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min, 220 nm) $t_{major(S)}$=5.26 min, $t_{minor(R)}$=6.61 min.

*4.2.28. (R)-2,2,2-Trifluoro-1-(2-naphthyl)ethanol (**3n**)*

Mp 84.2–84.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.0–7.8 (m, 4H), 7.6–7.5 (m, 3H), 5.21 (q, *J*=8.00 Hz, 1H), 2.62 (s, 1H); ^{19}F NMR (376 MHz): −77.99 (d, *J*=6.77 Hz); MS (EI, 70 eV) *m*/*z*: 226 (M^+, 73), 227 (10), 157 (85), 128 (59), 129 (100), 127 (36), 158 (11), 77 (9); IR (KBr, cm^{-1}): 3344, 2920, 2851, 1238, 1125, 817; ee=95.7%, $[\alpha]_D^{26.3}$ −27 (*c* 0.44, $CHCl_3$) {lit.[4c] 71% ee, $[\alpha]_D^{20}$ −23.7 (*c* 0.16, CH_2Cl_2) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min, 254 nm) $t_{major(R)}$=8.66 min, $t_{minor(S)}$=11.80 min.

*4.2.29. (E)-(S)-1,1,1-Trifluoro-4-phenyl-3-buten-2-yl iso-butyrate (**2o**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.29 (m, 5H), 6.85 (d, *J*=15.92 Hz, 1H), 6.12 (dd, *J*=7.68, 15.92 Hz, 1H), 5.86–5.79 (m, 1H), 2.62–2.68 (m, 1H), 1.23–1.26 (m, 6H); ^{19}F NMR (376 MHz): −76.50 (d, *J*=6.76 Hz, 3F); MS *m*/*z*: 272 (M^+, 6), 71 (100), 43 (80), 57 (39), 85 (17), 41 (12), 252 (11), 55 (10), 73 (8); HR-EI calcd for $C_{14}H_{15}O_2F_3$: 272.1024, found: 272.1016; IR (film, cm^{-1}): 3030, 2978, 2936, 1754, 1652, 1470, 1388, 1268, 1185, 1136, 968, 750, 689; ee=45.1%, $[\alpha]_D^{25}$ 35.7 (*c* 1.6 $CHCl_3$); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 0.2 ml/min, 254 nm) $t_{major(S)}$=25.71 min, $t_{minor(R)}$=28.04 min.

*4.2.30. (E)-(R)-1,1,1-Trifluoro-4-phenyl-3-buten-2-ol (**3o**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.36–7.18 (m, 5H), 6.79 (d, *J*=15.89 Hz, 1H), 6.13 (dd, *J*=6.50, 15.96 Hz, 1H), 4.60–4.64 (m, 1H), 2.33 (s, 1H); ^{19}F NMR (376 MHz): −79.04 (d, *J*=6.76 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 202 (M^+, 55), 133 (100), 115 (36), 77 (23), 91 (20), 103 (17); IR (film, cm^{-1}): 3435, 2920, 2843, 1635, 1127, 1090, 913, 744; ee=67.6%, $[\alpha]_D^{25}$ −20.3 (*c* 0.17, CH_3OH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:05, 1.0 ml/min, 220 nm) $t_{major(R)}$=20.21 min, $t_{minor(S)}$=24.48 min.

*4.2.31. (R)-2,2,2-Trifluoro-1-(2-thienyl)ethyl iso-butyrate (**2p**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.33–6.95 (m, 3H), 6.38 (dd, *J*=6.68, 13.32 Hz, 1H), 2.60–2.64 (m, 1H), 1.14 (q, *J*=7.00 Hz, 6H); ^{19}F NMR (376 MHz): −76.37 (d, *J*=5.64 Hz, 3F); MS *m*/*z*: 252 (M^+, 1), 71 (100), 43 (95), 165 (11), 57 (10), 41 (9), 115 (9), 45 (6), 69 (3); HR-EI calcd for $C_{10}H_{11}O_2F_3S$: 252.0432, found: 252.0428; IR (film, cm^{-1}): 3011, 2969, 1738, 1365, 1216, 1091, 1019, 798, 530; ee=80%, $[\alpha]_D^{20}$ 67.6 (*c* 0.54, CH_3OH); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=100:0, 1.0 ml/min, 220 nm) $t_{major(R)}$=7.94 min, $t_{minor(S)}$=8.55 min.

*4.2.32. (S)-2,2,2-Trifluoro-1-(2-thienyl) ethanol (**3p**)*

^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (dd, *J*=1.00, 5.08 Hz, 1H), 7.13–7.08 (m, 1H), 6.93 (dd, *J*=3.64, 5.04 Hz, 1H), 5.16 (q, *J*=6.16 Hz, 1H), 2.63 (s, 1H); ^{19}F NMR (376 MHz): −78.67 (d, *J*=4.88 Hz, 3F); MS (EI, 70 eV) *m*/*z*: 182 (M^+, 41), 113 (100), 111 (78), 85 (68), 149 (28), 165 (8), 69 (22); IR (film, cm^{-1}): 3435, 2921, 2847, 1640, 1128, 1089, 706, 592; ee=41%, $[\alpha]_D^{20}$ −7.28 (*c* 0.88, CH_3OH) {lit.[3b] 99% ee, $[\alpha]_D^{25}$ 27.6 (*c* 0.88, CH_3OH) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min, 220 nm) $t_{major(S)}$=6.16 min, $t_{minor(R)}$=7.95 min.

4.3. Examples of preparative kinetic resolution for 2,2,2-trifluoro-1-(1-naphthyl)ethanol (1m) and 2,2,2-trifluoro-1-(2-naphthyl)ethanol (1n)

A 25 ml toasted flask was flushed with N_2 for several times, then charged with 30 mg (0.12 mmol) of (*R*)-BTM and 678.6 mg (3 mmol) of the racemic substrate (**1m** or **1n**) in 5 ml of diisopropyl ether. A solution of 474.6 mg (3 mmol) of isobutyric anhydride in 5 ml diisopropyl ether was added slowly with stirring over a period of 0.5 h. The content was stirred at 0 °C under N_2 atmosphere and monitored by HPLC (C_{18} column, MeOH/H_2O=80:20, 254 nm). When the reaction reached about 50% conversion, the reaction was quenched with MeOH (5 ml) and evaporated in vacuo. The residue was dissolved in chloroform and washed with brine and water, and then chromatographed on silica gel (petroleum ether/ethyl acetate=20:1–10:1) to separate the acylated (*S*)-enantiomer and the unreacted (*R*)-enantiomer. The outcomes are as follows.

(*S*)-2,2,2-Trifluoro-1-(1-naphthyl)ethyl *iso*-butyrate (**2m**): 266.6 mg (30% yield), 86.2% ee, colorless oil.
(*R*)-2,2,2-Trifluoro-1-(1-naphthyl)ethanol (**3m**): 257.8 mg (38% yield), 92% ee, colorless oil.

(*S*)-2,2,2-Trifluoro-1-(2-naphthyl)ethyl *iso*-butyrate (**2n**): 222.2 mg (25% yield), 77% ee, colorless oil.
(*R*)-2,2,2-Trifluoro-1-(2-naphthyl)ethanol (**3n**): 284.9 mg (42% yield), >99% ee, white solid, mp 84.2–84.4 °C (lit.[5c] mp 83–83.3 °C).

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Supplementary data

Supplementary data includes synthetic procedures of the catalyst, the racemic substrates, ^{1}H MNR, ^{19}F NMR spectra, and chiral HPLC chromatograms. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.058.

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