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Highly enantioselective synthesis of α-fluoro-α-nitro esters via organocatalyzed asymmetric Michael addition

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ABSTRACT

Primary amines catalyzed the asymmetric Michael addition of ethyl 2-fluoro-2-nitroacetate to enones to provide chiral α-fluoro-α-nitro ester ketones with two contiguous stereogenic centers, one of which is a fluorinated quaternary chiral center, with excellent enantioselectivities and in moderate to good yields.

1. Introduction

Due to the unique properties of the fluorine atom, fluorine-containing organic compounds have many important applications in materials, medicinal, pharmaceutical and agrochemical science.[1] There are two common strategies for the introduction of the fluorine atom:[2–4] (a) direct fluorination of organic compounds with kinds of electrophilic or nucleophilic fluorinating reagents and (b) the use of easily available simple fluorine-containing building blocks. Recently, with the rapid development of organocatalysis, organocatalytic asymmetric synthesis of chiral fluorinated molecules with both strategies has received considerable attentions among organic chemists.[3g–m,4] Particularly, the catalytic construction of chiral fluorinated quaternary carbon centers using simple monofluorinated building blocks, which could provide a class of versatile monofluorinated synthons utilized in organic synthesis,[5] has recently gained significant progress, is still a very challenging subject in organic chemistry.[4,5] For examples, Lu et al.[4d] and Wang et al.[4c] independently reported asymmetric Michael and Mannich addition using racemic α-fluoro-β-keto esters as nucleophiles with good to excellent enantioselectivities; Tan et al. reported the construction of chiral quaternary carbon centers bearing a fluorine atom via enantio- and diastereo-selective guanidine-catalyzed additions of fluorocarbon nucleophiles to *N*-alkyl maleimides or imines.[4b]

Nitro compounds are also valuable synthons due to the rich chemistry involved with the nitro group[6] and many of them have also shown important biological activity.[7] Therefore, it would be interesting to have compounds containing both the nitro group and fluorine atom. Togni et al. firstly reported asymmetric electrophilic fluorination of α-nitro esters with Selectfluor to synthesize chiral α-fluoro-α-nitro esters with up to 40% ee.[8] As an alternative way, the direct use of racemic α-fluoro-α-nitro esters as nucleophiles in organocatalytic asymmetric Michael addition reactions would also provide the desired chiral α-fluoro-α-nitro esters. Surprisingly, to our best knowledge, there has been no precedent with this strategy. During the preparation of this manuscript, Wang et al. reported a primary amine-catalyzed Michael addition of nitro esters to enones and they also provided an example of the preparation of a chiral α-fluoro-α-nitro ester via electrophilic fluorination of the Michael adduct, but the conjugate addition could not proceed catalyzed by primary amine/(+)-CSA Salt when α-fluorinated nitroacetate was used,[9] fortunately, in our research when other organic acids were employed, good results were gained. So we report herein

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an asymmetric Michael addition reaction of α-fluoro-α-nitro esters to enones catalyzed by chiral primary amine catalysts.

2. Results and discussion

We have recently developed a series of novel amino acid-derived primary amine catalysts for the Michael reaction of enones.[10,11] Here, catalyst **1a** of this type (Fig. 1) catalyzed the model reaction with an excellent yield while the enantioselectivities of the products were not very satisfactory (Table 1, entry 1). Notably, the two diastereoisomers of the product **4a** were easily separated by flash column chromatography on silica gel. Further catalysts screening proved that primary amines **1b**–**e** derived from cinchona alkaloids excelled in this reaction, with quinidine-derived **1b** being the best one (Table 1, entries 2–5). Then, some other solvents were screened (entries 6–11) and toluene was selected as the optimal solvent for that a slightly better diastereoselectivity was obtained (entry 11). Furthermore, three other acid additives examined all gave inferior results than the initially used PNBA (entries 12–14). The different representations between (+)-CSA and PNBA may due to their different acidic ability and stereo effect. Therefore, the reaction was best performed with 10 mol % of catalyst **1b** and PNBA in toluene at room temperature (Table 1, entry 11).

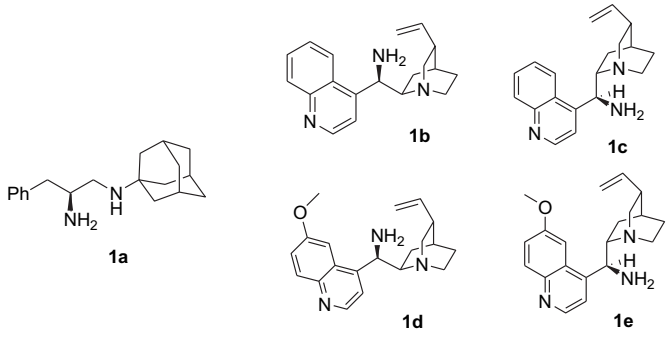
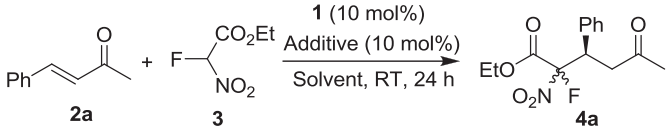


Fig. 1. Structures of catalysts studied.

Table 1
The optimization of reaction condition[a]

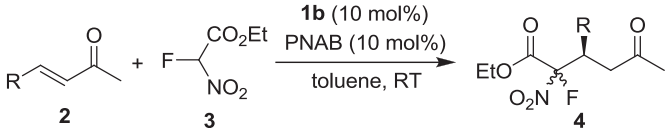


Entry	Cat.	Sol.	Additive	Yield **4a**/%[b]	dr[c]	ee of **4a**/%[d]
1	**1a**	$CHCl_3$	PNBA[e]	95	1.2:1.0	−93, −90
2	**1b**	$CHCl_3$	PNBA	95	1.5:1.0	99, 99
3	**1c**	$CHCl_3$	PNBA	93	1.5:1.0	−99, −99
4	**1d**	$CHCl_3$	PNBA	70	1.5:1.0	99, 99
5	**1e**	$CHCl_3$	PNBA	95	1.2:1.0	−99, −99
6	**1b**	CH_2Cl_2	PNBA	80	1.4:1.0	99, 98
7	**1b**	CCl_4	PNBA	85	2.0:1.0	94, 97
8	**1b**	DCE	PNBA	89	1.5:1.0	98, 99
9	**1b**	Xylene	PNBA	90	1.8:1.0	99, 98
10	**1b**	Et_2O	PNBA	95	1.7:1.0	98, 98
11	**1b**	Toluene	PNBA	90	1.8:1.0	99, 99
12	**1b**	Toluene	TsOH	92	1.8:1.0	96, 92
13	**1b**	Toluene	TfOH	93	1.8:1.0	96, 86
14	**1b**	Toluene	TFA	10	1.8:1.0	ND

[a] Unless otherwise noted, the reaction was carried out with **1** (10 mol %), additive (10 mol %) in solvent (1.0 mL) at rt.
[b] Isolated yield.
[c] Determined by ^{19}F NMR.
[d] Determined by HPLC analysis.
[e] PNBA (4-nitrobenzoic acid), TfOH (trifluoromethanesulfonic acid), TFA (trifluoroacetic acid).

With the optimized reaction conditions in hand, a selected spectrum of different substrates was examined to test the scope of this reaction. For substrates **2** with different substituents on the phenyl ring (R=aryl), generally excellent ee values and yields with 1.8:1 to 2.4:1 dr values were obtained irrespective of the electronic nature or positions of the substituents (Table 2, entries 1–9), though slightly lower yields were observed for substrates bearing electron-donating substituents (Table 2, entries 5 and 6). Excellent results were also obtained when R was a heterocyclic 2-furyl or an aliphatic *n*-butyl (Table 2, entries 11 and 12). Notably, as **4a**, all of diastereoisomers of the product **4** could be easily separated by flash column chromatography on silica gel. The absolute configurations of two isomers of **4** were determined by X-ray crystallographic analysis.[12]

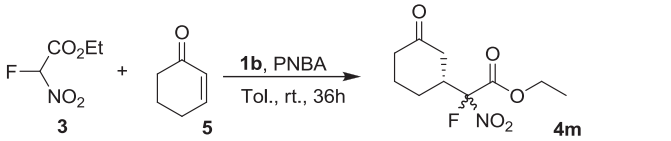
Table 2
Investigation of reaction scope[a]



Entry	R	Product	Time/h	Yield of **4**/%[b]	Ratio of (2*S*, 3*R*) /(2*R*, 3*R*)[c]	ee of **4**/%[d]
1	Ph	**4a**	24	90	1.8:1.0	99, 99
2	*p*-FC_6H_4	**4b**	36	95	1.8:1.0	99, 99
3	*p*-ClC_6H_4	**4c**	36	95	1.8:1.0	98, 99
4	*p*-BrC_6H_4	**4d**	36	93	1.8:1.0	99, 99
5	*p*-$CH_3C_6H_4$	**4e**	36	86	1.8:1.0	98, 99
6	*p*-$CH_3OC_6H_4$	**4f**	36	85	1.8:1.0	98, 99
7	*p*-$NO_2C_6H_4$	**4 g**	36	95	1.8:1.0	97, 98
8	*o*-ClC_6H_4	**4 h**	36	85	2.4:1.0	99, 99
9	*m*-ClC_6H_4	**4i**	36	90	2.2:1.0	99, 99
10	1-Naphthyl	**4j**	36	90	1.8:1.0	99, 97
11	2-Furyl	**4 k**	36	75	1.5:1.0	98, 99
12	*n*-Butyl	**4l**	36	80	1.2:1.0	93, 98

[a] Unless otherwise noted, the reaction was carried out with **1b** (10 mol %), PNBA (10 mol %).
[b] Isolated yield.
[c] Determined by ^{19}F NMR.
[d] Determined by HPLC analysis.

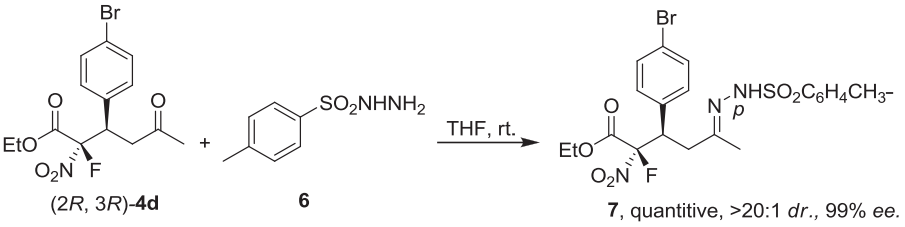
To our delight, besides open chain enones, cyclohexenone also performed well as an acceptor of the Michael addition and excellent enantioselectivities were achieved (Scheme 1).



84% yield, 1.2:1 *dr.*, 99%, 99% *ee.*

Scheme 1. Michael addition of **5** to cyclohexenone.

The products obtained from Michael additions are easily transformed into corresponding α-fluorinated esters or nitro compounds following the procedures reported.[13] Otherwise, (2*R*, 3*R*)-**4d** could be inverted to **7** quantitatively in excellent stereoselectivity (Scheme 2).



Scheme 2. Conversion of (2*R*, 3*R*)-**4d** to **7**.

3. Conclusion

In summary, we have developed an asymmetric Michael addition system to synthesize multiply substituted α-fluoro-α-nitro ester with two contiguous stereogenic centers, one of which is a fluorinated quaternary chiral center. Using readily available primary amines as the catalysts, the desired products were obtained with excellent enantioselectivities in moderate to good yields.

4. Experimental

4.1. General

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers and purified by standard techniques. Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. For NMR spectroscopy, samples were dissolved in $CDCl_3$ and run in room temperature. The ^1H NMR (300 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (282 MHz) were recorded on 300, 400 MHz spectrometer.

4.2. General procedure for the synthesis of compound 4a

To a solution of **2a** (58 mg, 0.4 mmol) and **3** (67 mg, 0.44 mmol) in 2 mL toluene, **1b** (12 mg, 0.04 mmol, 10 mol %) and PNBA (7 mg, 0.04 mmol, 10 mol %) were added. The mixture was stirred at room temperature and monitored by TLC. After completion (24 h), the mixture was concentrated by rotary evaporation and the residue was purified by flash chromatography (dichloromethane/pet. ether: 1/1) to provide **4a** as a mixture of two isomers, 107 mg, 90%, then the mixture was further purified by flash chromatography (ethyl acetate/pet. ether: 1/4) to provide pure (2*S*,3*R*)-**4a** 71 mg as colorless oil and (2*R*,3*R*)-**4a** 36 mg as colorless oil.

*4.2.1. Compound (2S,3R)-**4a**.* Colorless oil. $[\alpha]_D^{26}$ 75.6 (*c* 0.90 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 4.72–4.55 (m, 1H), 4.37 (q, *J*=7.0 Hz, 2H), 3.11–3.06 (m, 2H), 2.08 (s, 3H), 1.35 (t, *J*=7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.08 (d, *J*=32.5 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 160.4 (d, *J*=27.9 Hz), 134.5, 128.8 (d, *J*=1.7 Hz), 128.3, 128.2, 114.9 (d, *J*=255.3 Hz), 64.2, 43.7 (d, *J*=18.2 Hz), 43.4 (d, *J*=1.9 Hz), 29.7, 13.2; IR (film) ν 2987, 1764, 1723, 1580, 1456, 1356, 1249 cm^{-1}; EIMS (*m*/*z*): 43 (100), 208 (31), 163 (24), 115 (20), 205 (17), 133 (13), 251 (12), 162 (11); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{16}FNO_5$: 297.1013; found: 297.1011 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=15.6 min (minor enantiomer), 17.5 min (major enantiomer).

*4.2.2. Compound (2R,3R)-**4a**.* Colorless oil. $[\alpha]_D^{26}$ 6.8 (*c* 0.55 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5H), 4.77–4.63 (m, 1H), 4.10 (q, *J*=7.3 Hz, 2H), 3.18–3.05 (m, 1H), 2.83–2.70 (m, 1H), 2.05 (s, 3H), 1.08 (t, *J*=7.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.68 (d, *J*=27.1 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 159.4 (d, *J*=28.3 Hz), 133.7 (d, *J*=1.2 Hz), 129.0 (d, *J*=1.9 Hz), 128.4, 128.2, 115.3 (d, *J*=254.9 Hz), 63.7, 44.0 (d, *J*=17.9 Hz), 42.4 (d, *J*=3.0 Hz), 29.9, 13.0; IR (film) ν 2986, 1767, 1723, 1577, 1251 cm^{-1}; EIMS (*m*/*z*): 43 (100), 205 (31), 115 (26), 251 (23), 84 (20), 208 (19), 133 (17), 86 (13); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{16}FNO_5$: 297.1013; found: 297.1010 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=10.7 min (minor enantiomer), 13.1 min (major enantiomer).

*4.2.3. Compound (2S,3R)-**4b**.* Colorless oil. $[\alpha]_D^{25}$ 68.1 (*c* 1.03 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.02–6.96 (m, 2H), 4.70–4.55 (m, 1H), 4.38 (q, *J*=7.4, 14.6 Hz, 2H), 3.04 (d, *J*=6.7 Hz, 2H), 2.09 (s, 3H), 1.35 (t, *J*=7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.51 (s, 1F), −135.30 (d, *J*=33.1 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 162.7 (d, *J*=247.9 Hz), 160.6 (d, *J*=27.7 Hz), 131.0 (dd, *J*=1.6, 8.4 Hz), 129.7 (d, *J*=3.5 Hz), 115.8 (d, *J*=21.6 Hz), 115.2 (d, *J*=256.1 Hz), 64.7, 43.9, 43.5 (d, *J*=18.2 Hz), 30.1, 13.6; IR (film) ν 3020, 1765, 1724, 1583, 1512, 1216 cm^{-1}; EIMS (*m*/*z*): 315 (M^+, 1), 43 (100), 226 (24), 223 (13), 133 (13), 151 (9), 181 (8), 227 (7), 269 (7); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{15}NF_2O_5$: 315.0918; found: 315.0924 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=10.4 min (major enantiomer), 14.9 min (minor enantiomer).

*4.2.4. Compound (2R,3R)-**4b**.* Colorless oil. $[\alpha]_D^{27}$ 8.0 (*c* 1.10 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 2H), 7.04–6.99 (m, 2H), 4.76–4.60 (m, 1H), 4.13 (q, *J*=6.8 Hz, 2H), 3.13–3.03 (m, 1H), 2.79–2.72 (m, 1H), 2.07 (s, 3H), 1.12 (t, *J*=6.8 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.45 (s, 1F), −135.89 (d, *J*=28.3 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 162.2 (d, *J*=248.0 Hz), 159.3 (d, *J*=28.0 Hz), 130.8 (dd, *J*=2.2, 8.4 Hz), 129.7 (d, *J*=8.6 Hz), 129.6 (dd, *J*=0.9, 3.4 Hz), 115.7 (d, *J*=22.1 Hz), 115.4 (d, *J*=21.5 Hz), 114.8 (d, *J*=254.1 Hz), 63.8, 43.3 (d, *J*=18.2 Hz), 42.4 (d, *J*=2.8 Hz), 29.8, 13.1; EIMS (*m*/*z*): 43 (100), 223 (19), 133 (16), 269 (14), 226 (13), 151 (10), 149 (10), 227 (8); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{15}NF_2O_5$: 315.0918; found: 315.0907 $[M]^+$. HPLC separation conditions: Chiralcel ODH-ASH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=19.9 min (major enantiomer), 23.6 min (minor enantiomer).

*4.2.5. Compound (2S,3R)-**4c**.* White solid. Mp: 92–93 °C; $[\alpha]_D^{26}$ 63.6 (*c* 1.00 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.21 (m, 4H), 4.69–4.54 (m, 1H), 4.37 (q, *J*=6.8 Hz, 2H), 3.10–2.98 (m, 2H), 2.09 (s, 3H), 1.35 (t, *J*=7.5, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.07 (d, *J*=27.3 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 160.5 (d, *J*=28.1 Hz), 134.7, 132.5, 130.6, 129.0, 115.1 (d, *J*=254.5 Hz), 64.7, 43.7, 43.5 (d, *J*=18.2 Hz), 30.1, 13.6; IR (KBr) ν 2993, 1768, 1724, 1578, 1512, 1251 cm^{-1}; EIMS (*m*/*z*): 331 (M^+, 1), 43 (100), 242 (17), 239 (9), 197 (7), 133 (7), 244 (6), 243 (5), 285 (5); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{15}ClFNO_5$: 331.0623; found: 331.0624 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=11.9 min (major enantiomer), 16.5 min (minor enantiomer).

*4.2.6. Compound (2R,3R)-**4c**.* Colorless oil. $[\alpha]_D^{26}$ 6.0 (*c* 0.90 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.27 (m, 4H), 4.77–4.61 (m, 1H), 4.14 (q, *J*=7.5 Hz, 2H), 3.12–3.03 (m, 1H), 2.80–2.73 (m, 1H),

2.07 (s, 3H), 1.13 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.57 (d, J=70.9 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 159.8 (d, J=18.0 Hz), 134.8, 132.8, 130.9, 129.1, 115.4 (d, J=254.6 Hz), 64.3, 43.8 (d, J=18.6 Hz), 42.8 (d, J=2.7 Hz), 30.3, 13.5; IR (film) ν 2987, 1766, 1723, 1579, 1494, 1351, 1251, 1095 cm^{-1}; ESI-MS (m/z): 354.0 $[M+1]^+$; HRMS (ESI): m/z: calcd for $C_{14}H_{15}ClFNO_5Na$: 354.0515; found: 354.0509 $[M]^+$. HPLC separation conditions: Chiralcel ASH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=20.5 min (minor enantiomer), 24.0 min (major enantiomer).

*4.2.7. Compound (2S,3R)-**4d**.* Colorless oil. $[\alpha]_D^{26}$ 56.2 (c 1.23 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (AB, J=8.9 Hz, 2H), 7.16 (AB, J=8.9 Hz, 2H), 4.68–4.53 (m, 1H), 4.37 (q, J=6.8 Hz, 2H), 3.09–3.00 (m, 2H), 2.09 (s, 3H), 1.35 (t, J=7.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.01 (d, J=29.5 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 160.5 (d, J=27.7 Hz), 133.0, 132.0, 130.9, 123.0, 115.0 (d, J=255.2 Hz), 64.7, 43.7, 43.6 (d, J=19.6 Hz), 30.2, 13.7; IR (KBr) ν 2987, 1764, 1723, 1580, 1491, 1356, 1249 cm^{-1}; EIMS (m/z): 43 (100), 296 (10), 288 (10), 133 (8), 134 (6), 285 (6), 283 (5), 120 (4); HRMS (EI): m/z: calcd for $C_{14}H_{15}BrFNO_5$: 375.0118; found: 375.0115 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=13.2 min (major enantiomer), 17.7 min (minor enantiomer).

*4.2.8. Compound (2R,3R)-**4d**.* White solid. Mp: 45–46 °C; $[\alpha]_D^{26}$ 9.1 (c 5.15 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (AB, J=8.7 Hz, 2H), 7.23 (AB, J=8.7 Hz, 2H), 4.75–4.59 (m, 1H), 4.14 (q, J=6.8 Hz, 2H), 3.12–3.03 (m, 1H), 2.79–2.72 (m, 1H), 2.06 (s, 3H), 1.13 (t, J=6.8 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.52 (d, J=28.7 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 159.3 (d, J=28.0 Hz), 132.8, 131.5, 130.7 (d, J=2.0 Hz), 122.5, 114.8 (d, J=255.9 Hz), 63.9, 43.4 (d, J=18.0 Hz), 42.3 (d, J=1.9 Hz), 29.8, 13.1; IR (KBr) ν 3054, 1766, 1724, 1580, 1491, 1265, 1217 cm^{-1}; EIMS (m/z): 43 (100), 285 (12), 283 (11), 133 (11), 286 (10), 288 (8), 329 (8), 331 (8); HRMS (EI): m/z: calcd for $C_{14}H_{15}BrFNO_5$: 375.0118; found: 375.0119 $[M]^+$. HPLC separation conditions: Chiralcel ASH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=21.0 min (minor enantiomer), 28.4 min (major enantiomer).

*4.2.9. Compound (2S,3R)-**4e**.* Colorless oil. $[\alpha]_D^{26}$ 74.1 (c 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (AB, J=8.4 Hz, 2H), 7.09 (AB, J=8.4 Hz, 2H), 4.66–4.51 (m, 1H), 4.37 (q, J=7.1 Hz, 2H), 3.13–2.96 (m, 2H), 2.29 (s, 3H), 2.11 (s, 3H), 1.35 (t, J=7.1 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.17 (d, J=31.4 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 160.8 (d, J=28.0 Hz), 138.5, 130.6, 129.5, 129.1, 115.4 (d, J=254.9 Hz), 64.5, 43.9 (d, J=18.5 Hz), 43.8 (d, J=1.9 Hz), 30.2, 21.0, 13.7; IR (film) ν 3026, 2924, 1764, 1723, 1581, 1516, 1355, 1249, 756 cm^{-1}; EIMS (m/z): 311 (M^+, 1), 43 (100), 222 (34), 177 (30), 129 (21), 223 (13), 219 (11), 133 (11), 176 (10); HRMS (EI): m/z: calcd for $C_{15}H_{18}FNO_5$: 311.1169; found: 311.1165 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=10.7 min (major enantiomer), 12.0 min (minor enantiomer).

*4.2.10. Compound (2R,3R)-**4e**.* Colorless oil. $[\alpha]_D^{27}$ 10.2 (c 0.37 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.20 (AB, J=7.7 Hz, 2H), 7.13–7.10 (AB, J=7.7 Hz, 2H), 4.81–4.57 (m, 1H), 4.11 (q, J=7.1, 14.0 Hz, 2H), 3.15–3.06 (m, 1H), 2.78–2.70 (m, 1H), 2.30 (s, 3H), 2.05 (s, 3H), 1.11 (t, J=7.1 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.74 (d, J=33.0 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 159.5 (d, J=28.3 Hz), 138.1, 130.4 (d, J=0.9 Hz), 129.0, 128.8 (d, J=1.9 Hz), 115.3 (d, J=254.3 Hz), 63.6, 43.7 (d, J=17.9 Hz), 42.4 (d, J=3.0 Hz), 29.9, 20.6, 13.1; IR (film) ν 2923, 1765, 1723, 1578, 1516, 1250 cm^{-1}; EIMS (m/z): 43 (100), 129 (33), 265 (30), 219 (26), 222 (24), 223 (20), 177 (19), 147 (17); HRMS (EI): m/z: calcd for $C_{15}H_{18}FNO_5$: 311.1169; found: 311.1168 $[M]^+$. HPLC separation conditions: Chiralcel ADH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.6 mL/min; t_R=12.9 min (minor enantiomer), 14.2 min (major enantiomer).

*4.2.11. Compound (2S,3R)-**4f**.* Colorless oil. $[\alpha]_D^{26}$ 60.6 (c 1.12 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (AB, J=9.0 Hz, 2H), 6.87 (AB, J=9.0 Hz, 2H), 4.65–4.50 (m, 1H), 4.36 (q, J=6.9, 14.1 Hz, 2H), 3.76 (s, 3H), 3.11–2.95 (m, 2H), 2.08 (s, 3H), 1.35 (t, J=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.41 (d, J=30.3 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 160.8 (d, J=27.9 Hz), 159.7, 130.4, 125.6, 115.5 (d, J=254.5 Hz), 114.2, 64.5, 55.1, 43.9 (d, J=1.8 Hz), 43.6 (d, J=18.2 Hz), 30.2, 13.7; IR (film) ν 2938, 1764, 1722, 1611, 1580, 1515, 1254 cm^{-1}; EIMS (m/z): 327 (M^+, 7), 43 (100), 238 (29), 145 (27), 193 (20), 239 (16), 280 (14), 133 (10), 163 (9); HRMS (EI): m/z: calcd for $C_{15}H_{18}FNO_6$: 327.1118; found: 327.1122 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=13.6 min (major enantiomer), 16.7 min (minor enantiomer).

*4.2.12. Compound (2R,3R)-**4f**.* Colorless oil. $[\alpha]_D^{26}$ 10.8 (c 1.35 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (AB, J=8.6 Hz, 2H), 6.83 (AB, J=8.6 Hz, 2H), 4.71–4.57 (m, 1H), 4.07 (q, J=7.2, 14.3 Hz, 2H), 3.78 (s, 3H), 3.13–3.04 (m, 1H), 2.75–2.68 (m, 1H), 2.05 (s, 3H), 1.13 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −136.17 (d, J=28.3 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 159.4 (d, J=28.3 Hz), 159.2, 130.1, 125.3, 115.4 (d, J=254.4 Hz), 113.7, 63.7, 54.8, 43.3 (d, J=18.2 Hz), 42.4 (d, J=3.0 Hz), 29.9, 13.1; IR (film) ν 2938, 1767, 1723, 1611, 1576, 1515, 1253 cm^{-1}; EIMS (m/z): 327 (M^+, 4), 43 (100), 238 (29), 145 (47), 239 (29), 281 (27), 193 (19), 238 (18), 235 (18), 163 (17); HRMS (EI): m/z: calcd for $C_{15}H_{18}FNO_6$: 327.1118; found: 327.1121 $[M]^+$. HPLC separation conditions: Chiralcel ASH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=29.0 min (minor enantiomer), 30.8 min (major enantiomer).

*4.2.13. Compound (2S,3R)-**4g**.* Colorless oil. $[\alpha]_D^{26}$ 75.3 (c 1.18 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (AB, J=9.7 Hz, 2H), 7.50 (AB, J=9.7 Hz, 2H), 4.83–4.68 (m, 1H), 4.39 (q, J=7.3, 14.0 Hz, 2H), 3.21–3.04 (m, 2H), 2.12 (s, 3H), 1.36 (t, J=6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.46 (d, J=28.8 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 160.2 (d, J=27.4 Hz), 147.9, 141.4, 130.4, 123.8, 114.7 (d, J=256.4 Hz), 65.0, 43.7 (d, J=18.1 Hz), 43.6 (d, J=1.2 Hz), 30.0, 13.6; IR (KBr) ν 2987, 1765, 1723, 1581, 1525, 1421, 1351, 1299, 1250 cm^{-1}; EIMS (m/z): 43 (100), 250 (20), 253 (10), 296 (7), 133 (7), 134 (4), 254 (3), 251 (3); HRMS (EI): m/z: calcd for $C_{14}H_{15}FN_2O_7$: 342.0863; found: 342.0861 $[M]^+$. HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.85 mL/min; t_R=22.0 min (minor enantiomer), 30.5 min (major enantiomer).

*4.2.14. Compound (2R,3R)-**4g**.* Colorless oil. $[\alpha]_D^{27}$ 10.7 (c 0.52 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (AB, J=8.7 Hz, 2H), 7.56 (AB, J=8.7 Hz, 2H), 4.89–4.74 (m, 1H), 4.15 (q, J=7.5, 14.2 Hz, 2H), 3.18–3.09 (m, 1H), 2.90–2.82 (m, 1H), 2.09 (s, 3H), 1.14 (t, J=7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.41 (d, J=29.0 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 159.0 (d, J=27.7 Hz), 147.5, 141.3, 130.2, 123.4, 114.3 (d, J=255.9 Hz), 64.2, 43.5 (d, J=18.0 Hz), 42.3 (d, J=3.2 Hz), 29.7, 13.1; IR (film) ν 2922, 1767, 1723, 1580, 1526 cm^{-1}; EIMS (m/z): 43 (100), 250 (29), 296 (10), 133 (8), 253 (8), 251 (4), 204 (4), 134 (4); HRMS (EI): m/z: calcd for $C_{14}H_{15}FN_2O_7$: 342.0863; found: 342.0866 $[M]^+$. HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.85 mL/min; t_R=22.1 min (minor enantiomer), 27.0 min (major enantiomer).

*4.2.15. Compound (2S,3R)-**4h**.* Colorless oil. $[\alpha]_D^{26}$ 66.6 (c 0.90 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.27–7.19 (m, 2H), 5.45–5.25 (m, 1H), 4.47–4.32 (m, 2H), 3.19–2.95 (m, 2H), 2.11 (s, 3H), 1.36 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.06 (d, J=25.6 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 160.6 (d, J=27.9 Hz), 135.2, 132.5, 130.4, 129.7, 128.5, 127.3, 114.5 (d, J=256.0 Hz), 64.7,

44.5, 39.5 (d, J=18.1 Hz), 29.8, 13.7; IR (film) ν 2924, 1767, 1724, 1581, 1478 cm^{-1}; EIMS (m/z): 43 (100), 145 (54), 296 (16), 165 (12), 239 (9), 133 (9), 146 (7), 193 (6); HRMS (EI): m/z: calcd for $C_{14}H_{15}ClFNO_5$: 331.0623; found: 331.0619 $[M]^+$. HPLC separation conditions: Chiralcel ADH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=15.3 min (minor enantiomer), 17.1 min (major enantiomer).

*4.2.16. Compound (2R,3R)-**4h**.* Colorless oil. $[\alpha]_D^{25}$ 15.5 (c 0.98 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.24 (m, 4H), 5.43–5.30 (m, 1H), 4.22–4.06 (m, 2H), 3.10–2.89 (m, 2H), 2.09 (s, 3H), 1.12 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −136.09 (d, J=28.5 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 159.3 (d, J=28.7 Hz), 135.0, 132.1 (d, J=1.5 Hz), 129.8, 129.3, 128.3, 127.0, 114.6 (d, J=253.9 Hz), 63.9, 42.8 (d J=3.3 Hz), 39.4 (d, J=17.6 Hz), 29.5, 12.9; IR (film) ν 2987, 1767, 1725, 1580, 1254 cm^{-1}; EIMS (m/z): 43 (100), 145 (54), 296 (20), 165 (15), 239 (12), 133 (10), 195 (8), 193 (8); HRMS (EI): m/z: calcd for $C_{14}H_{15}ClFNO_5$: 331.0623; found: 331.0617 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=12.6 min (minor enantiomer), 14.9 min (major enantiomer).

*4.2.17. Compound (2S,3R)-**4i**.* Colorless oil. $[\alpha]_D^{26}$ 38.6 (c 0.45 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.13 (m, 4H), 4.69–4.54 (m, 1H), 4.37 (q, J=6.8, 14.2 Hz, 2H), 3.12–2.98 (m, 2H), 2.11 (s, 3H), 1.35 (t, J=6.8 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.76 (d, J=30.2 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 160.4 (d, J=27.5 Hz), 136.0, 134.5, 130.0, 129.2 (d, J=2.0 Hz), 128.9, 127.6 (d, J=1.8 Hz), 115.0 (d, J=255.5 Hz), 64.8, 43.8 (d, J=18.3 Hz), 43.7 (d, J=1.8 Hz), 30.1, 13.6; IR (film) ν 3022, 1765, 1722, 1581, 1478, 1434, 1358, 1249 cm^{-1}; EIMS (m/z): 331 (M^+, 1), 43 (100), 242 (15), 239 (14), 197 (9), 133 (7), 285 (6), 241 (5), 244 (5); HRMS (EI): m/z: calcd for $C_{14}H_{15}ClFNO_5$: 331.0623; found: 331.0614 $[M]^+$. HPLC separation conditions: Chiralcel ASH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R= 21.5 min (major enantiomer), 36.1 min (minor enantiomer).

*4.2.18. Compound (2R,3R)-**4i**.* Colorless oil. $[\alpha]_D^{26}$ 8.8 (c 1.30 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 4H), 4.76–4.60 (m, 1H), 4.15 (q, J=7.4, 14.3 Hz, 2H), 3.14–3.04 (m, 1H), 2.81–2.73 (m, 1H), 2.08 (s, 3H), 1.13 (t, J=7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.33 (d, J=28.7 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 159.2 (d, J=27.5 Hz), 135.8 (d, J=1.2 Hz), 134.1, 129.6, 129.2 (d, J=2.1 Hz), 128.5, 127.2 (d, J=2.0 Hz), 114.8 (d, J=255.1 Hz), 63.9, 43.6 (d, J=17.9 Hz), 42.2 (d, J=2.8 Hz), 29.8, 13.1; IR (film) ν 2985, 1767, 1723, 1576, 1478 cm^{-1}; EIMS (m/z): 43 (100), 239 (24), 285 (13), 242 (12), 133 (9), 241 (8), 197 (7), 149 (7); HRMS (EI): m/z: calcd for $C_{14}H_{15}ClFNO_5$: 331.0623; found: 331.0627 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=12.0 min (minor enantiomer), 14.0 min (major enantiomer).

*4.2.19. Compound (2S,3R)-**4j**.* Colorless oil. $[\alpha]_D^{26}$ 59.8 (c 1.00 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.76 (m, 4H), 7.50–7.39 (m, 3H), 4.88–4.74 (m, 1H), 4.38 (q, J=8.7 Hz, 2H), 3.25–3.08 (m, 2H), 2.07 (s, 3H), 1.36 (t, J=8.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −134.61 (d, J=28.2 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 160.8 (d, J=28.0 Hz), 133.1, 133.0(7), 131.4, 128.9, 128.6, 128.1, 127.6, 126.4, 126.3 (d, J=1.9 Hz), 115.5 (d, J=254.8 Hz), 64.7, 44.3 (d, J=18.1 Hz), 44.0 (d, J=1.8 Hz), 30.2, 13.7; IR (film) ν 3020, 1764, 1722, 1581, 1357, 1216 cm^{-1}; EIMS (m/z): 347 (M^+, 19), 43 (100), 165 (41), 258 (31), 213 (26), 183 (21), 152 (13), 259 (13); HRMS (EI): m/z: calcd for $C_{18}H_{18}NFO_5$: 347.1169; found: 347.1176 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=18.1 min (minor enantiomer), 23.1 min (major enantiomer).

*4.2.20. Compound (2R,3R)-**4j**.* White solid. Mp: 77–78 °C; $[\alpha]_D^{26}$ 9.2 (c 1.40 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.78 (m, 4H), 7.52–7.44 (m, 3H), 4.95–4.81 (m, 1H), 4.05 (q, J=7.2 Hz, 2H), 3.28–3.19 (m, 1H), 2.87–2.81 (m, 1H), 2.05 (s, 3H), 1.01 (t, J=7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −135.36 (d, J=28.7 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 159.4 (d, J=28.2 Hz), 132.6 (d, J=1.3 Hz), 131.2 (d, J=1.0 Hz), 128.6 (d, J=1.9 Hz), 128.2, 127.6, 127.2, 126.3 (d, J=2.1 Hz), 126.2, 126.1, 115.4 (d, J=254.8 Hz), 63.7, 44.1 (d, J=17.9 Hz), 42.5 (d, J=3.0 Hz), 29.9, 13.0; IR (KBr) ν 2921, 1767, 1723, 1577, 1251 cm^{-1}; EIMS (m/z): 347 (M^+, 17), 43 (100), 165 (59), 183 (29), 259 (26), 255 (23), 258 (21), 213 (19), 152 (19); HRMS (EI): m/z: calcd for $C_{18}H_{18}NFO_5$: 347.1169; found: 347.1164 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=15.4 min (minor enantiomer), 22.7 min (major enantiomer).

*4.2.21. Compound (2S,3R)-**4k**.* Brown oil. $[\alpha]_D^{26}$ 33.0 (c 0.10 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.32 (m, 1H), 6.32–6.24 (m, 2H), 4.86–4.73 (m, 1H), 4.36 (q, J=7.4, 14.3 Hz, 2H), 3.25–3.16 (m, 1H), 2.98–2.90 (m, 1H), 2.16 (s, 3H), 1.34 (t, J=7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −132.95 (d, J=28.6 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 160.3 (d, J=26.9 Hz), 146.8, 143.3, 113.2 (d, J=255.7 Hz), 110.7, 110.2, 64.6, 41.1, 38.6 (d, J=19.9 Hz), 29.9, 13.6; IR (film) ν 3020, 1764, 1721, 1583, 1216 cm^{-1}; EIMS (m/z): 43 (100), 83 (16), 198 (16), 195 (10), 55 (10), 84 (9), 240 (8), 199 (8); HRMS (EI): m/z: calcd for $C_{12}H_{14}NFO_6$: 287.0805; found: 287.0810 $[M]^+$. HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=11.6 min (major enantiomer), 14.3 min (minor enantiomer).

*4.2.22. Compound (2R,3R)-**4k**.* Brown oil. $[\alpha]_D^{27}$ 5.6 (c 1.20 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.35 (m, 1H), 6.33–6.30 (m, 2H), 4.91–4.78 (m, 1H), 4.27 (q, J=7.4, 14.8 Hz, 2H), 3.26–3.17 (m, 1H), 2.75–2.68 (m, 1H), 2.13 (s, 3H), 1.25 (t, J=7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −133.30 (d, J=25.1 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 159.4 (d, J=27.7 Hz), 146.6, 142.7, 113.6 (d, J=255.5 Hz), 110.3, 109.8, 64.0, 40.0, 38.2 (d, J=19.6 Hz), 29.6, 13.2; IR (film) ν 1765, 1721, 1580 cm^{-1}; EIMS (m/z): 43 (100), 198 (19), 195 (18), 199 (18), 241 (14), 170 (9), 151 (9), 83 (9); HRMS (EI): m/z: calcd for $C_{12}H_{14}NFO_6$: 287.0805; found: 287.0807 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=13.0 min (minor enantiomer), 14.3 min (major enantiomer).

*4.2.23. Compound (2S,3R)-**4l**.* Colorless oil. $[\alpha]_D^{26}$ 39.6 (c 0.45 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (q, J=7.4 Hz, 2H), 3.50–3.34 (m, 1H), 2.82–2.46 (m, 2H), 2.19 (s, 3H), 1.49–1.14 (m, 9H), 0.87 (t, J=7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −133.06 (d, J=29.7 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 161.0 (d, J=28.0 Hz), 116.3 (d, J=252.0 Hz), 64.2, 42.5 (d, J=1.9 Hz), 37.4 (d, J=19.8 Hz), 29.9, 28.7, 28.5 (d, J=12.5 Hz), 22.4, 13.7, 13.6; IR (film) ν 2962, 1766, 1722, 1579, 1358 cm^{-1}; ESI-MS (m/z): 300.2 $[M+Na]^+$; HRMS (ESI): m/z: calcd for $C_{12}H_{20}NFO_5Na$: 300.1218; found: 300.1212 $[M]^+$. HPLC separation conditions: Chiralcel OD, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=6.9 min (major enantiomer), 8.0 min (minor enantiomer).

*4.2.24. Compound (2R,3R)-**4l**.* Colorless oil. $[\alpha]_D^{26}$ 3.0 (c 1.10 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J=6.7 Hz, 2H), 3.52–3.35 (m, 1H), 2.74–2.46 (m, 2H), 2.17 (s, 3H), 1.60–1.18 (m, 9H), 0.87 (t, J=6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −132.41 (d, J=22.2 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 160.4 (d, J=27.7 Hz), 116.1 (d, J=252.4 Hz), 63.8, 41.8 (d, J=2.8 Hz), 36.9 (d, J=19.4 Hz), 29.5, 28.7 (d, J=1.7 Hz), 28.3, 22.1, 13.3, 13.2(7); IR (film) ν 2960, 1765, 1721, 1578 cm^{-1}; EIMS (m/z): 43 (100), 173 (15), 147 (15), 95 (13), 55 (11), 58 (11), 41 (10), 129 (9); HRMS (EI): m/z: calcd for $C_{12}H_{20}NFO_5$: 277.1326; found: 277.1322 $[M]^+$. HPLC separation conditions: Chiralcel ODH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.7 mL/min; t_R=7.9 min (major enantiomer), 8.9 min (minor enantiomer).

*4.2.25. Compound (2S,3R)-**4m**.* Colorless oil. $[\alpha]_D^{27}$ 50.7 (c 0.64 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, J=7.0 Hz, 2H), 3.24–3.06 (m, 1H), 2.54–2.02 (m, 6H), 1.81–1.60 (m, 2H), 1.36 (t, J=7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −138.62 (d, J=21.0 Hz,

1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 159.7 (d, J=27.5 Hz), 114.7 (d, J=254.9 Hz), 64.1, 41.3 (d, J=21.2 Hz), 40.1, 39.0 (d, J=2.3 Hz), 24.1 (d, J=2.3 Hz), 23.3, 13.7; IR (film) ν 2961, 1765, 1720, 1579, 1255 cm^{-1}; EIMS (m/z): 247 (M^+, 5), 55 (100), 79 (66), 41 (58), 81 (51), 42 (44), 97 (43), 68 (41), 155 (38); HRMS (EI): m/z: calcd for $C_{10}H_{14}NFO_5$: 247.0856; found: 247.0860 $[M]^+$. HPLC separation conditions: Chiralcel ADH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.6 mL/min; t_R=22.9 min (major enantiomer), 31.6 min (minor enantiomer).

*4.2.26. Compound (2R,3R)-**4m**.* Colorless oil. $[\alpha]_D^{27}$ −6.7 (*c* 0.96 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (q, J=7.4 Hz, 2H), 3.27–3.09 (m, 1H), 2.59–2.09 (m, 5H), 1.80–1.65 (m, 3H), 1.35 (t, J=6.8 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −139.00 (d, J=24.6 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 159.4 (d, J=27.7 Hz), 114.4 (d, J=254.3 Hz), 64.1, 41.3 (d, J=20.2 Hz), 40.0 (d, J=1.9 Hz), 39.9, 23.0 (d, J=2.5 Hz), 22.9, 13.2; IR (film) ν 2958, 1767, 1720, 1579, 1260 cm^{-1}; EIMS (m/z): 247 (M^+, 3), 55 (100), 79 (76), 81 (59), 41 (55), 127 (52), 97 (50), 155 (48), 200 (48); HRMS (EI): m/z: calcd for $C_{10}H_{14}NFO_5$: 247.0856; found: 247.0850 $[M]^+$. HPLC separation conditions: Chiralcel ADH, 20 °C, 254 nm, 9:1 hexane/*i*-PrOH, 0.6 mL/min; t_R=19.0 min (minor enantiomer), 22.4 min (major enantiomer).

4.3. General procedure for the synthesis of compound 7

*4.3.1. Compound (2R, 3R)-**4d**.* Compound (2*R*, 3*R*)-**4d** (90 mg, 0.24 mmol) and **6** (93 mg, 0.50 mmol) were dissolved in dry tetrahydrofuran (5 mL). The mixture was stirred at room temperature and monitored by TLC. After completion (53 h), the mixture was concentrated by rotary evaporation and the residue was purified by flash chromatography (ethyl acetate/pet. ether: 1/3) to provide pure product **7** 130 mg in quantitative yield as white solid.

Mp: 55–56 °C; $[\alpha]_D^{26}$ −31.5 (*c* 1.35 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96–7.84 (m, 1H), 7.68 (AB, J=8.3 Hz, 2H), 7.31 (AB, J=7.7 Hz, 2H), 7.24 (AB, J=8.3 Hz, 1H), 7.02 (AB, J=7.7 Hz, 2H), 4.55–4.42 (m, 1H), 4.09 (q, J=7.3 Hz, 2H), 2.78–2.69 (m, 1H), 2.57–2.41 (m, 4H), 1.63 (s, 3H), 1.09 (t, J=7.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.06 (d, J=29.4 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (d, J=27.8 Hz), 151.8 (d, J=5.2 Hz), 144.2, 135.4, 132.6, 131.7, 131.3 (d, J=1.4 Hz), 129.7, 127.8, 122.6, 115.5 (d, J=256.9 Hz), 64.3, 45.5 (d, J=18.2 Hz), 37.7 (d, J=4.5 Hz), 21.7, 16.3 (d, J=2.1 Hz), 13.5; IR (film) ν 2926, 1768, 1579, 1490, 1338, 1255, 1167 cm^{-1}; ESI-MS (m/z): 544.1 $(M+1)^+$.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.041.

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