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Henry reaction of fluorinated nitro compounds

Huawei Hu [a], Yangen Huang [a,*], Yong Guo [b,**]

[a] College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Road, Shanghai 201620, China
[b] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

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Dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

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ABSTRACT

The Henry (nitroaldol) reaction of fluorinated nitro compounds with various aromatic aldehydes and a fluorinated aliphatic aldehyde to give β-fluoro-β-nitroalcohols which bearing a fluorinated quaternary carbon center was reported. The relative configuration of the major diastereoisomer of 2-fluoro-2-nitro-1-(4-nitrophenyl)-3-phenylpropanol (**5bf**) was determined by X-ray single crystal analysis.

1. Introduction

Since its discovery in 1895, the Henry (nitroaldol) reaction becomes one of the most important carbon–carbon bond forming reactions in organic synthesis. The resulted β-nitroalcohol is versatile intermediate in the synthesis of a variety of natural products and medicinally important compounds [1–8]. While the Henry reaction has been extensively studied in numerous synthetic processes, few studies of halogenated nitroalkanes have been reported [9].

Fluorine-containing compounds have attracted considerable attention for introduction of fluorine to organic compounds can drastically change both their biological and physical properties [10–20]. It was reported that as many as 30–40% of agrochemicals and 20% of pharmaceuticals including four of the top ten best-selling drugs on market were estimated to contain fluorine [20,21]. Accordingly, the development of methodologies to incorporate fluorine into organic molecules has attracted great attention recently [10–20]. We envisioned that the addition of α-fluoronitroalkanes to carbonyl compounds to form fluorinated β-hydroxynitroalkanes could represent one of these important methods. Moreover, the Henry reaction of fluoronitroalkane gives rise to fluorinated quaternary carbon center, which is highly desirable motif in numerous drug molecules [22–25]. Fluoronitroalkane is less studied as a monofluorinated synthetic synthon compared to fluoronitroester [26–29]. For a recent example, using α-fluoro-α-nitro esters, Zhao and their coworkers reported an organocatalytic asymmetric Michael addition [28]. In contrast, few reactions of fluoronitroalkane have been reported, to the best of our knowledge [29]. Herein we report the Henry reaction of fluoronitroalkanes to give β-fluoro-β-nitroalcohols with a fluorine-containing quaternary carbon center in high yields.

2. Results and discussion

As shown in Tables 1 and 2, fluoronitroalkanes **3a–3e** were prepared via nitroalkanes **2a–2e** starting from halides **1a** to **1e** [30,31]. Reaction of 1-fluoro-1-nitroheptane **3a** and benzaldehyde **4a** was chosen as the model reaction to optimize the reaction conditions. A variety of bases including organic and inorganic bases were screened as the catalyst (Table 3, entries 1–8). It was found that 1,1,3,3-tetramethylguanidine (TMG) was found to be the most effective, giving product **5aa** in 67% yield with a diastereoselectivity of 30:70. Interestingly, The decrease in dosage of TMG from 50 mol% to 30 mol% resulted similar yield and the same diastereoselectivity (Table 3, entry 8 vs 9). The reaction conditions were further optimized by changing the solvents (Table 4, entries 1–5). Finally, THF (Table 4, entry 2) was found to be the preferential

* Corresponding author. Tel.: +86 21 67792612; fax: +86 21 67792608.
** Corresponding author. Tel.: +86 21 54925462; fax: +86 21 64166128.
E-mail addresses: hyg@dhu.edu.cn (Y. Huang), yguo@sioc.ac.cn (Y. Guo).

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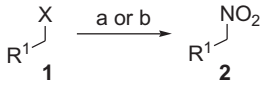
Table 1
Synthesis of nitro compounds.



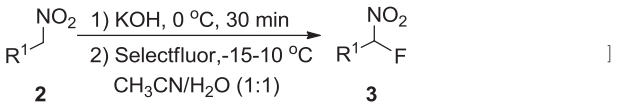
Entry	Substrate	R^1	X	Product	Temp (°C)	Yield (%)
1	**1a**	n-C_6H_{13}	I	**2a**	r.t.	62[a]
2	**1b**	$C_6H_5CH_2$	I	**2b**	60	60[b]
3	**1c**	Ph	Br	**2c**	−18	45[a]
4	**1d**		Br	**2d**	r.t.	35[a]
5	**1e**		Br	**2e**	r.t.	30[a]

[a] $NaNO_2$/urea in DMF.
[b] $AgNO_2$ in H_2O.

solvent in terms of the yield (67%). Reactions in other solvents, such as CH_2Cl_2, EtOH, toluene and MeCN, gave lower yields.

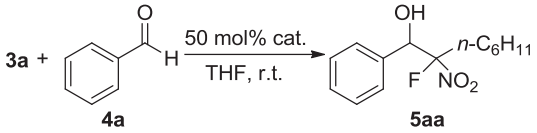
After the optimal reaction condition was found (30 mol% of TMG in THF), the diastereoselective Henry reactions of α-fluoronitroalkanes **3a–3e** and various aldehydes **4a–4h** were investigated. As summarized in Table 5, the Henry reaction between α-fluoronitroalkanes **3a/3b** and different aromatic aldehydes in the presence of 30 mol% TMG in THF at room temperature led to desired products in moderate to good yield (40–80%) (Table 5, entries 1–10). In general, aromatic aldehydes bearing electron-withdrawing groups showed higher reactivity than those with electron-donating groups. In contrast to α-fluoronitroalkanes **3a/3b**, compound **3c–3e** seemed to be more reactive since the reactions at ambient atmosphere produced a complex mixture. However, when the reactions of **3c–3e** were carried out at a lower temperature (approximately −30 °C), the reactions went smoothly to afford the nitroaldol products in 60–85% yields (Table 5, entries 11–15). Interestingly, some of the nitroaldol products were unstable when subjecting to silica gel chromatograph. The products **3c** and aromatic aldehydes (e.g. *p*-nitrobenzaldehyde) of retro Henry reaction were isolated. The Henry reaction of fluoroalkylaldehyde was studied. 1-Fluoro-1-phenyl-1-nitromethane **3c** reacted smoothly with 5-chloro-2,2,3,3,4,4,5,5-octafluoropentanal **4i** (Table 5, entry 12) under

Table 2
Monofluorination of nitro compounds.



Entry	Substrate	R^1	Product	Yield (%)
1	**2a**	n-C_6H_{13}	**3a**	82
2	**2b**	$C_6H_5CH_2$	**3b**	80
3	**2c**	Ph	**3c**	75
4	**2d**		**3d**	76
5	**2e**		**3e**	73

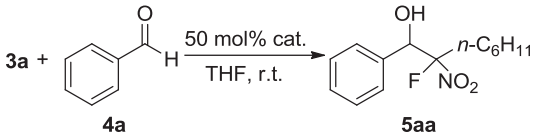
Table 3
Effects of base catalysts.



Entry	Cat.	Yield (%)[a]	Syn:anti[a]
1	K_2CO_3	38	26:74
2	Cs_2CO_3	36	26:74
3	f-BuONa	45	23:77
4	Et_3N	35	46:54
5	DBU	60	31:69
6	DABCO·$6H_2O$	26	57:43
7	DIPEA	29	44:56
8	TMG	67	30:70
9[b]	TMG	70	30:70

DABCO, triethylenediamine; DIPEA, ethyldiisopropylamine, TMG, tetramethylguanidine.
[a] Yields and Syn:anti determined by ^{19}F NMR.
[b] 30% TMG was used.

Table 4
Effects of the solvent.



Entry	Solvent	Yield (%)[a]	Syn:anti[a]
1	CH_2CL_2	32	33:67
2	THF	67	30:70
3	EtOH	60	31:69
4	toluene	45	37:63
5	MeCN	34	29:71

[a] Determined by ^{19}F NMR.

the same reaction conditions, giving a 73% yield of the nitroaldol product in a 27:73 diastereoselectivity. Both isomers except **5df** of nitroaldol products were obtained and fully characterized after a careful separation by column chromatography on silica gel. Owing

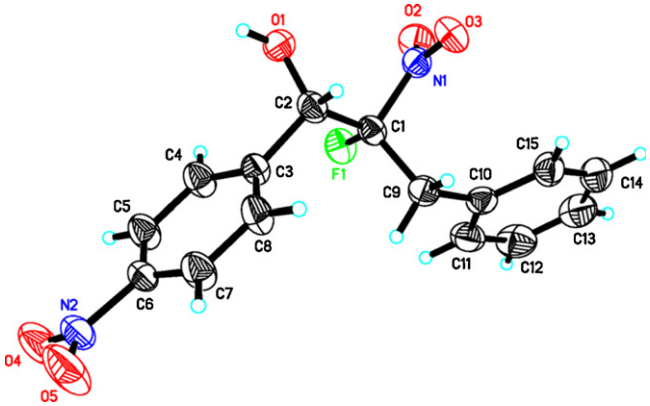
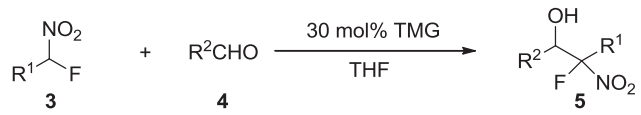


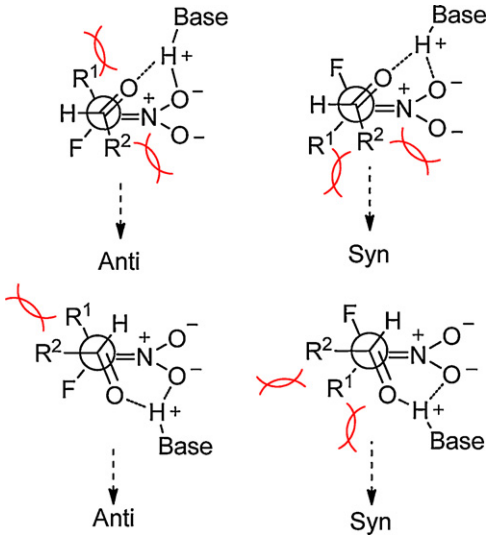
Fig. 1. X-ray structure of *anti*-**5bf**. Selected bond lengths (Å) and (torsion) angles (°): F(1)–C(1) 1.358(19), N(1)–O(2) 1.209(2), N(1)–O(3) 1.216(2), N(1)–C(1) 1.542(2), O(1)–C(2) 1.419(2), C(1)–C(9) 1.512(2), C(1)–C(2) 1.527(2); O(2)–N(1)–C(1) 118.85(16), O(3)–N(1)–C(1) 15.71(13), F(1)–C(1)–C(9) 110.32(15), F(1)–C(1)–C(2) 109.25(14), C(9)–C(1)–C(2) 117.09(14), F(1)–C(1)–N(1) 105.24(12), C(9)–C(1)–N(1) 108.35(13), C(2)–C(1)–N(1) 105.84(14), O(1)–C(2)–C(3) 111.90(15), O(1)–C(2)–C(1) 104.72(14), C(3)–C(2)–C(1) 112.81(15), C(1)–C(9)–C(10) 112.89(13); F(1)–C(1)–C(2)–O(1) −60.1(2).

Table 5
Henry reaction of 1-fluoronitroalkanes to aldehydes catalyzed by TMG.



Entry	R^1CHFNO_2		R^2CHO		Temp	Product		
	3	R^1	**4**	R^2			Yield[a]	Syn:anti[b]
1	**3a**	n-C_3H_{13}	**4a**	Ph	r.t.	**5aa**	70(64)	30:70
2	**3a**		**4b**	4-ClC_6H_4	r.t.	**5ab**	75(65)	34:66
3	**3a**		**4c**	4-BrC_6H_4	r.t.	**5ac**	51(48)	28:72
4	**3a**		**4d**	4-MeC_6H_4	r.t.	**5ad**	52(45)	31:69
5	**3a**		**4e**	3-OHC_6H_4	r.t.	**5ae**	45(40)	34:66
6	**3b**	Bn	**4a**		r.t.	**5ba**	63(65)	35:65
7	**3b**		**4b**		r.t.	**5bb**	73(70)	37:63
8	**3b**		**4d**		r.t.	**5bd**	47(43)	34:66
9	**3b**		**4f**	4-$NO_2C_6H_4$	r.t.	**5bf**	80(80)	39:61
10	**3b**		**4g**	4-FC_6H_4	r.t.	**5bg**	62(60)	35:65
11	**3c**	Ph	**4h**	4-$CF_3C_6H_4$	−30 °C	**5ch**	76(60)	18:82
12	**3c**		**4i**	ClC_4F_8	−30 °C	**5ci**	70(62)	27:73
13	**3d**		**4f**		−30 °C	**5df**	81(78)	43:57[c]
14	**3e**		**4f**		−30 °C	**5ef**	70(69)	50:50
15	**3e**		**4h**		−30 °C	**5eh**	83(85)	43:57

[a] Yields determined by ^{19}F NMR using an internal standard and isolated yields in parentheses.
[b] Determined by ^{19}F NMR.
[c] Downfield/upfield.



Scheme 1. Newman projection of transition state.

to only one α-proton within our starting nitro compounds, a quaternary carbon center was built in the final products, where elimination of vicinal hydroxyl group would not happen.

In order to determine the relative configuration of the newly generated stereogenic center, X-ray single crystal analysis of one major isomer of compound **5bf** was carried out (Fig. 1). It was found that F atom was *anti* to –OH group in **5bf**. The *anti*-selectivity in this reaction can be explained by steric hindrance in the cyclic transition state, as can readily be seen in the Newman projection (Scheme 1). According to the coupling constant of tertiary fluorine and hydrogen geminal to the hydroxyl, *syn*/*anti* isomers were determined (*anti*-isomer with larger $J_{HF\ or\ FH}$, see Section 4 for details).

3. Conclusion

In summary, a series of novel α-fluoronitroalkanes were prepared and applied to the Henry reaction with various aldehydes. The desired products with a fluorine-containing quaternary center were obtained in good yields. This method provides a practical method for the preparation of biologically useful fluorinated derivatives. Asymmetry version of the reaction is undergoing in our laboratory, and will be reported in due course.

4. Experimental

4.1. General information

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Melting points are measured on a Temp-Melt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer with TMS as an internal standard (negative for upfield). ^{19}F NMR spectra were recorded on a Bruker AM 300 (282 MHz) with $CFCl_3$ as an external standard (negative for upfield). ^{13}C NMR spectra were recorded on a Bruker AV-400 (100 MHz) spectrometer with $CDCl_3$ as an internal standard (negative for upfield). MS and HRMS were recorded on a Hewlett–Packard HP-5989A spectrometer and a Finnigan MAT-8483 mass spectrometer. Infrared spectra were measured with a Perkin-Elmer 983 spectrometer. TLC analyses were performed on silica gel plates (RP-18 WF254s, Merck, 0.25 mm), and column

chromatography was performed using silica gel (mesh 300–400). All solvents were purified by standard methods.

4.2. General procedure and spectra data

4.2.1. Preparation of nitro compounds [30,31]

4.2.1.1. 1-Nitroheptane (2a). **2a**: To a solution of 1-iodoheptane (6.78 g, 30 mmol) in DMF (60 mL) was added $NaNO_2$ (3.5 g, 50 mmol). The mixture was stirred at r.t. for 6 h. The reaction mixture was then poured into ice-water (60 mL) and layered over with petroleum ether (100 mL). The aqueous phase was extracted with petroleum ether (60 mL × 3). Then the extracts were washed with then with water (50 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated, and the residue was distilled in vacuum. A colorless liquid **2a** was obtained (2.70 g, 62%). Colorless oil; bp. 73 °C/4.5 mmHg; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.22–1.46 (m, 8H), 1.95–2.08 (m, 2H), 4.38 (t, J = 6.9 Hz, 2H).

4.2.1.2. 2-Phenylnitroethane (2b). **2b:** To a water solution (40 mL) of (2-iodoethyl)benzene (4.68 g, 20 mmol) was added $AgNO_2$ (3.06 g, 20 mmol) and the reaction flask was wrapped with aluminum foil to avoid light. After being stirred at 60 °C for 1.5 h, the reaction mixture was filtered, extracted with EtOAc (30 mL × 3), and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (hexane: EtOAc, 97:3) to afford **2b** (1.8 g, 60%) as pale yellow liquid.

Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 3.31 (t, J = 7.2 Hz, 2H), 4.60 (t, J = 7.2 Hz, 2H), 7.18–7.37 (m, 5H).

4.2.1.3. Phenylnitromethane (2c). **2c**: Benzyl bromide (5.1 g, 30 mmol) was added to a stirred mixture of $NaNO_2$ (3.5 g, 50 mmol) and urea (3.6 g, 60 mmol) in DMF (60 mL) at −18 °C. After stirring at −18 °C for 6 h, the reaction mixture was poured into ice-water (60 mL) and layered over with petroleum ether (100 mL). The aqueous phase was extracted with diethyl ether (60 mL × 3). Then the extracts were washed with 10% aqueous sodium thiosulfate solution (20 mL × 2) and water (50 mL × 2) in sequence. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated, and the residue was distilled in vacuum (b.p. 75 °C/4.5 mmHg) to afford **2c** (2.1 g, 45%) as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 5.44 (s, 2H), 7.45 (m, 5H).

4.2.1.4. 2-(2-Nitroethyl)-1,3-dioxolane (2d). **2d**: To a solution of bromo compound (5.4 g, 30 mmol) in DMF (60 mL) was added $NaNO_2$ (3.5 g, 50 mmol). After stirring at r.t. for 6 h, the reaction mixture was poured into ice-water (60 mL) and layered over with petroleum ether (100 mL). The aqueous phase was extracted with diethyl ether (60 mL × 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated, and the residue was purified by flash column chromatography on silica gel with 5% Et_2O in hexane as eluent to afford **2d** (1.5 g, 35%) as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.40–2.47 (m, 1H), 3.85–4.02 (m, 4H), 4.51 (t, J = 7.2 Hz, 2H), 5.03 (t, J = 3.6 Hz, 1H).

4.2.1.5. 4-Nitrobut-1-ene (2e). The procedure described above for the preparation of **2d** was followed. The product **2e** as pale yellow oil was purified by flash column chromatography on silica gel with 5% Et_2O in hexane as eluent, yield: 30%; ^{1}H NMR ($CDCl_3$): δ 2.72–2.79 (m, 2H), 4.44 (t, J = 6.6 Hz, 2H), 5.13–5.23 (m, 2H), 5.70–5.84 (m, 1H).

4.2.2. Preparation of α-fluoronitro compounds [29,32,33]

Solid KOH (82%, 1.6 g, 20 mmol) was added to a mixture of the respective nitro compound (20 mmol), MeCN (15 mL) and H_2O (30 mL) at 0 °C. The mixture was vigorously stirred for 1 h, and then cooled to −17 °C to provide partial precipitation of the nitronate. CH_2Cl_2 (50 mL, pre-cooled to −78 °C) and Selectfluor (8.13 g, 23.0 mmol) were added in one portion. The cooling bath was removed, and the mixture was vigorously stirred. The reaction temperature was allowed to rise to 10 °C, at which point petroleum ether (50 mL) was added, after stirring about 10 min, The mixture was filtered through Celite, the organic layer were separated, and the aqueous layer was extracted with portions of CH_2Cl_2–hexanes (1:1, 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated, and the residue was purified by distillation in vacuum or flash column chromatography on silica gel to give the corresponding products **3a–3e**.

4.2.2.1. 1-Fluoro-1-nitroheptane (3a). Colorless oil (82% yield); bp. 75 °C/7.5 mmHg; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 6.6 Hz, 3H), 1.25–1.60 (m, 8H), 2.05–2.22 (m, 2H), 5.80 (dt, J = 51, 5.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −146.5 (dt, J = 50.2, 22.8 Hz).

4.2.2.2. 1-Fluoro-2-phenylnitroethane (3b). Colorless oil (80% yield); bp.102 °C/4.5 mmHg; ^{1}H NMR ($CDCl_3$): δ 3.30–3.58 (m, 2H), 5.94 (ddd, J = 50.6, 6.7, 3.8 Hz, 1H), 7.18–7.42 (m, 5H); ^{19}F NMR ($CDCl_3$): δ −145.7 (dt, J = 50.5, 23.7 Hz).

4.2.2.3. 1-Fluoro-1-phenylnitromethane (3c). Colorless oil (75% yield); bp.96 °C/7.5 mmHg; ^{1}H NMR ($CDCl_3$): δ 6.61 (d, J = 48.6 Hz, 1H), 7.55–7.59 (m, 5H); ^{19}F NMR ($CDCl_3$): δ −139.9 (d, J = 48.5 Hz).

4.2.2.4. 2-(2-Fluoro-2-nitroethyl)-1, 3-dioxolane (3d). Pale yellow oil (76% yield); 5% Et_2O in hexane; ^{1}H NMR ($CDCl_3$): δ 2.42–2.61 (m, 2H), 3.91–4.02 (m, 4H), 5.12 (t, J = 4.2 Hz, 1H), 5.97 (ddd, J = 50.2, 6.9, 4.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −146.2 (ddd, J = 50.5, 24.5, 18.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6 (d, J = 18.6 Hz), 65.1, 65.3, 99.2 (d, J = 3.7 Hz), 108.4 (d, J = 238.7 Hz).

4.2.2.5. 4-Fluoro-4-nitrobut-1-ene (3e). Pale yellow oil (73% yield); 5% Et_2O in hexane; ^{1}H NMR ($CDCl_3$): δ 2.84–2.97 (m, 2H), 5.13–5.23 (m, 2H), 5.70–5.94 (m, 3H).

4.2.3. Typical experiment procedure for the nitro-aldol reaction of α-fluoronitrocompounds with aldehydes

To a solution of 1-fluoro-1-nitroheptane **3a** (195 mg, 1.2 mmol) in THF (5 mL) was added benzaldehyde **4a** (106 mg, 1 mmol) and TMG (35 mg, 0.3 mmol). The mixture was stirred at indicated temperature overnight, and then neutralized by acetic acid. The crude products were purified by flash column chromatography on silica gel.

4.2.3.1. 2-Fluoro-2-nitro-1-phenyloctan-1-ol (5aa). Syn-isomer: Colorless oil. IR (neat) ν_{max} 3426, 2954, 2931, 2870, 2852, 1558, 1497, 1460, 1362, 1305, 1173, 1084, 1057, 844, 743, 712, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 6.6 Hz, 3H), 1.05–1.50 (m, 8H), 2.08–2.52 (m, 2H), 2.70 (d, J = 4.5 Hz, 1H), 5.15 (dd, $J_{H,F}$ = 15.6 Hz, J = 4.5 Hz, 1H), 7.35–7.39 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.0 (ddd, J = 33.0, 15.5, 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6 (CH_3), 23.3 (d, J = 2.5 Hz, CH_2), 24.1 (CH_2), 30.3 (CH_2), 33.0 (CH_2), 34.5 (d, J = 21.2 Hz, CH_2), 77.6 (d, J = 23.1 Hz, CHOH), 122.6 (d, J = 249.9 Hz, CF), 129.2 (d, J = 1.9 Hz), 130.3, 131.2, 136.8; HRMS(ESI) calcd for $C_{14}H_{20}ClFNO_3$ $[M+Cl]^-$: 304.1121, found: 304.1122.

Anti-isomer: white solid, Mp 42–44 °C. IR (KBr) ν_{max} 3458, 2932, 2859, 1569, 1495, 1456, 1362, 1172, 1058, 831, 738, 705, 620, 580 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J = 6.6 Hz, 3H), 1.01–1.50 (m, 8H), 1.52–1.71 (m, 1H), 2.04–2.16 (m, 1H), 2.83 (d, J = 6.3 Hz, 1H), 5.22 (dd, $J_{H,F}$ = 20.4, 6.0 Hz, 1H), 7.38–7.42 (m, 5H);

^{19}F NMR (282 MHz, $CDCl_3$): δ −145.1 (ddd, J = 32.8, 20.6, 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.6 (d, J = 3.9 Hz, CH_2), 22.4 (CH_2), 28.6 (CH_2), 31.3 (CH_2), 32.8 (d, J = 21.3 Hz, CH_2), 76.0 (d, J = 22.9 Hz, CHOH), 122.0 (d, J = 246.5 Hz, CF), 127.6 (d, J = 1.6 Hz), 128.6, 129.5, 135.2; HRMS(ESI) calcd for $C_{14}H_{20}FNO_3Na$ $[M+Na]^+$: 292.1319, found: 292.1320.

*4.2.3.2. 2-Fluoro-2-nitro-1-(4-chlorophenyl)octan-1-ol (**5ab**). Syn-isomer*: white solid, Mp 62–63 °C. IR (KBr) ν_{max} 3423, 2958, 2931, 2871, 2851, 1557, 1497, 1464, 1362, 1172, 1092, 1057, 1015, 855, 822, 795, 766, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.0 Hz, 3H), 1.05–1.56 (m, 8H), 2.04–2.54 (m, 2H), 2.82 (s, 1H), 5.15 (d, $J_{H,F}$ = 14.7 Hz, 1H), 7.22–7.45 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.5 (ddd, J = 30.7, 13.8, 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (d, J = 3.3 Hz, CH_2), 22.4 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 32.6 (d, J = 21.2 Hz, CH_2), 75.3 (d, J = 17.6 Hz, CHOH), 120.7 (d, J = 246.7 Hz, CF), 128.8, 128.9 (d, J = 1.7 Hz), 133.5, 135.5; HRMS(ESI) calcd for $C_{14}H_{19}ClFNO_3Na$ $[M+Na]^+$: 326.0930, found: 326.0924.

Anti-isomer: Colorless oil. IR (neat) ν_{max} 3414, 2958, 2932, 2859, 1569, 1493, 1466, 1363, 1172, 1092, 1015, 826, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.6 Hz, 3H), 1.01–1.50 (m, 8H), 1.52–1.71 (m, 1H), 2.04–2.16 (m, 1H), 2.83 (d, J = 6.0 Hz, 1H), 5.23 (dd, $J_{H,F}$ = 19.8, 6.0 Hz, 1H), 7.35–7.45 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.5 (ddd, J = 31.9, 20.0, 5.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (d, J = 2.7 Hz, CH_2), 22.3 (CH_2), 28.4 (CH_2), 31.2 (CH_2), 34.1 (d, J = 20.9 Hz, CH_2), 75.7 (d, J = 20.3 Hz, CHOH), 122.1 (d, J = 239.1 Hz, CF), 129.0, 129.1 (d, J = 2.1 Hz), 134.3, 135.6; HRMS(ESI) calcd for $C_{14}H_{19}ClFNO_3Na$ $[M+Na]^+$: 326.0930, found: 326.0933.

*4.2.3.3. 2-Fluoro-2-nitro-1-(4-bromophenyl)octan-1-ol (**5ac**). Syn-isomer*: white solid, Mp 61–63 °C. IR (KBr) ν_{max} 3419, 2956, 2931, 2851, 1557, 1493, 1463, 1361, 1173, 1076, 1055, 1011, 854, 820, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 6.9 Hz, 3H), 1.05–1.56 (m, 8H), 2.03–2.52 (m, 2H), 2.82 (s, 1H), 5.14 (d, $J_{H,F}$ = 14.7 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.4 (ddd, J = 33.6, 15.8, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (d, J = 3.1 Hz, CH_2), 22.4 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 32.6 (d, J = 21.1 Hz, CH_2), 75.3 (d, J = 23.7 Hz, CHOH), 121.7 (d, J = 246.3 Hz, CF), 123.7, 129.2 (d, J = 1.5 Hz), 131.6, 134.1; HRMS(ESI) calcd for $C_{14}H_{19}BrClFNO_3$ $[M+Cl]^-$: 382.0226, found: 382.0229.

Anti-isomer: Colorless oil. IR (neat) ν_{max} 3418, 2957, 2931, 2871, 2858, 1568, 1489, 1466, 1362, 1170, 1074, 1011, 824, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.3 Hz, 3H), 1.01–1.50 (m, 8H), 1.52–1.71 (m, 1H), 2.04–2.16 (m, 1H), 2.78 (s, 1H), 5.23 (d, $J_{H,F}$ = 20.1 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.1 (ddd, J = 33.0, 20.6, 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (d, J = 11.3 Hz, CH_2), 22.3 (CH_2), 28.4 (CH_2), 31.2 (CH_2), 34.1 (d, J = 21.6 Hz, CH_2), 75.8 (d, J = 20.3 Hz, CHOH), 121.9 (d, J = 248.4 Hz, CF), 123.9, 129.4 (d, J = 2.1 Hz), 132.0, 134.7; HRMS(ESI) calcd for $C_{14}H_{19}BrClFNO_3$ $[M+Cl]^-$: 382.0227, found: 382.0229.

*4.2.3.4. 2-Fluoro-2-nitro-1-(4-tolyl)octan-1-ol (**5ad**). Syn-isomer*: white solid, Mp 50–51 °C. IR (KBr) ν_{max} 3428, 2955, 2931, 2856, 1557, 1463, 1362, 1173, 1094, 1057, 1021, 851, 758, 762, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 6.9 Hz, 3H), 1.05–1.56 (m, 8H), 2.16–2.54 (m, 5H), 2.55 (d, J = 4.2 Hz, 1H), 5.14 (dd, $J_{H,F}$ = 16.1, 4.5 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.4 (ddd, J = 33.0, 15.5, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.2, 21.6 (d, J = 3.1 Hz, CH_2), 22.4 (CH_2), 28.6 (CH_2), 31.3 (CH_2), 32.9 (d, J = 21.1 Hz, CH_2), 75.9 (d, J = 22.5 Hz, CHOH), 122.1 (d, J = 237.6 Hz, CF), 127.4 (d, J = 2.0 Hz), 129.3, 132.2, 139.4; HRMS(ESI) calcd for $C_{15}H_{22}ClFNO_3$ $[M+Cl]^-$: 318.1278, found: 318.1276.

Anti-isomer: colorless oil. IR (neat) ν_{max} 3440, 2957, 2931, 2859, 1567, 1463, 1363, 1172, 1095, 1059, 1020, 825, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 7.2 Hz, 3H), 1.01–1.50 (m, 8H), 1.52–1.74 (m, 1H), 2.08–2.28 (m, 1H), 2.38 (s, 3H), 2.46 (d, J = 6.0 Hz, 1H) 5.22 (dd, $J_{H,F}$ = 20.3, 6.3 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.5 (ddd, J = 33.8, 21.7, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.2, 21.5 (d, J = 3.2 Hz, CH_2), 22.3 (CH_2), 28.4 (CH_2), 31.3 (CH_2), 34.2 (d, J = 21.1 Hz, CH_2), 76.4 (d, J = 19.6 Hz, CHOH), 122.5 (d, J = 243.6 Hz, CF), 127.6 (d, J = 2.0 Hz), 129.6, 132.8, 139.6; HRMS(ESI) calcd for $C_{15}H_{22}ClFNO_3$ $[M+Cl]^-$: 318.1272, found: 318.1274.

*4.2.3.5. 2-Fluoro-2-nitro-1-(3-hydroxyphenyl)octan-1-ol (**5ae**). Syn-isomer*: white solid, Mp 98–101 °C. IR (KBr) ν_{max} 3312, 2961, 2933, 2856, 1606, 1565, 1465, 1364, 1288, 1229, 1168, 1058, 873, 843, 794, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J = 7.2 Hz, 3H), 1.05–1.56 (m, 8H), 2.13–2.56 (m, 2H), 2.65 (d, J = 3.0 Hz, 1H), 4.86 (s, 1H), 5.12 (dd, $J_{H,F}$ = 15.8, 3.0 Hz, 1H), 6.81–6.95 (m, 3H), 7.20–7.25 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.5 (ddd, J = 33.0, 16.6, 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (d, J = 3.5 Hz, CH_2), 22.4 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 32.8 (d, J = 21.1 Hz, CH_2), 75.7 (d, J = 23.1 Hz, CHOH), 114.5, 116.5, 120.0 (d, J = 1.5 Hz), 121.8 (d, J = 245.7 Hz, CF), 129.9, 136.9, 155.7; HRMS(ESI) calcd for $C_{14}H_{20}FNO_4Na$ $[M+Na]^+$: 308.1269, found: 308.1265.

Anti-isomer: white solid, Mp 103–105 °C. IR (KBr) ν_{max} 3312, 2961, 2933, 2857, 1607, 1564, 1465, 1364, 1288, 1230, 1058, 873, 794, 766 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.6 Hz, 3H), 0.98–1.50 (m, 8H), 1.51–1.70 (m, 1H), 1.94–2.16 (m, 1H), 5.20 (d, $J_{H,F}$ = 20.4 Hz, 1H), 6.86–7.00 (m, 3H), 7.26–7.32 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.8 (ddd, J = 34.7, 21.4, 5.9 Hz); HRMS(ESI) calcd for $C_{14}H_{20}FNO_4Na$ $[M+Na]^+$: 308.1269, found: 308.1273.

*4.2.3.6. 2-Fluoro-2-nitro-1,3-diphenylpropan-1-ol (**5ba**). Syn-isomer*: white solid, Mp 118–120 °C. IR (KBr) ν_{max} 3445, 3026, 1557, 1496, 1454, 1432, 1360, 1208, 1166, 1081, 1052, 1029, 844, 753, 742, 710, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (d, J = 4.2 Hz, 1H), 3.56–3.81 (m, 2H), 5.30 (dd, $J_{H,F}$ = 16.4, 4.2 Hz, 1H), 7.14–7.17 (m, 2H), 7.25–7.29 (m, 3H), 7.38–7.42 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −139.0 (ddd, J = 31.0, 15.5, 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.0 (d, J = 21.1 Hz, CH_2), 76.0 (d, J = 22.1 Hz, CHOH), 121.0 (d, J = 248.0 Hz, CF), 127.6 (d, J = 1.5 Hz), 128.1, 128.6, 128.7, 129.6, 130.2, 130.7 (d, J = 1.3 Hz), 134.9; HRMS(ESI) calcd for $C_{15}H_{14}ClFNO_3$ $[M+Cl]^-$: 310.0652, found: 310.0655.

Anti-isomer: white solid, Mp 78–80 °C. IR (KBr) ν_{max} 3512, 3068, 2913, 1560, 1496, 1457, 1420, 1367, 1290, 1204, 1150, 1049, 1026, 834, 784, 739, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (d, J = 6.6 Hz, 1H), 3.04 (dd, J = 14.5, 10.7 Hz, 1H), 3.45 (dd, J = 33.0, 14.5 Hz, 1H), 5.33 (dd, $J_{H,F}$ = 18.3, 6.9 Hz, 1H), 7.08–7.12 (m, 2H), 7.24–7.27 (m, 3H), 7.44–7.48 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.8 (ddd, J = 33.0, 18.6, 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.3 (d, J = 20.1 Hz, CH_2), 76.4 (d, J = 20.5 Hz, CHOH), 121.4 (d, J = 248.7 Hz, CF), 127.7 (d, J = 2.0 Hz), 128.2, 128.7, 129.0, 129.8, 130.1, 130.3, 135.6; HRMS(ESI) calcd for $C_{15}H_{14}ClFNO_3$ $[M+Cl]^-$: 310.0652, found: 310.0654.

*4.2.3.7. 2-Fluoro-2-nitro-1-(4-chlorophenyl)-3-phenylpropan-1-ol (**5bb**). Syn-isomer*: white solid, Mp 84–86 °C. IR (KBr) ν_{max} 3444, 3065, 3027, 2917, 1598, 1558, 1495, 1455, 1429, 1361, 1220, 1152, 1090, 1055, 1014, 878, 851, 798, 750, 708 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (d, J = 4.2 Hz, 1H), 3.51–3.78 (m, 2H), 5.28 (dd, $J_{H,F}$ = 15.8, 4.2 Hz, 1H), 7.13–7.17 (m, 2H), 7.24–7.32 (m, 3H), 7.38–7.42 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.5 (ddd, J = 33.0,

16.6, 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.0 (d, J = 20.9 Hz, CH_2), 75.3 (d, J = 23.2 Hz, CHOH), 120.9 (d, J = 247.7 Hz, CF), 127.6 (d, J = 1.5 Hz), 128.2, 128.8, 129.1 (d, J = 1.5 Hz), 129.2, 130.2, 130.6 (d, J = 1.5 Hz), 133.5, 135.7; HRMS(ESI) calcd for $C_{15}H_{13}Cl_2FNO_3$ $[M+Cl]^-$: 344.0262, found: 344.0264.

Anti-isomer: colorless oil. IR (neat) ν_{max} 3555, 3066, 3034, 2934, 1706, 1570, 1496, 1465, 1362, 1261, 1162, 1090, 1048, 1015, 837, 774, 749, 724, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (d, J = 6.6 Hz, 1H), 2.98–3.12 (m, 1H), 3.46 (dd, J = 23.2, 14.7 Hz, 1H), 5.30 (dd, $J_{H,F}$ = 17.4, 6.3 Hz, 1H), 7.08–7.12 (m, 2H), 7.25–7.29 (m, 3H), 7.40–7.44 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −145.5 (ddd, J = 31.9, 17.4, 11.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2 (d, J = 20.3 Hz, CH_2), 75.5 (d, J = 20.9 Hz, CHOH), 121.0 (d, J = 248.4 Hz, CF), 128.3, 128.7, 129.0 (d, J = 2.3 Hz), 129.2, 130.0, 130.6 (d, J = 1.4 Hz), 133.9, 135.8; HRMS(ESI) calcd for $C_{15}H_{13}Cl_2FNO_3$ $[M+Cl]^-$: 344.0262, found: 344.0263.

*4.2.3.8. 2-Fluoro-2-nitro-1-(4-tolyl)3-phenylpropan-1-ol (**5bd**). Syn-isomer*: white solid, Mp 67–70 °C. IR (KBr) ν_{max} 3445, 1606, 1569, 1511, 1431, 1364, 1228, 1155, 1045, 837, 810, 744, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.67 (d, J = 3.6 Hz, 1H), 3.52–3.78 (m, 2H), 5.26 (dd, $J_{H,F}$ = 16.8, 3.6 Hz, 1H), 7.15–7.32 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −137.9 (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (CH_3), 39.1 (d, J = 21.1 Hz, CH_2), 75.9 (d, J = 22.1 Hz, CHOH), 121.1 (d, J = 248.5 Hz, CF), 127.5 (d, J = 1.4 Hz), 128.0, 128.7, 129.4, 130.2 (d, J = 1.3 Hz), 130.8 (d, J = 1.4 Hz), 132.0, 139.7; HRMS(ESI) calcd for $C_{16}H_{16}ClFNO_3$ $[M+Cl]^-$: 324.0808, found: 324.0802.

Anti-isomer: white solid, Mp 78–80 °C. IR (KBr) ν_{max} 3440, 3035, 2922, 1607, 1569, 1514, 1456, 1369, 1225, 1185, 1037, 831, 806, 741, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.60 (d, J = 6.9 Hz, 1H), 3.02 (dd, J = 14.6, 10.5 Hz, 1H), 3.44 (dd, J = 33.0, 14.8 Hz, 1H), 5.29 (dd, $J_{H,F}$ = 18.6 Hz, J = 6.9 Hz, 1H), 7.08–7.12 (m, 2H), 7.24–7.28 (m, 5H), 7.34–7.38 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.9 (ddd, J = 33.0, 18.3, 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (CH_3), 40.3 (d, J = 20.1 Hz, CH_2), 76.3 (d, J = 20.1 Hz, CHOH), 121.5 (d, J = 248.7 Hz, CF), 127.6 (d, J = 2.0 Hz,), 128.1, 128.7, 129.7, 130.1 (d, J = 1.0 Hz), 130.4, 132.6 (d, J = 1.0 Hz), 139.8; HRMS(ESI) calcd for $C_{16}H_{16}ClFNO_3$ $[M+Cl]^-$: 324.0808, found: 324.0803.

*4.2.3.9. 2-Fluoro-2-nitro-1-(4-nitrophenyl)-3-phenylpropan-1-ol (**5bf**). Syn-isomer*: white solid, Mp 103–105 °C. IR (KBr) ν_{max} 3564, 3064, 2918, 1607, 1553, 1518, 1470, 1432, 1348, 1226, 1178, 1075, 872, 800, 734, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.1 (s, 1H), 3.50–3.80 (m, 2H), 5.44 (d, $J_{H,F}$ = 14.7 Hz, 1H), 7.11–7.32 (m, 5H), 7.63 (d, J = 10.2 Hz, 2H), 8.24 (d, J = 10.2 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −136.2 (ddd, J = 31.9, 13.3, 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.9 (d, J = 20.7 Hz, CH_2), 74.8 (d, J = 22.7 Hz, CHOH), 120.6 (d, J = 247.1 Hz, CF), 123.7, 128.3, 128.7, 128.8 (d, J = 2.0 Hz), 130.0, 130.1 (d, J = 1.2 Hz), 141.9, 148.6; HRMS(ESI) calcd for $C_{15}H_{13}ClFN_2O_5$ $[M+Cl]^-$: 355.0503, found: 355.0505.

Anti-isomer: white solid, Mp 107–109 °C. IR (KBr) ν_{max} 3445, 3070, 2924, 1606, 1571, 1523, 1456, 1350, 1223, 1153, 1080, 1042, 863, 833, 780, 732, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (d, J = 7.2 Hz, 1H), 3.16–3.27 (m, 1H), 3.53 (dd, J = 30.2, 14.7 Hz, 1H), 5.39 (dd, $J_{H,F}$ = 15.2, 7.2 Hz, 1H), 7.08–7.32 (m, 5H), 7.65 (d, J = 7.8 Hz, 2H), 8.30 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −139.1 (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2 (d, J = 20.1 Hz, CH_2), 74.8 (d, J = 22.1 Hz, CHOH), 120.6 (d, J = 243.1 Hz, CF), 123.9, 128.5, 128.7 (d, J = 2.0 Hz), 128.9, 129.7, 130.1 (d, J = 1.2 Hz), 142.2, 148.6; HRMS(ESI) calcd for $C_{15}H_{13}ClFN_2O_5$ $[M+Cl]^-$: 355.0503, found: 355.0497.

*4.2.3.10. 2-Fluoro-2-nitro-1-(4-fluorophenyl)-3-phenylpropan-1-ol (**5bg**). Syn-isomer*: white solid, Mp 78–80 °C. IR (KBr) ν_{max} 3451, 3079, 2920, 1608, 1570, 1512, 1452, 1431, 1363, 1227, 1163, 990, 851, 835, 785, 748, 710, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74 (d, J = 3.6 Hz, 1H), 3.57–3.78 (m, 2H), 5.30 (dd, $J_{H,F}$ = 16.2, 4.5 Hz, 1H), 7.05–7.44 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −137.9 (ddd, J = 30.0, 16.4, 10.4 Hz, 1F), −111.0 to −111.12 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.1 (d, J = 20.6 Hz, CH_2), 75.3 (d, J = 22.5 Hz, CHOH), 115.7 (d, J = 21.5 Hz, CH_{aron}), 120.8 (d, J = 248.4 Hz, CF), 128.1, 128.7, 129.6 (dd, J = 8.5, 2.0 Hz, CH_{aron}), 130.2 (d, J = 1.0 Hz, CH_{aron}), 130.6 (C_{aron}), 130.7 (d, J = 3.5 Hz, C_{aron}), 163.4 (d, J = 249 Hz, CF_{aron}); HRMS(ESI) calcd for $C_{15}H_{13}ClF_2NO_3$ $[M+Cl]^-$: 328.0558, found: 328.0553.

Anti-isomer: white solid, Mp 87–90 °C. IR (KBr) ν_{max} 3590, 3031, 2918, 1614, 1566, 1516, 1455, 1429, 1363, 1227, 1145, 1070, 989, 880, 846, 805, 743, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (d, J = 6.6 Hz, 1H), 3.07 (dd, J = 14.7, 11.4 Hz, 1H), 3.46 (dd, J = 32.4, 15.0 Hz, 1H), 5.31 (dd, $J_{H,F}$ = 17.7, 6.6 Hz, 1H), 7.10–7.49 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −142.1 (ddd, J = 33.0, 17.5, 11.3 Hz), −110.6 to −100.8 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.3 (d, J = 20.1 Hz, CH_2), 75.5 (d, J = 21.1 Hz, CHOH), 116.1 (d, J = 21.6 Hz, CH_{aron}), 121.1 (d, J = 246.0 Hz, CF), 128.3 (CH_{aron}), 128.7 (CH_{aron}), 129.6 (dd, J = 8.5, 2.0 Hz, CH_{aron}), 130.0 (CH_{aron}), 130.1 (C_{aron}), 131.3 (d, J = 3.5 Hz, C_{aron}), 163.5 (d, J = 252 Hz, CF_{aron}); HRMS(ESI) calcd for $C_{15}H_{13}ClF_2NO_3$ $[M+Cl]^-$: 328.0558, found: 328.0555.

*4.2.3.11. 2-Fluoro-2-nitro-1-(4-trifluoromethylphenyl)-2-ethanol (**5ch**). Anti-isomer* [34]: white solid, Mp 80–83 °C. IR (KBr) ν_{max} 3501, 2926, 1621, 1572, 1453, 1420, 1327, 1230, 1169, 1129, 1073, 1019, 995, 947, 845, 817, 746, 723, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (d, J = 6.9 Hz, 1H), 5.99 (dd, $J_{H,F}$ = 22.4, 6.0 Hz, 1H), 7.25–7.60 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −148.2 (d, J = 22.6 Hz, 1F), −62.5 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.2 (d, J = 19.5 Hz, CHOH), 119.8 (d, J = 247 Hz, CF), 123.7 (q, J = 272 Hz, CF_3), 125.1 (q, J = 3.8 Hz), 125.2 (d, J = 9.6 Hz), 128.3, 128.8 (d, J = 1.4 Hz), 130.4, 130.7 (q, J = 32.7 Hz), 131.2, 138.8; HRMS(ESI) calcd for $C_{15}H_{11}ClF_4NO_3$ $[M+Cl]^-$: 364.0369, found: 364.0369.

*4.2.3.12. 6-Chloro-1,3,3,4,4,5,5,6,6-nonafluoro-1-nitro-1-phenyl-hexan-2-ol (**5ci**). Syn-isomer*: white solid, Mp 50–52 °C. IR (KBr) ν_{max} 3519, 1581, 1499, 1455, 1362, 1193, 1133, 976, 846, 817, 764, 708, 692, 656 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (d, J = 11.1 Hz, 1H), 5.58 (td, J = 20.7, 11.3 Hz, 1H), 7.45–7.55 (m, 3H), 7.68–7.73 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.7 to −144.9 (m, 1F), −125.3 to −112.3 (m, 6F), −67.9 to −68.2 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.8 (q, J = 25.1 Hz, CHOH), 105–125 (m), 118.3 (d, J = 248.8 Hz, CF), 124.9 (dd, J = 10.1, 2.3 Hz), 129.0 (d, J = 1.9 Hz), 129.4 (dd, J = 22.1, 1.9 Hz), 131.7; HRMS(ESI) calcd for $C_{12}H_7Cl_2F_9NO_3$ $[M+Cl]^-$: 453.9665, found: 453.9687.

Anti-isomer: colorless oil. IR (neat) ν_{max} 3511, 3072, 2924, 1581, 1499, 1455, 1360, 1193, 975, 846, 809, 761, 706, 692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (d, J = 8.1 Hz, 1H), 5.65 (ddd, J = 24.3, 18.0, 8.1 Hz, 1H), 7.45–7.57 (m, 3H), 7.67–7.74 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.8 (td, J = 23.7, 11.5, Hz, 1F), −125.1 to −118.0 (m, 6F), −67.7 (tm, J = 13.2 Hz, 2F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.1 (dt, J = 25.4, 21.2 Hz, CHOH), 105–125 (m), 116.2 (d, J = 251.2 Hz, CF), 125.4 (d, J = 9.7 Hz), 129.2 (d, J = 1.9 Hz), 130.0 (d, J = 22.3 Hz), 131.7 (d, J = 1.0 Hz); HRMS(ESI) calcd for $C_{12}H_7Cl_2F_9NO_3$ $[M+Cl]^-$: 453.9665, found: 453.9687.

*4.2.3.13. 3-(1,3-Dioxolan-2-yl)-2-fluoro-2-nitro-1-(4-nitrophenyl)-propan-1-ol (**5df**). Syn-anti mixture*: white solid, Mp 103–106 °C. IR (KBr) ν_{max} 3396, 3116, 2897, 1576, 1521, 1493, 1416, 1349, 1261, 1141, 1014, 953, 937, 821, 741, 642 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51–2.77 (m, 2H), 3.47 (d, J = 6.0 Hz, 0.6H), 3.83 (d, J = 4.5 Hz, 0.4H), 3.87–4.06 (m, 4H), 5.11 (t, J = 4.8 Hz, 0.6H), 5.24 (t, J = 4.8 Hz, 0.4H), 5.37 (dd, J = 15, 6.0 Hz, 0.6H), 5.41 (dd, J = 18.3, 4.5 Hz, 0.4H), 7.55 (d, J = 8.4 Hz, 0.8H), 7.62 (d, J = 8.4 Hz, 1.2H), 8.20–8.28 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −135.8 (td,

J = 18.3, 13.5 Hz, 0.4F), −136.9 (dt, J = 23.6, 15.3 Hz, 0.6F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1, 65.2, 74.7, 99.1, 120.5, 123.7, 128.6, 141.3, 148.6; HRMS(ESI) calcd for $C_{12}H_{13}ClFN_2O_7$ $[M+Cl]^-$: 351.0395, found: 351.0388.

*4.2.3.14. 2-Fluoro-2-nitro-1-(4-nitrophenyl)pent-4-en-1-ol (**5ef**). Syn-isomer*: white solid, Mp 65–66 °C. IR (KBr) ν_{max} 3374, 3115, 2920, 1607, 1568, 1522, 1434, 1357, 1316, 1240, 1202, 1082, 1053, 1014, 989, 941, 864, 784, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93–3.01 (m, 1H), 3.05–3.21 (m, 2H), 5.21–5.29 (m, 2H), 5.37 (dd, $J_{H,F}$ = 14.4, 3.2 Hz, 1H), 5.63–5.68 (m, 1H), 7.59 (d, J = 8.4 Hz, 2H), 8.22 (d, J = 8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −137.1 (ddd, J = 31.0, 14.4, 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.1 (d, J = 20.5 Hz, CH_2), 74.5 (d, J = 23.2 Hz, CHOH), 120.4 (d, J = 246.2 Hz, CF), 122.8, 126.3 (d, J = 4.2 Hz), 128.7 (d, J = 1.8 Hz), 141.7, 148.6; HRMS(ESI) calcd for $C_{11}H_{11}ClFN_2O_5$ $[M+Cl]^-$: 305.0346, found: 305.0339.

Anti-isomer: white solid, Mp 85–87 °C. IR (KBr) ν_{max} 3508, 3116, 2918, 1605, 1564, 1515, 1426, 1351, 1174, 1144, 1092, 1047, 990, 939, 829, 781, 744, 721 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50–2.59 (m, 1H), 2.86–3.00 (m, 1H), 3.26 (s, 1H), 5.16–5.26 (m, 2H), 5.40 (d, $J_{H,F}$ = 18.0 Hz, 1H), 5.55–5.64 (m, 1H), 7.63 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −144.3 (ddd, J = 31.3, 18.9, 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.1 (d, J = 20.5 Hz, CH_2), 74.5 (d, J = 20.9 Hz, CHOH), 120.7 (d, J = 247.9 Hz, CF), 123.1, 125.8 (d, J = 3.7 Hz), 128.8 (d, J = 1.8 Hz), 142.3, 148.6; HRMS(ESI) calcd for $C_{11}H_{11}ClFN_2O_5$ $[M+Cl]^-$: 305.0346, found: 305.0338.

*4.2.3.15. 2-Fluoro-2-nitro-1-(4-trifluorophenyl)pent-4-en-1-ol (**5eh**). Syn-isomer*: colorless oil. IR (neat) ν_{max} 3546, 3088, 2925, 1646, 1570, 1420, 1326, 1170, 1130, 1069, 1018, 937, 859, 781, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92–3.22 (m, 3H), 5.20–5.33 (m, 3H), 5.60–5.74 (m, 1H), 7.52 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −136.0 (ddd, J = 31.9, 13.3, 8.2 Hz, 1F), −63.1 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.1 (d, J = 20.9 Hz, CH_2), 74.5 (d, J = 23.2 Hz, CHOH), 120.6 (d, J = 247.0 Hz, CF), 122.6 (d, J = 1.0 Hz), 123.7 (q, J = 272.2 Hz, CF_3), 125.5 (q, J = 3.7 Hz), 126.6 (d, J = 4.6 Hz), 128.0 (d, J = 1.9 Hz), 131.6 (q, J = 32.5 Hz), 138.8; HRMS(ESI) calcd for $C_{12}H_{11}ClF_4NO_3$ $[M+Cl]^-$: 328.0369, found: 328.0366.

Anti-isomer: colorless oil. IR (neat) ν_{max} 3543, 3089, 2928, 1645, 1574, 1418, 1326, 1170, 1130, 1069, 1018, 937, 879, 850, 781, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48–2.56 (m, 1H), 2.81–3.00 (m, 2H), 5.15–5.26 (m, 2H), 5.36 (dd, $J_{H,F}$ = 18.0, 6.6 Hz, 1H), 5.54–5.63 (m, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −143.7 (ddd, J = 31.9, 17.8, 7.9 Hz, 1F), −63.3 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5 (d, J = 20.5 Hz, CH_2), 75.3 (d, J = 20.0 Hz, CHOH), 121.0 (d, J = 247.5 Hz, CF), 122.8, 123.7 (q, J = 272 Hz), 125.8 (q, J = 3.7 Hz), 126.0 (d, J = 4.1 Hz), 128.2, 131.8 (q, J = 32.7 Hz), 139.3; HRMS(ESI) calcd for $C_{12}H_{11}ClF_4NO_3$ $[M+Cl]^-$: 328.0369, found: 328.0363.

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References

[1] N. Ono, The Nitro Group in Organic Synthesis, Wiley-VCH, New York, 2001.
[2] J. Boruwa, N. Gogoi, P.P. Saikia, N.C. Barua, Tetrahedron: Asymmetry 17 (2006) 3315–3326.
[3] C. Palomo, M. Oiarbide, A. Laso, Eur. J. Org. Chem. (2007) 2561–2574.
[4] Y. Sohtome, Y. Hashimoto, K. Nagasawa, Adv. Synth. Catal. 347 (2005) 1643–1648.
[5] C. Palomo, M. Oiarbide, A. Mielgo, Angew. Chem. Int. Ed. 43 (2004) 5442–5444.
[6] S. Gao, G. Xi, N. Li, C. Wang, J. Ma, Chin. J. Org. Chem. 30 (2010) 1811–1819.
[7] F.A. Luzzio, Tetrahedron 57 (2001) 915–945.
[8] G. Rosini, R. Ballini, Synthesis (1988) 833–847.
[9] G. Blay, V. Hernández-Olmos, J.R. Pedro, Chem. Commun. (2008) 4840–8482.
[10] R.D. Chambers, Fluorine in Organic Chemistry, Blackwell Publishing Ltd./CRC Press, Boca Raton, FL, 2004.
[11] T. Hiyama, Organofluorine Compounds, Chemistry and Applications, Springer-Verlag, Berlin, 2000.
[12] P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2004.
[13] V.A. Soloshonok, Fluorine-Containing Synthons, ACS Symposium Series 911, Oxford University Press, Washington, DC, 2005.
[14] K. Uneyama, Organofluorine Chemistry, Blackwell Publishing, Oxford, 2006.
[15] K. Muller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886.
[16] M. Schlosser, Angew. Chem. Int. Ed. 37 (1998) 1496–1513.
[17] D. O'Hagan, Chem. Soc. Rev. 37 (2008) 308–319.
[18] S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330.
[19] K.L. Kirk, Org. Process Res. Dev. 12 (2008) 305–321.
[20] D. O'Hagan, J. Fluorine Chem. 131 (2010) 1071–1081.
[21] A.M. Thayer, Chem. Eng. News 84 (2006) 15–24.
[22] J. Ma, D. Cahard, Chem. Rev. 104 (2004) 6119–6146.
[23] A.M.R. Smith, K.K.M. Hii, Chem. Rev. 111 (2011) 1637–1656.
[24] K. Shibatomi, Synthesis (2010) 2679–2702.
[25] M. Bella, T. Gasperi, Synthesis (2009) 1583–1614.
[26] Y. Takeuchi, K. Nagata, T. Koizumi, J. Org. Chem. 52 (1987) 5061–5063.
[27] Y. Takeuchi, K. Nagata, T. Koizumi, J. Org. Chem. 54 (1989) 5453–5459.
[28] H. Cui, P. Li, X. Wang, Z. Chai, Y. Yang, Y. Cai, S. Zhu, G. Zhao, Tetrahedron 67 (2011) 312–317.
[29] R.A. Kunetsky, A.D. Dilman, M.I. Struchkova, P.A. Belyakov, V.A. Tartakovsky, S.L. Ioffe, Synthesis (2006) 2265–2270.
[30] R. Ballini, L. Barboni, G. Giarlo, J. Org. Chem. 69 (2004) 6907–6908.
[31] N. Kornblum, H.O. Larson, R.K. Blackwood, D.D. Mooberry, E.P. Oliveto, G.E. Graham, J. Am. Chem. Soc. 78 (1956) 1497–1501.
[32] W. Peng, J.M. Shreeve, Tetrahedron Lett. 46 (2005) 4905–4909.
[33] P. Butler, B.T. Golding, G. Laval, H.L. Khouzani, R.R. Karimib, M.M. Sadeghib, Tetrahedron 63 (2007) 11160–11166.
[34] *Syn*-isomer (δ_F: −139.2 ppm, d, J_{FH} = 20.6 Hz) was observed but without separation.