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Kinetic resolution of 2,2-difluoro-3-hydroxy-3-aryl-propionates catalyzed by organocatalyst (*R*)-benzotetramisole

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ABSTRACT

Kinetic resolution of a series of ethyl 2,2-difluoro-3-hydroxy-3-aryl-propionates catalyzed by (*R*)-benzotetramisole has been performed. It was found that when the aryl group was phenyl or phenyl substituted with electron-donating group (such as –Me, –OMe, and –SMe) or naphthyl groups, the enantio-selectivity factor (*s*) could reach 20 or higher; electron-withdrawing (such as fluorine) substitution on the benzene ring dramatically lowers the *s* value. Kinetic resolution in preparative scale for some of the substrates demonstrated the applicability of this method.

1. Introduction

Synthesis of chiral fluoroorganic compounds is important in chemistry in view of the unique biological and mechanical properties imparted by fluorine atom to the molecules.[1] Asymmetric fluorination, trifluoromethylation, and perfluoroalkylation reactions have recently been reviewed by Ma and Cahard.[2] Enantiopure 2,2-difluoro-3-hydroxy-3-aryl-propionic acids are a class of versatile synthons in the construction of chiral molecules containing a difluoromethylene moiety, as they bear a chiral hydroxyl group and a carboxylic group, which allow for further transformations to introduce an α,α-difluoromethylene moiety into molecules and form other functional groups derived from the –OH and $-CO_2Et$ groups. In addition, 2,2-difluoro-3-hydroxy-3-alkyl (or alkenyl, aryl) esters themselves have been reported to be precursors of potential inhibitors of the pheromone catabolism in insects.[3] So far, a number of methods have been reported to stereoselectively obtain enantio-pure 2,2-difluoro-3-hydroxy-3-alky(or aryl)-carboxylates, including enantioselective rhodium-catalyzed hydrogenation,[4] enantioselective Reformatsky reaction,[5] and asymmetric aldol addition reaction.[6]

Kinetic resolution (KR) is a powerful means for the preparation of enantiomerically pure compounds. KR of secondary alcohols catalyzed by acyl transfer organocatalysts has made remarkable progress.[7] For example, KR of arylalkylcarbinol,[8–12] cycloalkanol,[13a–d] allylic alcohols,[14a–c] and propargylic alcohol[15a,b] has been reported by several groups. However, there has been no report regarding the KR of fluorinated secondary alcohols.

2. Results and discussion

Birman and Li[8a] have developed an efficient acyl transfer catalyst, (*R*)-2,3-dihydro-2-phenyl-imidazo[2,1-*b*]benzothiazole [(*R*)-benzotetramisole], which displayed high efficiency and selectivity for the kinetic resolution of a series of α-alkyl benzylic alcohols. In our endeavor to prepare enantiomerically pure fluorinated secondary alcohols and their derivatives by means of kinetic resolution, we tried to use this catalyst in the aim for the KR of 2,2-difluoro-3-hydroxy-3-aryl-propionates. Herein we report the results.

As shown in Scheme 1, with (*R*)-benzotetramisole [(*R*)-BTM] as catalyst, various 2,2-difluoro-3-hydroxy-3-aryl-propionates were treated with propionic anhydride in chloroform at room temperature. After the conversion exceeded 40%, monitored by HPLC, the reaction was quenched by MeOH and worked up. The acylated product was separated from the unreacted alcohol on silica gel and the enantiomeric excess (ee) values of the two compounds were measured by chiral HPLC, respectively.

2.1. Enantio-selectivity factor

Enantio-selectivity factor (*s*) is a measurement of the strength of the interaction between a chiral catalyst and an enantiomer in a racemic mixture under given conditions, which is defined by the following equation:[16]

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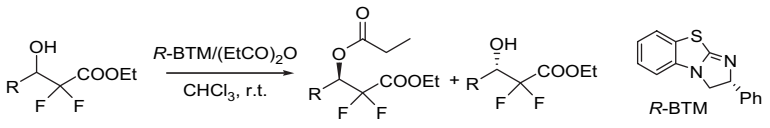


rac-1(a-m) 2(a-m) 3(a-m)

Scheme 1.

$s = \ln[(1 - C_{HPLC})(1 - ee_A)]/\ln[(1 - C_{HPLC})(1 + ee_A)]$,

where (C_{HPLC}) is defined as $C_{HPLC}=(ee_A/(ee_E+ee_A))\times 100$.

Values of *s* shown in Table 1 are average of two determinations.

The ee values in Table 1 can be altered by adjusting the conversion through changing the reaction time to obtain the desired product with high ee value and reasonable yield.

According to the transition state model proposed by Birman and Li,[8a] the enantio-selectivity depended on how strong are the π–π and the cation–π interactions between the benzene ring of substrate and the aromatic system of the catalyst (Fig. 1).

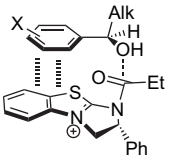
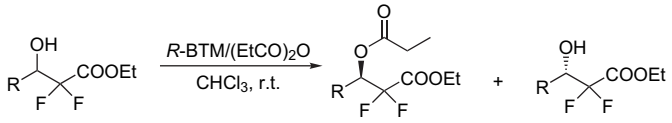
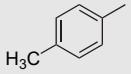
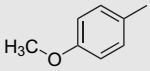
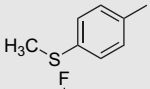
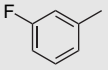
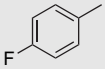
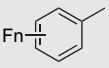
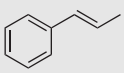
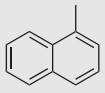
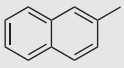


Figure 1.

Table 1
Kinetic resolution of 2,2-difluoro-3-hydroxy-3-aryl-propionates catalyzed by (*R*)-benzotetramisole (*R*-BTM)



rac-1(a-m) 2(a-m) 3(a-m)

Entry	R	ee₂ (%)	ee₃ (%)	*s*	C_{HPLC} (%)	Reaction time (h)
1		85 (**2a**)	98 (**3a**)	20	62	5
2		82 (**2b**)	71 (**3b**)	20	47	3
3		81 (**2c**)	75 (**3c**)	21	48	3
4		85 (**2d**)	58 (**3d**)	22	40	3
5		69 (**2e**)	63 (**3e**)	10	48	1
6		79 (**2f**)	13 (**3f**)	10	14	5.5
7		72 (**2g**)	52 (**3g**)	10	42	1
8		6 (**2h**)	23 (**3h**)	1	79	2.5
9		36 (**2i**)	39 (**3i**)	3	52	2.5
10		88 (**2j**)	72 (**3j**)	34	45	3
11		89 (**2k**)	85 (**3k**)	47	49	3
12		67 (**2l**)	76 (**3l**)	11	54	0.5
13		64 (**2m**)	56 (**3m**)	8	47	0.5

Enantio-selectivity factor was also affected by the electronegativity and the steric volume of the alkyl group, as reported by Birman and Li,[8a] benzylic alcohols with bulky alkyl group (e.g., *tert*-butyl group) gave higher *s* values.

In our case, the Alk group was invariably a $-CF_2-(C{=}O)OEt$ group, therefore, the *s* value is merely determined by the interaction between the two aromatic systems. By variation of aryl group in the substrate from phenyl (entry 1) to 1-naphthyl (entry 10) and 2-naphthyl (entry 11), the *s* value changed from 20 to 35 and 47, which showed the effect of extension of the aromatic system in the substrates on *s* values. 4-Me– (entry 2), 4-MeO– (entry 3), and 4-MeS– (entry 4) substitution on the benzene ring showed favorable effect on giving higher *s* values by their electron-donating and conjugate effects to the aromatic system. However, the *s* values were just slightly higher than the unsubstituted benzene ring itself (20, 21, and 22, respectively, vs 20). This indicated that the interaction between the two aromatic systems was a sum of electronic and steric ones in nature. Electron-donating groups might favor the interaction electronically, while this favorable effect might be compromised sterically due to the bulky volume of the substitution groups. Fluorine substitution on the benzene ring dramatically lowers the *s* values (s=10 in entry 5, 6, and 7 for mono-F phenyl, s=1 in entry 8 for perfluoro-phenyl), which showed that the electron-withdrawing effect of fluoro group remarkably weakened the interaction of two aromatic systems.

2.2. Configuration of the fast react enantiomer and the slow react enantiomer

According to the transition state model proposed by Birman and Li[8a] (Fig. 1), the (*S*)-enantiomer was favorable to interact with the catalyst leading to the acylated product. Therefore, the (*S*)-enantiomer was the fast react enantiomer, which was isolated from the reaction mixture as the acylated product, while the (*R*)-enantiomer was the slow react one, remaining in the reaction system as the unacylated alcohol. Configuration of some of the acylated products and the unreacted alcohols (**2a**, **3a**; **5a**,[5a,5b,6b] **2c**, **3c**;[5b] **2i**, **3i**;[5b,6b] **2k**, **3k**;[5b] and **2m**, **3m**[5a]) is further proved to have (*S*)- and (*R*)-configurations by comparison of the optical rotations of the obtained products with those reported in the literatures. Configuration of the other products (**2b**, **2d**, **2e**–**2h**, **2j**, and **2l**) was proposed to have the same designation as the known ones based on the transfer state model. However, in the case of furyl (**1l**) and thienyl (**1m**), the fast react enantiomers were proposed to have (*R*)-configuration while the slow react ones were proposed to have (*S*)-configuration, due to the Cahn–Ingold–Prolog rule.

2.3. KR examples in preparative scale

We have chosen ethyl 2,2-difluoro-3-hydroxy-3-(1-naphthyl)-propionate (**1j**) and ethyl 2,2-difluoro-3-hydroxy-3-(2-naphthyl)-propionate (**1k**), which have *s* values of 34 and 47, respectively, to carry out preparative KR to demonstrate the applicability of this method. In the case of (**1j**), we obtained the (*S*)-acylated product (**2j**) with 89% ee (yield 39%) and the (*R*)-unreacted alcohol (**3j**) with 75% ee (yield 44%); while in the case of (**1k**), the (*S*)-acylated product (**2k**) with 90% ee (yield 40%) and the (*R*)-unreacted alcohol (**3k**) with 78% ee (yield 45%) 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-difluoro-3-hydroxy-3-aryl-propionates with high ee in reasonable yield.

3. Conclusion

In this article, we have investigated the KR of a series of 2,2-difluoro-3-hydroxy-3-aryl-propionates 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 equal to or higher than 20. Preparative KR examples demonstrated the applicability of this method in the preparation of enantiomerically pure 2,2-difluoro-3-hydroxy-3-aryl-propionates.

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 values were performed by a Breeze LC system (Waters Corporation) on a Chiralcel OJ-H column using isopropanol/hexanes as mobile phase. All solvents used in the reaction were purified by redistillation. Anhydrides were purified by redistillation over P_2O_5. Other reagents were used as purchased from commercial suppliers without further purification.

Catalyst (*R*)-benzotetramisole was synthesized according to known procedure[8a] starting from 2-chlorobenzothiazole and (*R*)-phenyl-glycinol and confirmed by comparison of the melting point, mass and ^{1}H NMR spectra, and specific optical rotation values with the reported data. Racemic 2,2-difluoro-3-hydroxy-3-aryl-propionic ethyl esters were prepared from various aldehydes and ethyl bromodifluoroacetate by Reformatsky reaction and the acylated derivatives were prepared according to known method.[5]

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 were added the racemic 2,2-difluoro-3-hydroxy-3-aryl-propionic ethyl ester (0.3 mmol) in chloroform (0.5 ml) and propionic anhydride (0.2 mmol) in chloroform (0.5 ml). The reaction mixture was stirred at room temperature and monitored by HPLC (C_{18} column, aqueous MeOH as the mobile phase, monitored at 254 nm). After the conversion reaching over 40%, the reaction mixture was worked up by adding MeOH (0.5 ml). The mixture was stirred for 1 h at room temperature, washed with 5% $NaHCO_3$ aqueous solution, brine and water, and evaporated. The residue was chromatographed on silica gel to separate the acylated product and the unreacted alcohol (petroleum ether/ethyl acetate). Enantiomeric excess was determined for the obtained acylated products and the unreacted alcohols, respectively, on a Chiralcel OJ-H column monitored at 254 nm using hexanes/*iso*-propyl alcohol as the mobile phase. The absolute configuration of the resolution compounds was obtained by comparison of the optical rotation signal with the literature data.

4.3. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-phenyl-propanoate (3a)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (5H, m), 5.15 (1H, dd, *J*=7.88, 15.52 Hz), 4.28 (2H, q, *J*=7.12 Hz), 1.27 (3H, d, *J*=7.12 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.78 (1F, dd, *J*=7.5, 251.9 Hz), −120.46 (1F, dd, *J*=15.4, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 230 (M^+, 3), 107 (100), 79 (37); IR (KBr): 3467, 2986, 1758, 1095, 1071; ee=98%, $[\alpha]_D$ −7.1 (*c* 0.65, CH_3Cl) {lit.[5b] 82% ee, $[\alpha]_D$ −9.5 (*c* 1.0, CH_3Cl); lit.[5a] 88% ee, $[\alpha]_D$ −3.3 (*c* 1.15, acetone) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 9.8 min, (*S*)-enantiomer: 17.0 min.

4.4. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-phenyl-propanoate (2a)

^{1}H NMR (400 Hz, $CDCl_3$): 7.42 (5H, m), 6.25 (1H, dd, *J*=9.2, 15.2 Hz), 4.29 (2H, m), 2.43 (2H, m), 1.29 (3H, t, *J*=7.2 Hz), 1.54 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.55 (1F, dd, *J*=7.5, 263.2 Hz), −117.08 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 287 (M+H, 7), 229 (12.86), 210 (16.55), 185 (7.58), 163 (14.56), 57 (100), 29 (30.98); EI-HRMS: *m*/*z* 286.1014 (M^+, $C_{14}H_{16}O_4F_2^+$ required 286.1017); IR (KBr): 2925.4, 2856.4, 1753.9, 1455.5, 1366.3, 1156.0, 1077.8, 744.3, 702.1; ee=85%, $[\alpha]_D$ 18.3 (*c* 0.2, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=100:0, 1.0 ml/min): (*S*)-enantiomer: 35.9 min, (*R*)-enantiomer: 58.6 min.

4.5. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(4-methylphenyl)-propanoate (3b)

^{1}H NMR (400 Hz, $CDCl_3$): 7.26 (2H, d, *J*=8.0 Hz), 7.13 (2H, d, *J*=8.0 Hz), 5.08 (1H, dd, *J*=8.0, 15.6 Hz), 4.24 (2H, q, *J*=7.2 Hz), 2.29 (3H, s), 1.23 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.93 (1F, dd, *J*=7.5, 263.2 Hz), −120.39 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 244 (M^+, 4), 121 (100), 93 (36), 91 (21); IR (KBr): 3479, 2984, 2926, 2856, 1759, 1516, 1446, 1375, 1316, 1192, 1074, 781, 697, 560; ee=71%, $[\alpha]_D$ −5.8 (*c* 0.2, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70: 30, 1.0 ml/min): (*R*)-enantiomer: 7.9 min, (*S*)-enantiomer: 15.8 min.

4.6. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(4-methyl-phenyl)propanoate (2b)

^{1}H NMR (400 Hz, $CDCl_3$): 7.32 (2H, d, *J*=8.0 Hz), 7.18 (2H, d, *J*=8.0 Hz), 6.21 (1H, dd, *J*=10.0, 16.0 Hz), 4.28 (2H, m), 2.46 (3H, s), 2.41 (2H, m), 2.35 (3H, m), 1.29 (3H, t, *J*=6.8 Hz), 1.14 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.68 (1F, dd, *J*=7.5, 251.9 Hz), −117.17 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 301 ($M+H^+$, 1.74), 243 (283.95), 227 (100), 224 (39.6), 199 (69.29), 155 (20.98), 121 (48.53), 119 (25.86); EI-HRMS: *m*/*z* 300.1165 (M^+, $C_{15}H_{18}O_4F_2^+$ required 300.1173); IR (KBr): 2984, 2923, 1761, 1197, 1160, 1073, 1020, 914, 784; ee=82%, $[\alpha]_D$ 27.5 (*c* 0.3, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70: 30, 1.0 ml/min): (*S*)-enantiomer: 37.4 min, (*R*)-enantiomer: 40.3 min.

4.7. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)-propanoate (3c)

^{1}H NMR (400 Hz, $CDCl_3$): 7.36 (2H, d, *J*=8.6 Hz), 6.91 (2H, d, *J*=9.2 Hz), 5.11 (1H, dd, *J*=7.6, 14.8 Hz), 4.23 (2H, q, *J*=7.2 Hz), 3.82 (3H, s), 1.30 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −114.21 (1F, dd, *J*=7.5, 263.2 Hz), −120.32 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 260 (M^+, 10), 138.0 (10.2), 137 (100), 109 (22), 94 (10.1), 77 (9.4); IR (KBr): 3468, 2982, 2937, 1759, 1613, 1515, 1252, 1073, 837, 791; ee=75%, $[\alpha]_D$ −8.9 (*c* 0.1, CH_3Cl) {lit.[5b] 60% ee, $[\alpha]_D$ −7.3 (*c* 1.0, CH_3Cl) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 12.2 min, (*S*)-enantiomer: 17.8 min.

4.8. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(4-methoxyphenyl)propanoate (2c)

^{1}H NMR (400 Hz, $CDCl_3$): 7.37 (2H, d, *J*=8.4 Hz), 6.89 (2H, d, *J*=8.4 Hz), 6.20 (1H, dd, *J*=10.0, 15.6 Hz), 4.28 (2H, m), 3.80 (3H, s), 2.41 (2H, m), 1.29 (3H, t, *J*=7.2 Hz), 1.14 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.95 (1F, dd, *J*=7.5, 260.6 Hz), −116.97 (1F, dd, *J*=15.6, 260.9 Hz); MS (EI, 70 eV): *m*/*z* 316 (M^+, 6.76), 243 (7.83), 240 (9.25), 193 (20.98), 138 (10.66), 137 (100), 135 (7.05), 57 (66.53); EI-HRMS: *m*/*z* 316.1125 (M^+, $C_{15}H_{18}O_5F_2^+$ required 316.1122); IR (KBr): 2983, 2941, 1760, 1613, 1517, 1306, 1255, 1160, 1073, 1030, 849, 793; ee=81%, $[\alpha]_D$ 20.6 (*c* 0.1, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*S*)-enantiomer: 12.5 min, (*R*)-enantiomer: 22.8 min.

4.9. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(4-methylthiophenyl)propanoate (3d)

^{1}H NMR (400 Hz, $CDCl_3$): 7.35 (2H, d, *J*=8.4 Hz), 6.25 (1H, d, *J*=8.8 Hz), 5.12 (2H, dd, *J*=8.0, 15.2 Hz), 4.30 (2H, q, *J*=7.2 Hz), 2.48 (3H, s), 1.30 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.63 (1F, dd, *J*=7.5, 259.4 Hz), −120.40 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 276 (M^+, 16.70), 155 (6.00), 154 (9.85), 153 (100), 125 (13.28), 109 (19.67), 57 (5.13); EI-HRMS: *m*/*z* 276.0638 (M^+, $C_{12}H_{14}O_3F_2S^+$ required 276.0632); IR (KBr): 3479, 2985, 2924, 1759, 1440, 1313, 1093, 1072; ee=58%, $[\alpha]_D$ −16.2 (*c* 0.6, CH_3Cl); HPLC (Chiralcel OD-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 15.9 min, (*S*)-enantiomer: 20.2 min.

4.10. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(4-methylthiophenyl)propanoate (2d)

^{1}H NMR (400 Hz, $CDCl_3$): 7.34 (2H, d, *J*=8.4 Hz), 7.25 (2H, d, *J*=8.0 Hz), 6.21 (1H, dd, *J*=9.2, 15.6 Hz), 4.30 (2H, m), 2.46 (3H, s), 2.43 (2H, m), 1.31 (3H, t, *J*=7.2 Hz), 1.16 (3H, t, *J*=8.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.44 (1F, dd, *J*=7.5, 276 Hz), −117.17 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 332 (M^+, 25.28), 275 (6.55), 256 (8.46), 209 (19.58), 154 (9.38), 153 (99.59), 151 (6.33), 57 (100); ESI-HRMS: *m*/*z* 332.0898 (M^+, $C_{15}H_{18}O_4F_2S^+$ required 304.0898); IR (KBr): 2985, 2921, 1762, 1199, 1160, 1073; ee=85%, $[\alpha]_D$ 19.5 (*c* 1.5, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*S*)-enantiomer: 11.3 min, (*R*)-enantiomer: 24.5 min.

4.11. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(2-fluorophenyl)-propanoate (3e)

^{1}H NMR (400 Hz, $CDCl_3$): 7.56 (1H, t, *J*=7.2 Hz), 7.36 (1H, m), 7.20 (1H, m), 7.07 (1H, m), 5.52 (1H, dd, *J*=7.2, 15.7 Hz), 4.33 (2H, q, *J*=7.12 Hz), 1.32 (3H, t, *J*=6.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.82 (1F, m, *J*=7.52, 263.2 Hz), −117.44 (1F, dt, *J*=7.5, 22.6 Hz), −120.97 (1F, ddd, *J*=7.5, 18.8, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 249 ($M+H^+$, 5.07), 231 (13.55), 159 (14.52), 155 (9.98), 127 (16.41), 125 (100), 97 (40.61), 77 (18.02), 71 (23.54); EI-HRMS: *m*/*z* 248.0664 (M^+, $C_{11}H_{11}O_3F_3^+$ required 248.0660); IR (KBr): 3485, 2988, 1760, 1590, 1491, 1459, 1313, 1199, 1108, 1070, 761; ee=63%, $[\alpha]_D$ −3.0 (*c* 0.4, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=90:10, 1.0 ml/min): (*S*)-enantiomer: 37.5 min, (*R*)-enantiomer: 42.6 min.

4.12. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(2-fluorophenyl)propanoate (2e)

^{1}H NMR (400 Hz, $CDCl_3$): 7.42 (1H, t, *J*=7.2 Hz), 7.31 (1H, m), 7.11 (1H, t, *J*=8.0 Hz), 7.02 (1H, t, *J*=9.6 Hz), 6.54 (1H, dd, *J*=8.0, 15.6 Hz), 2.33 (2H, m), 1.08 (3H, t, *J*=7.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.49 (1F, dd, *J*=7.5, 255.7 Hz), −116.18 (1F, s), −117.63 (1F, dd, *J*=15.0, 259.4 Hz); MS (EI, 70 eV): *m*/*z* 304 (M^+, 0.16), 228 (5.59), 200 (1.98), 181 (7.09), 158 (2.09), 125 (4.77), 123 (2.07), 58 (3.26), 57 (100); EI-HRMS: *m*/*z* 304.0918 (M^+, $C_{14}H_{15}O_4F_3^+$ required 304.0922); IR (KBr): 2987, 2944, 1766, 1493, 1460, 1154; ee=69%, $[\alpha]_D$ 2.7 (*c* 2.9, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 13.5 min, (*S*)-enantiomer: 14.8 min.

4.13. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(3-fluorophenyl)-propanoate (3f)

^{1}H NMR (400 Hz, $CDCl_3$): 7.35 (1H, m), 7.20 (2H, m), 7.06 (1H, m), 5.16 (1H, dd, *J*=8.0, 15.2 Hz), 4.31 (2H, q, *J*=7.2 Hz), 1.29 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −112.50 (1F, m), −113.17 (1F, dd, *J*=7.5, 263.2 Hz), −120.38 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 249 (M+1, 7.29), 231 (11.94), 203 (10.59), 159 (11.85), 127 (13.84), 125 (100), 97 (80.93), 77 (14.21), 71 (17.21); EI-HRMS: *m*/*z* 248.0670 (M^+, $C_{11}H_{11}O_3F_3^+$ required 248.0660); IR (KBr): 3483, 2987,1759,1594, 1452, 1376, 1312, 1074, 773, 720; ee=13%, $[\alpha]_D$ −0.7 (*c* 1.3, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 6.2 min, (*S*)-enantiomer: 7.2 min.

4.14. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(3-fluorophenyl)propanoate (2f)

^{1}H NMR (400 Hz, $CDCl_3$): 7.27 (1H, m), 7.14 (1H, d, *J*=7.75 Hz), 7.09 (1H, d, *J*=7.52 Hz), 7.02 (1H, m), 6.16 (1H, dd, *J*=8.5, 15.7 Hz), 4.24 (2H, m), 2.35 (2H, m), 1.23 (3H, t, *J*=7.2 Hz), 1.09 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −112.17 (1F, m), −112.99 (1F, dd, *J*=11.3, 263.2 Hz), −117.41 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 305 ($M+H^+$, 2.87), 231 (3.17), 228 (12.10), 203 (3.07), 159 (3.96), 158 (4.63), 123 (3.09), 58 (3.56), 57 (100); EI-HRMS: *m*/*z* 304.0915 (M^+, $C_{14}H_{15}O_4F_3^+$ required 304.0911); IR (KBr): 2986.6, 2945.4, 1761.0, 1595.2, 1491.0, 1373.9, 1303.7, 1271.9, 1238.9, 1148.2, 1073.1, 779.5, 723.4, 692.4; ee=79%, $[\alpha]_D$ 9.3 (*c* 0.1, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=98:2, 1.0 ml/min): (*R*)-enantiomer: 10.2 min, (*S*)-enantiomer: 11.2 min.

4.15. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(4-fluorophenyl)-propanoate (3g)

^{1}H NMR (400 Hz, $CDCl_3$): 7.44 (2H, dd, *J*=5.2, 8.47 Hz), 7.08 (2H, m, J=8.4 Hz), 5.17 (1H, dd, *J*=8.0, 15.2 Hz), 4.32 (2H, q, *J*=6.8 Hz), 1.31 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −112.30 (1F, m), −113.67 (1H, dd, *J*=7.5, 263.2 Hz), −120.41 (1H, ddd, *J*=3.8, 15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 248 (M^+, 3), 158 (6.5), 126 (7.1), 127 (9.7), 125 (100), 124 (6.7), 97 (33.2), 77 (9.5), 29 (13.6); IR (KBr): 3479.1, 2987.7, 2937.6, 1759.6, 1606.4, 1513.1, 1375.9, 1313.8, 1227.8, 1103.8, 1074.4, 855.0, 841.2, 797.3, 560.5; ee=52% $[\alpha]_D$ −7.9 (*c* 0.3, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 23.4 min, (*S*)-enantiomer: 59.0 min.

4.16. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(4-fluorophenyl)propanoate (2g)

^{1}H NMR (400 Hz, $CDCl_3$): 7.36 (2H, dd, *J*=5.2, 8.8 Hz), 7.01 (2H, t, *J*=8.4 Hz), 6.16 (1H, dd, *J*=9.2, 16.0 Hz), 4.23 (2H, m), 2.35 (2H, m), 1.23 (3H, t, *J*=7.2 Hz), 1.08 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −111.41 (1F, m), −113.34 (1F, dd, *J*=7.5, 263.2 Hz), −117.45 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 304 ($M+H^+$, 0.55), 247 (14.92), 228 (11.35), 97 (10.61), 71 (15.15), 69 (10.52), 57 (100), 43 (14.95); ESI-HRMS: *m*/*z* 304.0916 (M^+, $C_{14}H_{15}O_4F_3^+$ required 304.0911); IR (KBr): 2986.1, 2945.3, 1608.2, 1766.4, 1513.6, 1464.1, 1306.3, 1233.6, 914.6, 853.3, 840.9, 801.0; ee=72%, $[\alpha]_D$ 10.9 (*c* 0.8, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=98:2, 0.5 ml/min): (*R*)-enantiomer: 82.2 min, (*S*)-enantiomer: 92.9 min.

4.17. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(pentafluorophenyl)propanoate (3h)

^{1}H NMR (400 Hz, $CDCl_3$) 5.56 (1H, m), 4.21 (1H, q, *J*=7.2 Hz), 1.39 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −111.24 (1F, m), −122.75 (1H, m), −140.67 (2F, m), −151.30 (1F, m), −160.85 (2F, m); MS (EI, 70 eV): *m*/*z* 321 ($M+H^+$, 71.76), 303 (61.29), 259 (37.88), 199 (46.26), 197 (100), 124 (76.92), 71 (34.96); EI-HRMS: *m*/*z* 320.0283 (M^+, $C_{11}H_7O_3F_7^+$ required 320.0283); IR (KBr): 3459.4, 2991.9, 2916.6, 1760.1, 1525.2, 1506.0, 1377.2, 1307.8, 1205.0, 1122.3, 1079.3, 993.9, 947.8, 777.3; ee=23%.

4.18. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(pentafluorophenyl)propanoate (2h)

^{1}H NMR (400 Hz, $CDCl_3$): 7.44 (1H, dd, *J*=6.7, 17.5 Hz), 4.31 (2H, m), 2.35 (2H, m), 1.29 (3H, t, *J*=7.2 Hz), 1.08 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −110.26 (1F, m), −117.65 (1F, m), −138.81 (2F, m), −150.55 (1F, m), −160.83 (2F, m); MS (EI, 70 eV): *m*/*z* 377 ($M+H^+$, 0.55), 230 (3.32), 180 (1.54), 161 (1.33), 71 (1.59), 58 (3.54), 57 (100), 55 (1.45), 43 (1.86); EI-HRMS: *m*/*z* 376.0543 (M^+, $C_{14}H_{11}O_4F_7^+$ required 376.0546); IR (KBr): 2988.4, 2929.4, 1767.0, 1508.9, 1525.8, 1305.5, 1150.9, 1079.2, 999.4, 912.5, 743.2; ee=6%, $[\alpha]_D$ −1.0 (*c* 0.11, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 12.3 min, (*S*)-enantiomer: 14.8 min.

4.19. Ethyl (*E*)-(*R*)-2,2-difluoro-3-hydroxy-5-phenylpent-4-enoate (3i)

^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (5H, m), 6.85 (1H, d, *J*=15.9 Hz), 6.28 (1H, dd, *J*=6.7, 15.9 Hz), 4.78 (1H, m), 4.40 (2H, *J*=7.15 Hz), 1.39 (3H, t, *J*=7.02 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −114.21 (1F, dd, *J*=7.5, 263.6 Hz), −112.56 (1F, dd, *J*=15.4, 263.6 Hz); MS (EI, 70 eV): *m*/*z* 256 (M^+, 7), 133 (100), 115 (33.41); IR (KBr): 3451, 1749, 1371, 1200, 1094. ee=39%, $[\alpha]_D$ −0.6, (*c* 0.52, CH_3Cl) {lit.[5b] 41% ee, $[\alpha]_D$ −1.0 (*c* 1, CH_3Cl); lit.[6b] 96% ee, $[\alpha]_D$ −1.0 (*c* 1.1, CH_3Cl) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 6.25 min, (*S*)-enantiomer: 7.43 min.

4.20. Ethyl (*E*)-(*S*)-2,2-difluoro-3-propionyloxy-5-phenylpent-4-enoate (2i)

^{1}H NMR (400 Hz, $CDCl_3$): 7.41 (2H, m), 7.32 (3H, m), 6.83 (1H, d, *J*=16.0 Hz), 6.14 (1H, dd, *J*=8.0, 15.6 Hz), 5.93 (1H, m), 4.33 (2H, q, *J*=7.2 Hz), 2.41 (2H, q, *J*=7.2 Hz), 1.33 (3H, t, *J*=7.2 Hz), 1.16 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.73 (1F, dd, *J*=11.3, 263.2 Hz), −117.15 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 312 (M^+, 0.76), 292 (34.82), 255 (98.91), 236 (53.04), 170 (47.34), 165 (49.43), 133 (97.7), 115 (16.77), 57 (100); EI-HRMS: *m*/*z* 312.1176 (M^+, $C_{16}H_{18}O_4F_2^+$ required 312.1173); IR (KBr): 3116.3, 2986.8, 2099.9, 1760.7, 1399.7, 1205.0, 1161.1, 1106.3, 913.3, 745.8; ee=36%, $[\alpha]_D$ 35.1 (*c* 1.0, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*S*)-enantiomer: 7.3 min, (*R*)-enantiomer: 10.7 min.

4.21. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(1-naphthyl)-propanoate (3j)

^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (1H, d, *J*=8.8 Hz), 7.94 (2H, m), 7.83 (1H, d, *J*=7.2 Hz), 7.58 (3H, m), 6.11 (1H, dd, *J*=7.03, 15.6 Hz), 4.32 (2H, q, *J*=7.14 Hz), 1.28 (3H, t, *J*=7.14 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −112.25 (1F, dd, *J*=7.5, 259.4 Hz), −119.54 (1F, dd, *J*=16.9, 263.2 Hz); ESI-MS: *m*/*z* 303.1 ($M+Na^+$), 335.1 ($M+2Na^+$); ESI-HRMS: *m*/*z* 303.0816 ($M+Na^+$, $C_{15}H_{14}O_3F_2Na^{+1}$ required 303.0813); IR (KBr): 3494, 2982, 1758, 1087, 790; ee=72%, $[\alpha]_D$ −13.2 (*c* 0.2, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 15.7 min, (*S*)-enantiomer: 18.4 min.

4.22. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(1-naphthyl)-propanoate (2j)

^{1}H NMR (400 Hz, $CDCl_3$): 8.24 (1H, d, *J*=8.6 Hz), 7.89 (2H, t, *J*=8.5 Hz), 7.43 (1H, d, *J*=7.2 Hz), 7.59 (1H, m), 7.52 (2H, m), 7.14 (1H, dd, *J*=8.4, 16 Hz), 4.25 (2H, m), 2.46 (2H, m), 1.22 (3H, t, *J*=7.1 Hz), 1.16 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −112.26 (1F, dd, *J*=7.5, 263.2 Hz), −116.2 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 337 (M+1, 4.13), 336 (M^+, 19.57), 213 (19.05), 158 (8.98), 157 (83.25), 155 (3.98), 129 (9.98), 57 (100); EI-HRMS: *m*/*z* 336.1176 (M^+, $C_{18}H_{18}O_4F_2^+$ required 336.1173); IR (KBr): 3052.0, 2982.5, 2945.7, 1760.7, 1329.9, 1294.5, 1214.7, 1159.0, 1086.8, 1067.3, 792.9; ee=88%, $[\alpha]_D$ 25.4 (*c* 1.9, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*S*)-enantiomer: 18.2 min, (*R*)-enantiomer: 23.0 min.

4.23. Ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(2-naphthyl)-propanoate (3k)

^{1}H NMR (400 Hz, $CDCl_3$): 7.84 (4H, m), 7.50 (3H, m), 5.30 (1H, dd, *J*=8.0, 15.6 Hz), 4.26 (2H, q, *J*=6.8 Hz), 1.22 (3H, t, *J*=6.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.29 (1F, dd, *J*=7.5, 263.2 Hz), −119.80 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 280 (M^+, 14.78), 281 ($M+H^+$, 3), 157 (100), 129 (85); IR (KBr): 3484, 3059, 2986, 2935, 1759, 1374, 1306, 1197, 1073, 796, 746, 479; ee=85%, $[\alpha]_D$ −13.1 (*c* 1.9, CH_3Cl) {lit[5b] 83% ee, $[\alpha]_D$ −10.3 (*c* 1, CH_3Cl) for the (*R*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 13.2 min, (*S*)-enantiomer: 20.4 min.

4.24. Ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(2-naphthyl)-propanoate (2k)

^{1}H NMR (400 Hz, $CDCl_3$): 7.94 (1H, s), 7.87 (3H, m), 7.53 (3H, m), 6.43 (1H, dd, *J*=9.6, 16.0 Hz), 4.30 (2H, q, *J*=7.2 Hz), 2.48 (2H, m), 1.28 (3H, t, *J*=7.2 Hz), 1.17 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.24 (1F, dd, *J*=7.5, 263.2 Hz), −116.66 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 336 (M^+, 18.58), 279 (14.64), 260 (11.52), 213 (11.15), 157 (60.42), 155 (7.55), 129 (8.12), 57 (100); EI-HRMS: *m*/*z* 336.1162 (M^+, $C_{18}H_{18}O_4F_2^+$ required 336.1173); IR (KBr): 3061.3, 2984.3, 2943.8, 1761.1, 1463.4, 1372.8, 1295.6, 1156.1, 1125.0, 1073.2, 802.3, 746.2; ee=89%, $[\alpha]_D$ 10.3 (*c*=1.9, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70: 30, 1.0 ml/min): (*S*)-enantiomer: 17.0 min, (*R*)-enantiomer: 31.6 min.

4.25. Ethyl (*S*)-2,2-difluoro-3-hydroxy-3-(2-furyl)-propanoate (3l)

^{1}H NMR (400 Hz, $CDCl_3$): 7.49 (1H, m), 6.54 (1H, d, *J*=3.02 Hz), 6.44 (1H, dd, *J*=2, 3.6 Hz), 5.23 (1H, m), 4.38 (2H, q, *J*=7.2 Hz), 1.36 (3H, t, *J*=7.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −114.41 (1F, dd, *J*=7.5, 263.2 Hz), −119.60 (1F, dd, *J*=11.3, 263.2 Hz); MS (EI, 70 eV): *m*/*z*

220 (M^+, 4), 97 (100), 69 (7.72), 29 (15.67); EI-HRMS *m*/*z* 220.0541 (M^+, $C_9H_{10}O_4F_2^+$ required 220.0547); ee=76%, $[\alpha]_D$ −0.85 (*c* 0.4, CH_3Cl); IR (KBr): 3452, 2982, 1760, 1309, 1055, 1010, 745.2. HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=95:5, 1.0 ml/min): (*S*)-enantiomer: 10.8 min, (*R*)-enantiomer: 12.7 min.

4.26. Ethyl (*R*)-2,2-difluoro-3-propionyloxy-3-(2-furyl)-propanoate (2l)

^1H NMR (400 Hz, $CDCl_3$): 7.45 (1H, d, *J*=0.97), 6.55 (1H, d, *J*=3.3 Hz), 6.41 (2H, m), 4.30 (2H, q, *J*=7.17 Hz), 2.41 (2H, m), 1.29 (3H, t, *J*=7.2 Hz), 1.14 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −114.07 (1F, dd, *J*=11.3, 263.2 Hz), −117.15 (1F, dd, *J*=11.3, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 276 (M^+, 0.41), 256 (5.72), 219 (15.31), 203 (4.36), 200 (15.66), 191 (6.41), 97 (6.82), 83 (8.87), 57 (100); EI-HRMS: *m*/*z* 276.0802 (M^+, $C_{15}H_{14}O_3F_2Na^{+1}$ required 276.0809); IR (KBr): 2982.5, 2941.7, 1763.4, 1376.6, 1298.9, 1153.0, 1084.0, 912.9, 744.7; ee=67%, $[\alpha]_D$ 14.3 (*c* 2.9, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 10.8 min, (*S*)-enantiomer: 16.2 min.

4.27. Ethyl (*S*)-2,2-difluoro-3-hydroxy-3-(2-thienyl)-propanoate (3m)

^1H NMR (400 Hz, $CDCl_3$): 7.36 (1H, dd, *J*=1.6, 5.2 Hz), 7.15 (1H, d, *J*=4.0 Hz), 7.02 (1H, dd, *J*=3.6, 5.2 Hz), 5.40 (1H, dd, *J*=8.0, 14.8 Hz), 4.30 (2H, q, *J*=7.2 Hz), 1.29 (3H, t, *J*=7.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −113.49 (1F, dd, *J*=7.5, 262.2 Hz), −120.06 (1F, dd, *J*=15.0, 276 Hz); MS (EI, 70 eV): *m*/*z* 236 (M^+, 7.27), 113 (100), 85 (24.52); IR (KBr): 3489, 2987, 2938, 1760, 1377, 1313, 1214, 1107, 1074, 856, 712; ee=56%, $[\alpha]_D$ −2.1 (*c* 0.5, CH_3Cl) {lit.[5a] 90% ee, $[\alpha]_D$ −11.0 (*c* 0.58, CH_3Cl) for the (*S*)-enantiomer}; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 13.6 min, (*S*)-enantiomer: 24.11 min.

4.28. Ethyl (*R*)-2,2-difluoro-3-propionyloxy-3-(2-thienyl)-propanoate (2m)

^1H NMR (400 Hz, $CDCl_3$): 7.32 (1H, dd, *J*=1.2, 5.2 Hz), 7.16 (1H, d, *J*=3.6 Hz), 6.95 (1H, dd, *J*=3.6, 5.2 Hz), 6.51 (1H, dd, *J*=9.6, 14.4 Hz), 4.23 (2H, m), 2.34 (2H, m), 1.23 (3H, t, *J*=7.6 Hz), 1.08 (3H, t, *J*=8.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): −114.05 (1F, dd, *J*=7.5, 263.2 Hz), −116.32 (1F, dd, *J*=15.0, 263.2 Hz); MS (EI, 70 eV): *m*/*z* 292 (M^+, 0.12), 235 (13.40), 219 (5.28), 216 (10.80), 188 (5.08), 113 (22.82), 111 (4.28), 58 (4.23), 57 (100); EI-HRMS: *m*/*z* 292.0580 (M^+, $C_{12}H_{14}O_4F_2S^+$ required 292.0581); IR (KBr): 2984, 2916, 1762, 1229, 1190, 1152; ee=64%, $[\alpha]_D$ 20.0 (*c* 3.3, CH_3Cl); HPLC (Chiralcel OJ-H, hexane/*i*-PrOH=70:30, 1.0 ml/min): (*R*)-enantiomer: 18.6 min, (*S*)-enantiomer: 27.7 min.

4.29. Examples of preparative KR for ethyl 2,2-difluoro-3-hydroxy-3-(1-naphthyl)-propionate (1j) and ethyl 2,2-difluoro-3-hydroxy-3-(2-naphthyl)-propionate (1k)

A 25 ml flask charged with the racemate (**1j** or **1k**) (1120 mg, 4 mmol) and the catalyst (40 mg, 0.16 mmol) was flushed with nitrogen for several times, to the mixture propionic anhydride (390 mg, 3 mmol) in chloroform (13 ml) was added. The reaction mixture was stirred at room temperature and monitored by HPLC (C_{18} column, MeOH/H_2O, 254 nm). When the conversion 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 5% $NaHCO_3$ aqueous solution, brine and water, and then chromatographed on silica gel (petroleum ether/ethyl acetate=10:1) to separate the acylated (*S*)-enantiomer and the unreacted (*R*)-enantiomer. The outcome is:

ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(1-naphthyl)propanoate (**2j**): 524 mg (39% yield), 89% ee, as a clear oil; ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(1-naphthyl)-propanoate (**3j**): 493 mg (44% yield), 75% ee, as a clear oil;

ethyl (*S*)-2,2-difluoro-3-propionyloxy-3-(2-naphthyl)propanoate (**2k**): 538 mg (40% yield), 90% ee, as a clear oil; ethyl (*R*)-2,2-difluoro-3-hydroxy-3-(2-naphthyl)-propanoate (**3k**): 504 mg (45% yield), 78% ee, as a clear oil.

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Supplementary data

Supplementary data include whole synthetic procedure of the catalyst, the racemic substrates, ^1H NMR, ^{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.2008.04.055.

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