Chapter 3

Enantioselective Organocatalytic Direct α-Fluorination of Aldehydes*

Introduction

In the previous chapter, the utility of an asymmetric α-chloroaldehyde as an intermediate in the formation of valuable chiral synthons was discussed. Using the enamine catalysis platform, we felt that other halogen stereocenters such as bromine, iodine, and fluorine could be envisioned as well. We were particularly interested in the possibility of forming fluorine stereocenters due to the lack of direct methods for creating them and their pharmaceutical importance.[1] A key goal of drug design is to prevent rapid degradation and excretion due to unwanted metabolism. While many metabolites are rendered inactive, some may have adverse biological activity making the parent drug unsuitable for human use. Due to its high metabolic stability, the carbon-fluorine bond is widely used as a surrogate for carbon-hydrogen bonds as a method for circumventing unwanted metabolism.[2] Additionally, fluorine atoms provide improved lipohilicity and

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* A patent and communication of this work has been published: (a) Beeson, T. D.; MacMillan, D. W. C. Enantioselective alpha-Fluorination of Aldehydes Using Chiral Organic Catalysts. U.S. Patent 7,265,249, September 4, 2007. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.

[1] Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*, **2004**, *5*, 637.

[2] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

bioavailability of pharmaceuticals in the body due to their electron-withdrawing effect on nearby heteroatoms whose basicities hinder membrane permeability.[3]

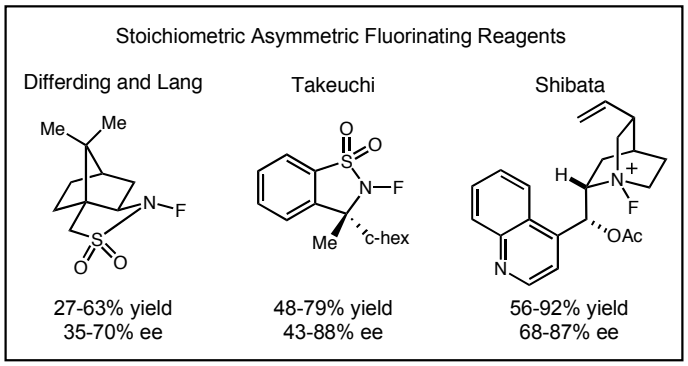

Figure 1. Examples of chiral stoichiometric fluorinating reagents reported in the literature.

It was therefore surprising that at the time of this work, most enantioselective methods for creating asymmetric C-F bonds required the use of stoichiometric amounts of chiral fluorinating agents[4] (Figure 1) and the few known catalytic methods had focused exclusively on highly enolizable substrates such as β-ketoesters and malonates.[5] The first transition metal-catalyzed fluorinations reported by Togni and coworkers using titanium TADDOL complexes[6] had been further developed by Sodeoka using palladium BINAP complexes[7] (equation 1) and Cahard using copper oxazolines[8] to achieve high levels of

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[3] (a) Avdeef, A. *Curr. Top. Med. Chem.* **2001**, *1*, 277. (b) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem.* **2007**, *2*, 1100.

[4] (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708. (c) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N.; *Org. Lett.* **2000**, *2*, 3699. (d) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (e) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.

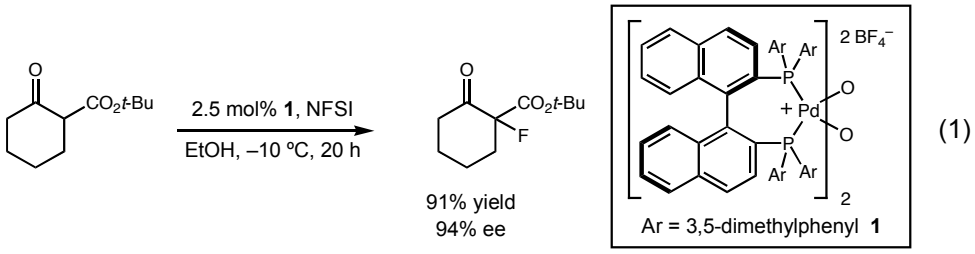
[5] (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.

[6] (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55*, 801.

[7] (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.

[8] Ma, J. A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007.

enantioselectivity for a variety of cyclic and acyclic β-ketoesters. At the same time, Kim and Park demonstrated that phase-transfer catalysis using quaternized cinchona alkaloid derivatives could also effectively induce high levels of enantiocontrol for the fluorination of β-ketoesters (equation 2).[9]



The Enamine Approach to α-Fluorinations

Since catalytic asymmetric fluorinations were limited to highly enolizable substrates that were structurally precluded from product epimerization, we felt that a direct catalytic asymmetric α-fluorination of aldehydes would be a valuable addition to the current methods for generating fluorine stereocenters. Initial studies in our lab performed by postdoctoral fellow Young-Kwan Kim involved the use of 20 mol% of L-proline (Figure 2) as a catalyst and *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorine source (equation 3). Unfortunately, proline was ineffective as a catalyst for the fluorination reaction and very poor conversions were obtained.

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[9] Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.

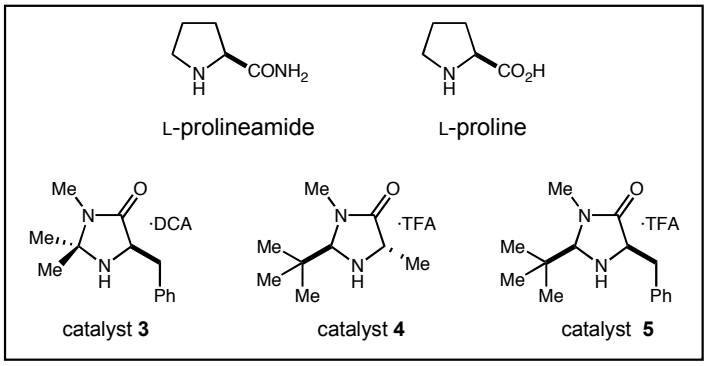
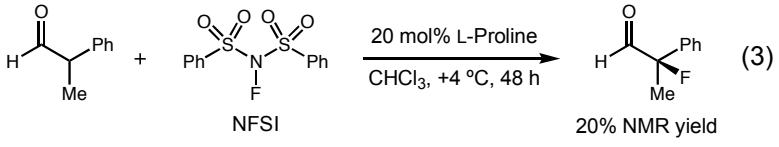
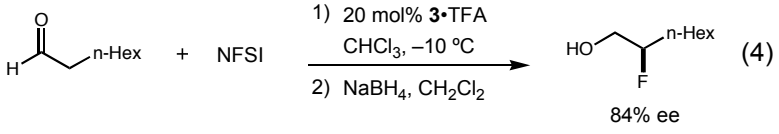


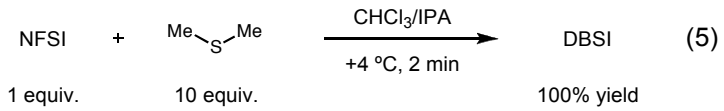
Figure 2. Catalysts for the enantioselective α-fluorination of aldehydes

Subsequently, graduate student Michael Brochu showed that our lab's first-generation imidazolidinone catalyst **3** (Figure 2) could achieve good levels of enantioselectivity (equation 4); however, attempts to isolate the α-fluoroaldehyde products from the residual NFSI were hindered by tedious separations and significant product decomposition. To complicate matters further, attempts at in situ reduction of the sensitive α-fluoroaldehydes were unsuccessful unless all NFSI and its acidic byproduct, dibenzenesulfonimide (DBSI) were first removed, which was accomplished only with difficulty and not reproducibly. For these reasons, it was first necessary to develop a method for the consumption of excess NFSI in the reaction and subsequent removal of the DBSI byproduct.





Interestingly, a report by Umemoto and coworkers in 1986 showed that *N*-fluoropyridinium triflates are able to α-fluorinate sulfides at room temperature.[10] Based on this report, we speculated that if NFSI was capable of reacting with sulfides in the same manner, a volatile sulfide such as dimethylsulfide (DMS) could be used to transform any remaining fluorinating agent into the DBSI byproduct and the resultant fluorosulfide could simply be removed by evaporation. Gratifyingly, when DMS was added to a suspension of NFSI at +4 ºC, an instantaneous exothermic reaction occurred and the NFSI was completely consumed (equation 5). However, the addition of DMS to the α-fluorination reaction in the presence of imidazolidinone catalyst resulted in rapid epimerization of the fluorine stereocenter. On the other hand, it was observed that addition of DMS after removal of the catalyst by filtration had no effect on the stability of the fluoro stereocenter and product enantioselectivities remained stable over 24 hours.



(5)

This observed stereocenter stability led us to wonder whether washing the reactions with a mildly basic sodium bicarbonate solution could remove the acidic DBSI byproduct without epimerizing or decomposing the α-fluoroaldehyde products. Subsequent experiments showed that the α-fluoro stereocenter was indeed stable to the mildly basic conditions, and DBSI could be almost quantitatively removed with two or more bicarbonate washes.

With a successful method for removing excess reagents and reaction byproducts in hand, we began to optimize the reaction conditions by investigating the effect of solvents.

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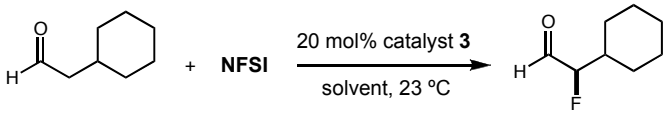
[10] Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625.

As shown in Table 1, solvents such as toluene, CH_2Cl_2, and $CHCl_3$ provided moderate enantioselectivites (entries 1–4), while THF and acetone achieved the highest levels of selectivity (entries 8 and 10). In all cases except isopropanol (IPA), rapid consumption of the α-fluoroaldehyde product to the α,α-difluoroaldehyde was observed, resulting in low conversions of the desired mono-fluorinated product.

Table 1. Survey of Solvents for Aldehyde α-Fluorination



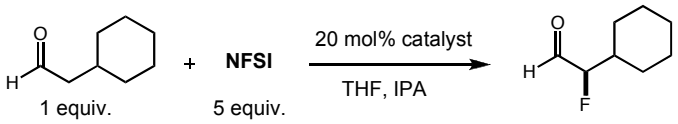
entry	solvent	equiv. NFSI	time (min)	% conv.[a]	% ee[b]
1	Toluene	5	30	46	55
2	CH_3CN	5	30	56	93
3	CH_2Cl_2	5	30	42	62
4	$CHCl_3$	5	60	58	80
5	$CHCl_3$/10% IPA	5	60	70	96
6	$CHCl_3$/10% IPA	3	60	68	91
7	$CHCl_3$/10% IPA	1.2	60	59	82
8	Acetone	5	20	78	96
9	Acetone/10% IPA	5	60	85	97
10	THF	5	5	56	97
11	THF/10% IPA	5	30	75	98
12	IPA	5	360	60	92

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Interestingly, when 10% of IPA was added, difluoroaldehyde production was significantly slowed and enantioselectivities were enhanced (entries 5, 9, 11), presumably due to facile addition of IPA to the highly electrophilic carbonyl of the fluoroaldehyde, forming a hemi-acetal that serves as a protecting group to prevent the product from re-

reacting with the catalyst.[11] The excess of NFSI was also lowered to suppress difluoroaldehyde formation; however, reduced overall conversions and significantly lower enantioselectivities were obtained (entries 5–7). Notably, when the reaction temperature was lowered, significant increases in reaction efficiency were observed at +4 ºC (Table 2, entry 9) and at –10 ºC, complete inhibition of difluoroaldehyde formation was obtained (Table 2, entry 10).

Table 2. Effect of Catalyst and Temperature on the α-Fluorination



entry	catalyst	Temp. (°C)	time	% conversion[a]	% ee[b]
1	L-proline	+23	4 h	76	26
2	L-prolineamide	+23	10 h	46	20
3	**5**	+23	15 min	97	63
3	**4**	+23	7 h	91	94
4	**3**•TfOH	+23	4 h	22	87
5	**3**•HCl	+23	4 h	25	41
6	**3**•TFA	+23	15 min	71	97
7	**3**•TCA	+23	15 min	70	90
8	**3**	+23	30 min	78	98
9	**3**	+4	6 h	97	98
10	**3**	–10	8 h	98	98

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

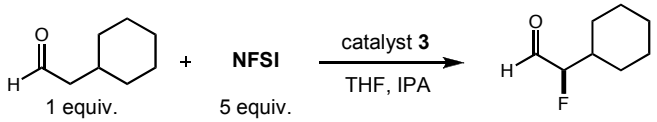
Further, using the optimized solvent conditions we compared catalyst **3** with imidazolidinone catalysts **4** and **5**, as well as L-proline and L-prolineamide (Table 2). While L-proline yielded reasonable levels of conversion under the new reaction conditions, the stereoselectivity remained low (entry 1). Catalyst **5** reacted very rapidly to excellent

[11] Other additives such as ethanol, methanol, and water had the same effect but required much longer reaction times and resulted in slightly lower enantioselectivities.

levels of conversion but yielded only moderate selectivity at this temperature (entry 3). While good levels of conversion and selectivity were achieved with catalyst **4** (entry 4), prolonged reaction times were required. Although imidazolidinone catalysts **4** and **5** could both be applied in this fluorination protocol, we pursued further optimization with catalyst **3** due to its low cost and ease of synthesis.

Subsequently, various co-catalysts were also analyzed. As shown in Table 2, dichloroacetic acid (DCA) and trifluoroacetic acid (TFA) salts of catalyst **3** were optimal for both reaction efficiency and enantioselectivity (entries 4–8). Additionally, catalyst loadings were evaluated to determine if lesser amounts of catalyst would reduce the preponderance for difluorination and allow reactions to be performed at ambient temperature (Table 3). Notably, catalyst loadings as low as 1 mol% achieved excellent levels of enantioselectivity and conversion. However, even with only 1 mol% of catalyst, difluorination was never fully inhibited at room temperature and conversions slowly decreased with time.

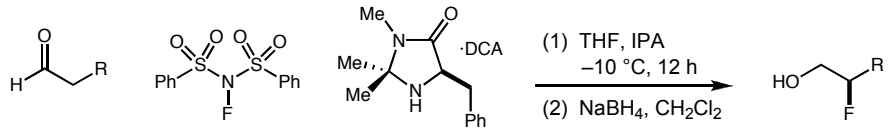
Table 3. Effect of Catalyst Loading on the α-Fluorination



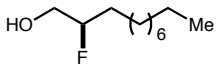
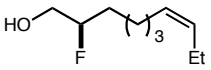
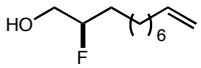
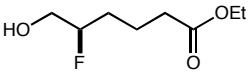
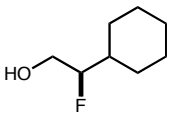
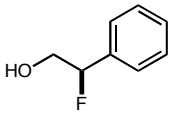
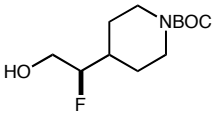
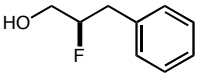
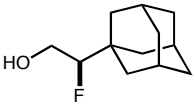
entry	mol% catalyst	Temp °C	time	% conv.[a]	% ee[b]
1	20	+23	30 min	74	98
2	20	–10	8 h	98	98
3	10	+23	1 h	77	98
4	10	+4	8 h	97	98
5	5	+23	3 h	79	98
6	5	+4	25 h	95	98
7	2.5	+23	6 h	77	98
8	1	+23	24 h	83	98

(a) Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). (b) Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Table 4. Enantioselective α-Fluorination: Substrate Scope



1 equiv. 5 equiv. 20 mol% **3** product

entry	product	% yield	% ee[a]	entry	product	% yield	% ee[a]
1		70	94	3		81	94
2		79	94	4		77	91
entry	product	% yield	% ee[a]	entry	product	% yield	% ee[a]
5		96	99	7		55	99
6		85	98	8		78	96
				9		82	98

(a) Entries 1–4, 6 and 9 enantiomeric excess determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel® OJ). Entries 5, 7 and 8 enantiomeric excess determined by chiral GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

Lastly, the generality of the reaction was studied and a variety of aldehyde substrates were chosen to determine the effect of sterics and functional group compatibility. As shown in Table 4, olefinic aldehydes were successfully α-fluorinated without isomerization of the double bond configuration (entries 2–3). Although NFSI is susceptible to electrophilic aromatic substitution,[12] aromatic substrates were also obtained in good yields with excellent enantioselectivities (entries 7–8). The acid-labile *tert*-butoxycarbonyl

[12] Differding, E.; Ofner, H. *Synlett* **1991**, 187.

(BOC) nitrogen protecting group was also unaffected by the acidic reaction conditions (entry 6). Surprisingly, there was no difference in reaction times between substrates of differing steric demands (entries 5–9), with even the highly hindered adamantyl acetaldehyde reacting in 12 hours to give excellent results for the α-fluoroaldehyde product (entry 9).

Conclusion

In summary, development of the direct and enantioselective α-fluorination of aldehydes has been described using an inexpensive and easily prepared imidazolidinone catalyst and NFSI as the fluorinating source.[13,14] The mild reaction conditions have allowed the α-fluorination of a wide variety of structures and functionalities, including those of high steric demand and catalyst loadings as low as 1 mol% were capable of inducing high yields and enantioselectivities. It is our hope that this new methodology for creating fluorine stereocenters will open the door for practitioners of pharmaceutical synthesis to pursue structural diversifications that have until now been inaccessible.

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[13] After submission of this work for publication, the following papers appeared in the literature also describing the enantioselective organocatalyzed α-fluorination of aldehydes: (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991. (b) Marigo, M.; Fielenbach, D. I.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

[14] For reviews on recent advances in the field of asymmetric fluorination see: (a) Brunet, V. A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179. (b) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469. (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544. (d) Prakash, G. K. S.; Beier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172. (e) Bobbio, C.; Gouberneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[15] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on EMD Silica Gel 60 230-400 mesh or Davisil® Silica Gel 200-425 mesh according to the method of Still.[16] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using potassium permanganate stain. High performance liquid chromatography (HPLC) and gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Varian Mercury 300 (300 MHz, 75 MHz and 282 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass

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[15] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd edition; Pergamon Press; Oxford, 1988.

[16] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 Series chromatograph using a Chiralcel® OJ column (25 cm, 5 cm guard) as noted.

General Procedure for the α-Fluorination of Aldehydes: To a 25 mL round-bottom flask equipped with a magnetic stir bar and charged with **1** (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (139 mg, 0.400 mmol) and *N*-fluorobenzenesulfonimide (3.15 g, 10.0 mmol) was added THF (9.0 mL) and IPA (1.0 mL). The mixture was stirred at rt until homogeneous then cooled to –10 °C. The aldehyde substrate (2.0 mmol) was added and the reaction mixture stirred 12 h. The reaction was cooled to –78 ºC, diluted with 10 mL Et_2O and filtered through a pad of Davisil® Silica Gel, eluting with Et_2O. Me_2S (5.0 mL) was added forming a white precipitate. The resulting mixture was washed with sat. $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (12 mL) and EtOH (8 mL), and $NaBH_4$ (189 mg, 5.0 mmol) was added. After 30 min the reaction was cooled to 0 ºC and sat. NH_4Cl (150 mL) was added. The mixture was warmed to rt and stirred vigorously 1 h. The cloudy suspension was allowed to separate and 75 mL of CH_2Cl_2 was added. The solution was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics washed with sat. $NaHCO_3$ (3 × 150 mL) and brine (1 × 150 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Purification of the resulting oil by forced flow chromatography afforded the title compounds. The enantioselectivity was determined either by chiral GLC analysis, or chiral HPLC analysis after acylation of the alcohol with 2-naphthoylchloride.

Starting Materials

Ethyl 5-formylpentanoate: To a flask containing ethyl 6-hydroxyhexanoate (4.07 mL, 25.0 mmol) in CH_2Cl_2 (25 mL) was added TEMPO (391 mg, 2.50 mmol) followed by iodobenzene diacetate (8.86 g, 27.5 mmol). The reaction was stirred 2 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20-40% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[17]

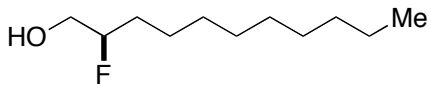
***tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate:** To a flask containing *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (4.4 g, 19.2 mmol) in CH_2Cl_2 (20 mL) was added TEMPO (300 mg, 1.92 mmol) followed by iodobenzene diacetate (6.8 g, 21.1 mmol). The reaction was stirred 3 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150

[17] Taber, D. F.; Teng, D. *J. Org. Chem.* **2002**, *67*, 1607.

mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (40–70% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[18] ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 154.7, 79.4, 50.3, 43.7, 31.9, 30.6, 28.4.

Adamantylacetaldehyde: To a flask containing 2-adamantyl-1-ethanol (5 g, 27.7 mmol) in CH_2Cl_2 (28 mL) was added TEMPO (433 mg, 2.77 mmol) followed by iodobenzene diacetate (9.8 g, 30.5 mmol). The reaction was stirred 1 h and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was added and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et_2O/pentanes) to provide the title compound, which was identical to the reported literature compound.[19]

α-Fluoro Alcohols



(*R*)-2-Fluoro-1-undecanol (Table 4, entry 1): Prepared according to the general procedure from undecanal (411 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-fluoro-1-undecanol as a colorless solid

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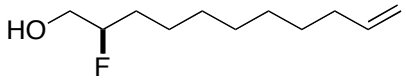
[18] Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747.

[19] Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(261 mg, 70% yield, 94% ee). IR (film) 3271 3171, 2954, 2914, 2848, 1470, 1071, 842.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$). δ 4.56 (dm, *J* = 46.8 Hz, 1H, FC**H**), δ 3.59–3.77 (m, 2H, OC$\mathbf{H_2}$), δ 1.89 (s, 1H, -O**H**), 1.20–1.78 (m, 16H, (C$\mathbf{H_2}$)$_\mathbf{8}$), δ 0.88 (t, *J* = 6.9 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 96.3 (d, *J* = 166.3 Hz), 65.1 (d, *J* = 21.3 Hz), 31.9, 30.9 (d, *J* = 20.3 Hz), 29.5, 29.4 (d, *J* = 3 Hz), 29.3, 24.9, 24.9, 22.7, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{11}H_{22}FO$) requires *m/z* 189.1655, found *m/z* 189.1660. $[\alpha]_D$ = 7.6 (c = 1.0, $CHCl_3$).[20] Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 11.4 min. t_R(minor) = 15.0 min.



(*R*)-2-Fluoroundec-10-en-1-ol (Table 4, entry 2): Prepared according to the general procedure from undec-10-enal (416 μL, 2.00 mmol) to afford a colorless oil. Purification on Davisil® silica gel (10–20% EtOAc/Pentanes) afforded (*R*)-2-fluoroundec-10-en-1-ol as a colorless solid (296 mg, 79% yield, 94% ee). IR (film) 3214, 2918, 2848, 1641, 1460, 1348, 1073, 990.7, 914.2, 837.8, 806.0, 757.8, 724.4, 668.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$). δ 5.74–5.87 (m, 1H, $CH_2C\mathbf{H}=CH_2$), δ 4.90–5.03 (m, 2H, $CH_2CH=C\mathbf{H_2}$), δ 4.57 (dm, 1H, *J* = 50.7 Hz, FC**H**); δ 3.60–3.80 (m, 2H, OC$\mathbf{H_2}$), δ 2.03 (q, 2H, *J* = 14.1, and 7.5 Hz, C$\mathbf{H_2}$CH=CH_2), δ 1.83 (t, 1H, *J* = 6.6 Hz, -O**H**), δ 1.26–1.76 (m, 12H, FCH(C$\mathbf{H_2}$)$_\mathbf{6}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 139.1, 114.2, 94.8 (d, *J* = 166.5 Hz), 65.1 (d, *J* = 21.8 Hz), 31.7, 30.9 (d, *J* = 20.0 Hz), 29.3, 29.3, 29.0, 28.8, 24.9 (d, *J* =

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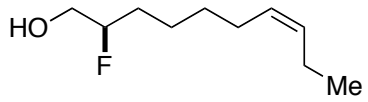
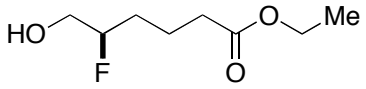
[20] $[\alpha]_D$ = -8.6 (c = 2.0, Et_2O) for (*S*)-2-fluoro-1-decanol and $[\alpha]_D$ = -7.2 (c = 2.0, Et_2O) for (*S*)-2-fluoro-1-dodecanol. Nohira, H.; Kamei, M.; Nakamura, S.; Yoshinaga, K.; Kai, M. JPN Patent 62093248, **1987**.

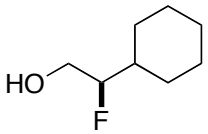
3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{21}FO$) requires *m/z* 188.1576, found *m/z* 188.1575. $[\alpha]_D$ = 8.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 15.7 min. t_R(minor) = 22.7 min.



(*R*)-(*Z*)-2-Fluorodec-7-en-1-ol (Table 4, entry 3): Prepared according to the general procedure from (*Z*)-dec-7-enal (366 μL, 2.00 mmol) to afford a yellow oil. Purification on silica gel (5–20% EtOAc/Pentanes) afforded (*R*)-(*Z*)-2-fluorodec-7-en-1-ol as a pale yellow liquid (283 mg, 81% yield, 94% ee). IR (film) 3369, 3006, 2935, 2861, 1462, 1376, 1172, 1056, 843.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26–5.42 (m, 2H, $CH_2C\mathbf{H}=\mathbf{H}CCH_2$), δ 4.56 (dm, 1H, *J* = 50.5 Hz, FC**H**), δ 3.62–3.76 (m, 2H, O$\mathbf{CH_2}$), δ 1.98–2.10 (m, 4H, $\mathbf{CH_2}CH=HC\mathbf{CH_2}$), δ 1.89 (t, 1H, *J* = 6.4 Hz, -O**H**), δ 1.32–1.74 (m, 6H, $CFH(\mathbf{CH_2})_3$), δ 0.95 (t, 3H, *J* = 7.4 Hz, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.0, 128.7, 94.7 (d, *J* = 166.5 Hz), 65.1 (d, *J* = 21.3 Hz), 30.9 (d, *J* = 20.0 Hz), 29.5, 26.8, 24.5 (d, *J* = 5.0 Hz), 20.5, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –189.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{10}H_{19}FO$) requires *m/z* 174.1420, found *m/z* 174.1421. $[\alpha]_D$ = 5.6 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 0.5% IPA/Hexanes). t_R(major) = 32.2 min. t_R(minor) = 51.9 min.

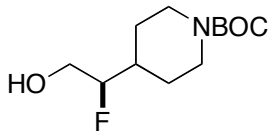


(*R*)-Ethyl 5-fluoro-6-hydroxyhexanoate (Table 4, entry 4): Prepared according to the general procedure from ethyl 5-formylpentanoate (319 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (20–40% EtOAc/Pentanes) afforded (*R*)-ethyl 5-fluoro-6-hydroxyhexanoate as a colorless liquid (274 mg, 77% yield, 91% ee). IR (film) 3436, 2942, 1733, 1453, 1376, 1165, 1096, 1065, 1035, 849.9, 772.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (dm, 1H, *J* = 49.4, FC**H**), δ 4.12 (q, 2H, *J* = 7.2 Hz, $CO_2C\mathbf{H_2}$), δ 3.60–3.78 (m, 2H, $OC\mathbf{H_2}$), δ 2.34 (t, 2H, *J* = 7.0 Hz, $C\mathbf{H_2}CO_2$), δ 2.04 (s, 1H, -O**H**), δ 1.50–1.88 (m, 4H, $CFH(C\mathbf{H_2})_2$), δ 1.24 (t, 3H, *J* = 7.2 Hz, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 94.2 (d, *J* = 167.3 Hz), 64.8 (d, *J* = 21.7 Hz), 60.4, 33.8, 30.2 (d, *J* = 20.6 Hz), 20.4 (d, *J* = 5.0 Hz), 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –190.3 (m). HRMS (EI+) exact mass calculated for $[M+H]^+$ ($C_8H_{16}FO_3$) requires *m/z* 179.1084, found *m/z* 179.1083. $[\alpha]_D$ = 5.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 10% EtOH/Hexanes). t_R(major) = 47.7 min. t_R(minor) = 68.7 min.



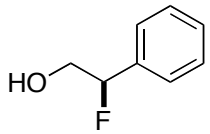
(*R*)-2-Cyclohexyl-2-fluoro-1-ethanol (Table 4, entry 5): Prepared according to the general procedure from 2-cyclohexyl-1-ethanol (291 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-cyclohexyl-2-fluoro-1-ethanol as a colorless liquid (282 mg, 96% yield, 99% ee). IR

(film) 3369, 2928, 2854, 1450, 1091, 1074, 1058, 1024, 977.7, 891.8, 858.9, 837.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (dm, 1H, *J* = 49.2 Hz, FC**H**), δ 3.68–3.81 (m, 2H, OC$\mathbf{H_2}$), δ 1.83–1.94 (m, 2H, C$\mathbf{H_2}$), δ 1.56–1.84 (m, 5H, (C$\mathbf{H_2}$)$_2$ and O**H**), δ 0.99–1.34 (m, 5H, (C$\mathbf{H_2}$)$_2$ and CFHC**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 98.4 (d, *J* = 168.3 Hz), 63.2 (d, *J* = 26.2 Hz), 30.2 (d, *J* = 19.1 Hz), 28.1 (dd, *J* = 22.7, 6.0 Hz), 26.1, 25.7 (d, *J* = 12.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.7 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_8H_{15}FO$) requires *m/z* 146.1107, found *m/z* 146.1101. $[\alpha]_D$ = –0.26 (c = 1.0, EtOH). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (100 °C isotherm); (*R*) isomer t_r = 79.9 min and (*S*) isomer t_r = 88.8 min.



(*R*)-*tert*-Butyl 4-(1-fluoro-2-hydroxyethyl)piperidine-1-carboxylate (Table 4, entry 6): Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate (455 mg, 2.00 mmol) to afford a colorless oil. Purification on silica gel (25–50% EtOAc/Pentanes) afforded (*R*)-*tert*-Butyl 4-(1-fluoro-2-hydroxyethyl)piperidine-1-carboxylate as a colorless oil (422 mg, 85% yield, 98% ee). IR (film) 3430, 2930, 1692, 1671, 1427, 1365, 1283, 1241, 1170, 1084, 1040, 971.6, 940.0, 857.2, 770.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06–4.40 (m, 3H, N(C$\mathbf{H_a}$CH$_b$)$_2$, and FC**H**), δ 3.69–3.83 (m, 2H, OC$\mathbf{H_2}$), δ 2.68 (br m, 2H, N(CH$_a$C$\mathbf{H_b}$)$_2$), δ 2.01 (t, 1H, *J* = 6.0 Hz, -O**H**), δ 1.80–1.87 (m, 2H, (C$\mathbf{H_a}$CH$_b$CH$_2$)$_2$N), δ 1.51–1.67 (m, 1H, CHFC**H**), δ 1.44 (s, 9H, (C$\mathbf{H_3}$)$_3$), δ 1.22–1.32 (m, 2H, (CH$_a$C$\mathbf{H_b}$CH$_2$)$_2$N); ^{13}C NMR (75 MHz,

$CDCl_3$) δ: 154.7, 97.3 (d, *J* = 170.0 Hz), 79.5, 62.8 (d, *J* = 22.0 Hz), 60.4, 37.1 (d, *J* = 19.7 Hz), 28.4, 27.3, 27.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.5 (bs). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{22}FNO_3$) requires *m/z* 247.1584, found *m/z* 247.1587. $[\alpha]_D$ = 3.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 10% EtOH/Hexanes). t_R(major) = 28.3 min. t_R(minor) = 41.1 min.



(*R*)-2-Fluoro-2-phenyl-1-ethanol (Table 4, entry 7): Prepared according to the general procedure from phenylacetaldehyde (234 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–50% Et_2O/Pentanes) afforded (*R*)-2-fluoro-2-phenyl-1-ethanol as a colorless liquid (152 mg, 54% yield, 99% ee), which matched literature data.[21] IR (film) 3369, 1496, 1454, 1078, 1043, 877.9, 834.2, 757.3, 698.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H, $C_6\mathbf{H_5}$), δ 5.57 (ddd, 1H, *J* = 48.9, 7.7, and 5.2 Hz, FC**H**), δ 3.73–4.01 (m, 2H, OC$\mathbf{H_2}$), δ 2.18 (dd, 1H, -O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.3 (d, *J* = 19.6 Hz), 128.8 (d, *J* = 2.0 Hz), 128.6, 125.7 (d, *J* = 6.9 Hz), 94.8 (d, *J* = 170.9 Hz), 66.6 (d, *J* = 24.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –187.0 (ddd, *J* = 12.8, 7.6, 4.5 Hz). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ (C_8H_9FO) requires *m/z* 140.0637, found *m/z* 140.0636. $[\alpha]_D$ = 47.9 (c = 1.0, $CHCl_3$). Reported rotation for the *S*-

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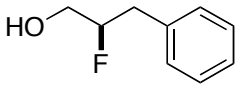
[21] Watanabe, S.; Fujita, T.; Usui, Y. *J. Fluorine Chem.* **1986**, *31*, 247.

enantiomer $[\alpha]_D = -52.5$ (c = 1.1, $CHCl_3$).[22] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (110 °C isotherm); (*R*) isomer t_r = 57.1 min and (*S*) isomer t_r = 59.4 min.



(*R*)-2-Fluoro-3-phenyl-1-propanol (Table 4, entry 8): Prepared according to the general procedure from hydrocinnamaldehyde (263 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (10–40% Et_2O/Pentanes) afforded (*R*)-2-fluoro-3-phenyl-1-propanol as a colorless liquid (218 mg, 71% yield, 96% ee), which matched literature data.[23] IR (film) 3369, 3029, 2932, 1497, 1455, 1052, 904.3, 835.6, 745.7, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.36 (m, 5H, $C_6\mathbf{H_5}$), δ 4.78 (dm, 1H, *J* = 48.6 Hz, FC**H**), δ 3.60–3.85 (m, 2H, OC$\mathbf{H_2}$), δ 2.87–3.10 (m, 2H, PhC$\mathbf{H_2}$), δ 1.97 (t, 1H, *J* = 6.1 Hz, -O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.3 (d, *J* = 6.0 Hz), 129.3, 128.6, 126.8, 95.6 (d, *J* = 170.6 Hz), 64.1 (d, *J* = 21.3 Hz), 37.4 (d, *J* = 20.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –187.6 (m). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_9H_{11}FO$) requires *m/z* 154.0794, found *m/z* 194.0797. $[\alpha]_D = 16.7$ (c = 1.0, $CHCl_3$). Reported rotation for the *S*-enantiomer $[\alpha]_D = -17.6$ (c = 1.7, $CHCl_3$).[23] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C isotherm); (*R*) isomer t_r = 76.1 min and (*S*) isomer t_r = 84.3 min.

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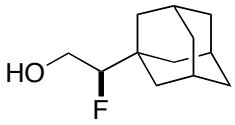
[22] Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.

[23] Takeuchi, Y.; Nagata, K.; Koizumi, T. *J. Org. Chem.* **1989**, *54*, 5453.



(*R*)-2-Adamantyl-2-fluoro-1-ethanol (Table 4, entry 9): Prepared according to the general procedure from adamantylacetaldehyde (334 μL, 2.00 mmol) to afford a colorless oil. Purification on silica gel (5–20% EtOAc/Pentanes) afforded (*R*)-2-adamantyl-2-fluoro-1-ethanol as a colorless solid (326 mg, 82% yield, 98% ee). IR (film) 3306, 2903, 2850, 1451, 1348, 1087, 1058, 1028, 989.3, 859.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (ddd, 1H, *J* = 49.7, 7.8, and 5.1 Hz, FC**H**), δ 3.62–3.88 (m, 2H, OC$\mathbf{H_2}$), δ 1.99 (s, 3H, C**H**$(CH_2)_3$) δ 1.54–1.84 (m, 13H, -O**H**, (C$\mathbf{H_2}$)$_6$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 101.8 (d, *J* = 170.3 Hz), 61.3 (d, *J* = 22.3 Hz), 37.7 (d, *J* = 4.1 Hz), 36.9, 35.4 (d, *J* = 19.6 Hz), 27.9 (*J* = 0.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –203.1 (ddd, *J* = 48.5, 34.2, 17.2 Hz). HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{19}FO$) requires *m/z* 198.1420, found *m/z* 198.1417. $[\alpha]_D$ = –9.5 (c = 1.0, $CHCl_3$). Enantiopurity was determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel®OJ Isocratic 3% IPA/Hexanes). t_R(major) = 20.8 min. t_R(minor) = 26.5 min.