Efficient Asymmetric Synthesis of β-Fluoro α-Amino Acids

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The ability of a strategically placed fluorine to enhance biological properties is well estabilizhed.[1,2] In this regard β-fluoro α-amino acids **1** are of particular significance because they have been shown to exhibit diverse biological properties including antibacterial, antihypertensive, and antitumor activities.[3] They act as metabolic antagonists to naturally occurring α-amino acids,[4] as competitive inhibitors of enzymes,[5] and as suicide substrates.[6] Consequently, a number of syntheses of β-fluoro α-amino acids have been devised involving fluorodehydroxylation of β-hydroxy α-amino acids,[7] ring-opening of aziridines,[8] reductive amination of β-fluoro-α-keto acids,[9] and others.[10] Unfortunately, the majority of these procedures are lengthy, racemic syntheses that usually result in mixtures of stereoisomers that are difficult to separate. Furthermore, conversion of intermediates to the free amino acids frequently results in defluorination. The one asymmetric synthesis of 3-fluorophenylalanine, where Schollkopf's bis lactim ether strategy was employed, resulted in low overall yields and mixtures of products.[11] Our interest in the asymmetric synthesis of α-fluoro carbonyl building blocks[12,13] and in the sulfinimine (*N*-sulfinyl imine)-mediated asymmetric Strecker synthesis[14] prompted studies aimed at the development of a general protocol for the asymmetric synthesis of β-fluoro α-amino acids.

Our strategy for the synthesis of nonracemic β-fluoro α-amino acids is outlined in Scheme 1. Hydrolysis of the β-fluoro α-amino nitrile **2** will afford the amino acid **1**. The β-fluoro α-amino nitrile is obtained by "HCN" addition to α-fluoro sulfinimine **3**, which in turn is prepared from a nonracemic α-fluoro aldehyde **4** and a chiral sulfinamide. We needed the *N*-sulfinyl group in the imine to control the introduction of cyanide because our earlier studies had indicated that fluorine is a poor stereodirecting group.[13b] Furthermore, not only is the *N*-sulfinyl group a powerful stereodirecting group, but it is easily deprotected in the product under mild conditions without epimerization.[15] This new protocol is illustrated for the enantioselective synthesis of *syn*- and *anti*-3-fluorophenylalanine (**11a** and **15**) and *syn*-3-fluoroleucine (**11b**).

The α-fluoro aldehydes (*S*)-**7** were prepared using the oxazolidone α-fluoro amide building blocks **5a** and **5b**, prepared by electrophilic fluorination of the corresponding oxazolidone sodium enolates with *N*-fluorobenzenesulfonimide (NFSi).[13a] Reductive removal of the auxiliary with $LiBH_4$ afforded the 2-fluorohydrins (*S*)-**6** in 79−84% yield and recovery of the oxazolidone auxiliary in >90% (Scheme 2).[13d] The fluorohydrins were isolated by flash chromatography, and their enantiomeric purity was determined by conversion into the Mosher esters.

Racemic α-fluoro aldehydes are characterized as unstable compounds that generally decompose on purification.[12,16] Previously, we prepared (*R*)-(−)-2-fluorophenylacetaldehyde (**7a**) by Dess−Martin periodinane[17] oxidation of the (*R*)-**6a** in 95% yield and 90% ee.[13b] The enantiomeric purity was very sensitive to the reaction conditions with oxidation times longer than 10 min resulting in significant epimerization. Addition of (*S*)-**6** (typically 3.0 mmol) to 1.6 equiv of the Dess−Martin reagent at room temperature in CH_2Cl_2 for 5−7 min produced (*S*)-(+)-**7a** and (*S*)-(−)-**7b** in 90 and 98% crude yield. Workup consisted of dilution with ether, addition of saturated solutions of $NaHCO_3$ and $Na_2S_2O_3$, stirring until the organic phase was colorless, and drying. The enantiomeric purities of (*S*)-(+)-**7a** and (*S*)-(−)-**7b** were estimated to be 80 and >95%, respectively, by forming the diaster-

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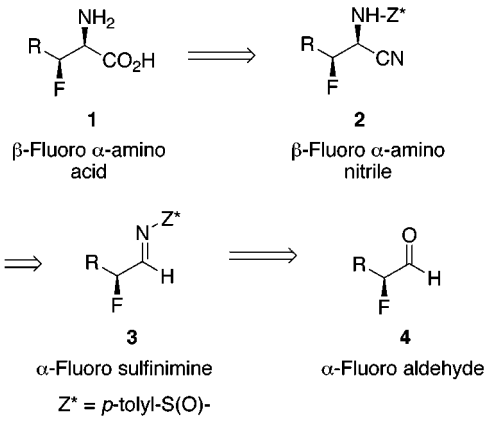
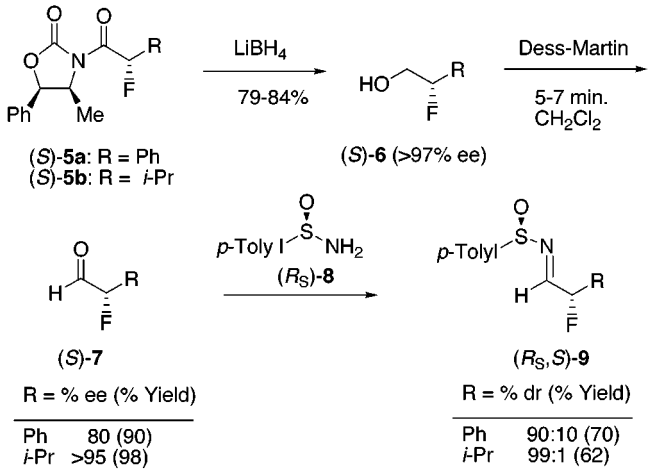
Scheme 1



Scheme 2



eomeric imines with (*R*)-α-phenylethylamine and immediately evaluating the ^{1}H NMR spectrum. Within 2 h, these α-fluoro imines had racemized. Attempts to purify **7** by chromatography resulted in decomposition, and it was used in crude form to prepare the α-fluoro sulfinimines. (*R*)-(−)-*N*-[2(*S*)-fluorophenylacetylidene]-*p*-toluenesulfinamide (**9a**) and (*R*)-(+)-*N*-[2(*S*)-fluoroisovalerylidene]-*p*-toluenesulfinamide (**9b**) were prepared by stirring **7a** and **7b** in CH_2Cl_2 with 1 equiv of (*R*)-(−)-*p*-toluenesulfinamide (**8**)[18] and activated 4 Å molecular sieves. Sulfinimines **9a** and **9b** were isolated in 70 and 62% yield by chromatography (Scheme 2).[19] The diastereomeric ratios were 80 and >95% for **9a** and **9b**, respectively, which is in excellent agreement with the ratios obtained using the more basic (*R*)-α-phenylethylamine.

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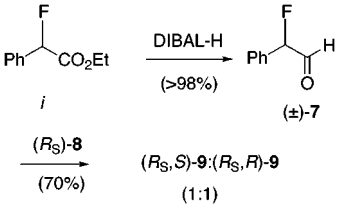
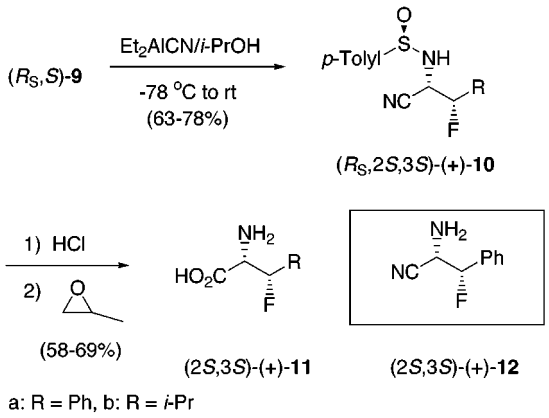
(19) An alternative route to **9** involving the resolution of racemic **7** with (R_S)-**8** was briefly explored. DIBAL-H reduction of 2-fluoroethyl phenylacetate (*i*), prepared in 82% yield by electrophilic fluorination of the sodium enolate of ethyl phenylacetate with NFSi, gave a nearly quantitative yield of (±)-**7**. Treatment of (±)-**7** with (R_S)-**8** afforded a 1:1 mixture of (R_S,*S*)-**9**/(R_S,*R*)-**9** in 70% yield. A tedious chromatography (EtOAc/*n*-hexane 2:98) produced a 48% yield of (R_S,*S*)-(−)-**9**.



Scheme 3



The sulfinimine-mediated asymmetric Strecker synthesis involves the addition of ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN], generated in situ by addition of *i*-PrOH to diethylaluminum cyanide (Et_2AlCN), to the sulfinimine.[20] Treatment of sulfinimines **9** (1.0 mmol) at −78 °C in THF with 1.5/1.0 equiv of Et_2AlCN/*i*-PrOH gave the β-fluoro α-amino nitriles **10a** and **10b** in 78 and >96% de by ^{19}F NMR (Scheme 3). Flash chromatography gave the major diastereoisomers (R_S,*S*,*S*)-(+)-**10a** and (R_S,*S*,*S*)-(+)-**10b** in 78 and 63% isolated yields. Refluxing the amino nitriles with 6 N HCl for 3−5 h, removal of the aqueous solvent, washing with ether, and treating the residue with propylene oxide/*i*-PrOH afforded *syn*-(2*S*,3*S*)-(+)-3-fluorophenylalanine (**11a**) and *syn*-(2*S*,3*S*)-(+)-3-fluoroleucine (**11b**) in 69 and 58% isolated yields, respectively. When the hydrolysis of **10a** was conducted under biphasic conditions by stirring with 5 mL of 1 N HCl and 5 mL of CH_2Cl_2 for 2 h at room temperature, (2*S*,3*S*)-(+)-2-amino-3-fluoro-3-phenylpropionitrile (**12**) was isolated in ca. 20% yield following washing with ether and treatment with propylene oxide/*i*-PrOH.

The configurational assignments for syn and anti β-fluoro α-amino acids have proven difficult and were originally made based on reaction sequences for nonfluorinated compounds.[3] More recently, X-ray analysis[9a] and crown ether complexation studies of the ammonium group have been utilized.[20] The $^3J_{HH}$ and $^3J_{HF}$ proton coupling constants of 6.6 and 14.3 Hz for **11a** and 2.2 and 28.2 Hz for **11b** agrees well with literature values suggested for racemic *syn*-**11a** (3.3 and 16 Hz)[9a] and *syn*-**11b** (2.2 and 25.6 Hz).[10b] Furthermore, the X-ray structure of α-amino nitrile (+)-**12** firmly establishes the syn nature of the fluorine and amino groups (Figure 1). As expected, fluorine has little if any effect on the stereoselective introduction of "CN" and the primary stereocontrol element is the sulfinyl auxiliary.

The fact that the sulfinyl group controls addition of CN to **9** means that the corresponding anti β-fluoro α-amino acids can be prepared simply by starting with the opposite enantiomeric fluoro aldehyde or sulfinamide. This is illustrated in Scheme 4 for the enantioselective synthesis of *anti*-(2*S*,3*R*)-(−)-3-fluorophenylalanine (**15**). The α-fluoro sulfinimine (R_S,*R*)-**13** was prepared in the usual way from (*R*)-**7**[13b] and (*R*)-**8** in 80% yield, which was converted into a diastereomeric mixture of amino nitriles **14** (80% de). It is interesting to note that the

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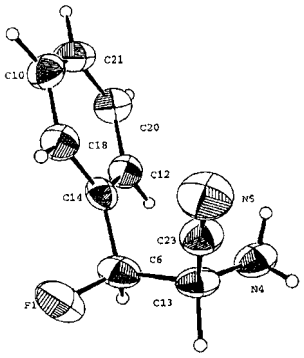
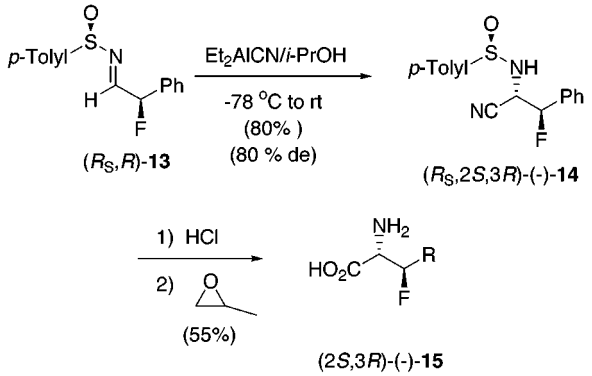


Figure 1. X-ray structure of (2*S*,3*S*)-(+)-**12**.

Scheme 4



diastereoselectivity for CN addition to (*R*$_S$,*S*)-**9a** and (*R*$_S$,*R*)-**14** are the same, suggesting the absence of any cooperating or double diastereodifferentiating effect. The major diastereoisomer was isolated by flash chromatography in 80% yield and hydrolyzed to give *anti*-(2*S*,3*R*)-(−)-**15** in 55% yield. The $^3J_{HH}$ and $^3J_{HF}$ proton coupling constants of 3.0 and 26.4 Hz are in good agreement with literature values.[9a]

In summary, new methodology is presented for the asymmetric synthesis of *syn*- and *anti*-*β*-fluoro α-amino acids involving the sulfinimine mediated asymmetric Strecker synthesis employing a new α-fluoro sulfinimine building block.

Experimental Section

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 microns) purchased from Analtech Inc. TLC plates were visualized with UV, in an iodine chamber or with phosphomolybdic acid unless noted otherwise. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone.

Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. (*S*)-(+)-2-Fluoro-2-phenylethanol (**6a**),[13d] (*R*)-(−)-2-fluorophenylacetaldehyde (**7a**),[13b] and (*R*)-(+)-*p*-toluenesulfinamide (**8**)[18] were prepared as previously described.

Preparation of (4*S*,5*R*)-(−)-3-(1′-Oxoisovaleryl)-4-methyl-5-phenyloxazolidin-2-one. In an oven-dried, two-neck 500 mL round-bottom flask equipped with a rubber septum, magnetic stir bar, under argon, were placed (4*S*,5*R*)-(−)-4-methyl-5-phenyloxazolidine-2-one (8.85 g, 50 mmol, Aldrich Chemical Co.) in THF (120 mL). The solution was cooled to −78 °C, *n*-BuLi (24 mL, 60 mmol, 2.5 M, 1.2 equiv) was added, and the mixture was stirred for 1 h. A solution of isovaleryl chloride (6.6 mL, 55 mmol) in THF (10 mL) was added, and after 3 h, the reaction mixture was quenched with NH_4Cl (120 mL), extracted with EtOAc (3 × 50 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. The solid was and crystallized from EtOAc\hexane to give 8.6 g (65%): mp 34 °C; $[\alpha]^{23}_D$ −32.46 (*c* 1.3, CH_2Cl_2); IR (KBr) 1778, 1701, 1462 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.9 (d, *J* = 6.6 Hz, 3H), 1.0 (2d, *J* = 6.6 Hz, 6H), 2.2 (m, 1H), 2.9 (2dd, *J* = 7, 16 Hz, 2H), 4.8 (q, *J* = 7 Hz, 1H), 5.7 (d, *J* = 7.3 Hz, 1H), 7.3−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 14.07, 22.2, 22.3, 24.9, 43.8, 54.4, 78.6, 125.3, 128.5, 128.6, 133.4, 152.8, 172.1. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.32; N, 5.35. Found: C, 69.60; H, 7.64; N, 5.18.

(4*S*,5*R*)-(−)-3-(1′-Oxo-2′(*S*)-fluoroisovaleryl)-4-methyl-5-phenyloxazolidin-2-one (5b). In an oven-dried 250 mL two-neck round-bottom flask equipped with a rubber septum and magnetic stir bar, and under an argon balloon was placed (4*S*,5*R*)-(−)-3-(1′-oxoisovaleryl)-4-methyl-5-phenyloxazolidin-2-one (4.95 g, 19 mmol) in THF (15 mL). The solution was cooled to −78 °C, and NaHMDS (21.0 mL, 21.0 mmol THF solution) in THF was added dropwise. After being stirred for 1.5 h, the enolate was cannulated to a −78 °C of *N*-fluorobenzenesulfonimide (NFSi, 6.0 g, 19 mmol) in THF (30 mL) and stirred for 1 h. The reaction mixture was quenched with NH_4Cl (25 mL), extracted with EtOAc (3 × 15 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/hexane 8:92) gave 4.0 g (76%) of (−)-**5b** as a thick gel: $[\alpha]^{23}_D$ −19.5 (*c* 0.63, $CHCl_3$); IR (NaCl) 1782, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.9 (d, *J* = 6.6 Hz, 3H), 1.0 (d, *J* = 6.6 Hz, 3H), 1.2 (d, *J* = 6.5 Hz, 3H), 2.3 (m, 1H), 4.7 (q, *J* = 7.0 Hz, 1H), 5.7 (d, *J* = 7.3 Hz, 1H), 5.8 (dd, *J* = 3.0, 49.5 Hz, 1H), 7.3 (d, *J* = 7.3 Hz, 2H), 7.4 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 14.2, 15.2, 18.9, 30.6 (d, *J* = 22 Hz), 55.2, 79.8, 92.5 (d, *J* = 183 Hz), 125.5, 128.7, 128.9, 132.6, 152.4, 169.1 (d, *J* = 24.4 Hz); ^{19}F NMR *δ* −206.7 (dd, *J* = 24.4, 48.8 Hz); HRMS calcd for $C_{15}H_{18}NO_3F$ (M + H) 280.134896, found 280.134716.

Preparation of (*S*)-(−)-2-Fluoroisovaleryl-1-ol (6b). In an oven-dried, two-neck 250 mL round-bottom flask fitted with a magnetic stir bar, rubber septum and argon balloon, was placed (−)-**5b** (3.9 g, 14 mmol) in THF (30 mL). The reaction flask was cooled to 0 °C and $LiBH_4$ (2 M, 8.5 mL, 17 mmol) in THF was added via syringe. The reaction mixture was stirred until TLC indicated the reaction was complete (2−3 h) at which time the reaction mixture was quenched with H_2O (20 mL), extracted with EtOAc (3 × 15 mL), dried (Mg_2SO_4), and concentrated. Chromatography (EtOAc/hexane 15:85) followed by distillation (bp 144 °C at 760 mm) gave 1.2 g (79%) of (−)-**6b**: $[\alpha]^{23}_D$ −35.04 (*c* 2.2, $CHCl_3$); IR (NaCl) 3649−3061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.95 (d, *J* = 6.6 Hz, 3H), 1.0 (d, *J* = 6.6 Hz, 3H), 1.9 (m, 2H), 3.75 (dd, *J* = 4.4, 24.9 Hz, 2H), 4.6 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 17.4, 18.1, 29.2 (d, *J* = 20 Hz), 63.1 (d, *J* = 22.4 Hz), 99 (d, *J* = 170.9 Hz); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) *δ* −194.0 (m); CIMS for Mosher amide calcd $C_{15}H_{18}O_3F_4$ 322.0 (M + H), found 322.0.

Typical Procedure for the Preparation of α-Fluoro Aldehydes. (*S*)-(+)-2-Fluorophenylacetaldehyde (7a). In an oven-dried, one-neck 250 mL round-bottom flask fitted with a magnetic stir bar, rubber septum, and an argon balloon was placed 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess−Martin periodine reagent)[17] (2.0 g, 4.8 mmol) in CH_2Cl_2 (30 mL). After stirring at room temperature for 5 min a solution **6a** (0.420 g, 3 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was stirred for 5−7 min. At this time, the solution was diluted with ether (40 mL), saturated $NaHCO_3$ (20 mL) and saturated $Na_2S_2O_3$ (20 mL) were added, and the reaction mixture was stirred until the ether phase became clear (10 min). The organic phases were washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried (Mg_2SO_4), and concentrated to give 0.41 g (90%) of **7a**, which was used in the next reaction without further purification due to its instability: IR (NaCl) 1705 cm^{-1}; $[\alpha]^{23}_D$ 42.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 5.7 (d, *J* = 46 Hz, 1 H), 7.3−7.5 (m, 5 H), 9.78 (d, *J* = 4 Hz).

(*S*)-(−)-2-Fluoroisovaleryl aldehyde (7b): 98% (crude); $[\alpha]^{23}_D$ −23.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 0.95 (d, *J* = 6.3 Hz, 3 H), 1.0 (d, *J* = 6.3 Hz, 3 H), 1.95 (m, 1H), 3.75 (dd, *J* = 26 Hz, 4.1 Hz, 1H), 9.75 (d, *J* = 4.3 Hz, 1H).

Method for Estimated the Enantiomeric Purity of the α-Fluoro Aldehydes. To a dilute solution of the α-fluoro aldehyde in $CDCl_3$ (1 mL) in an NMR tube was added a few drops of a dilute solution of (*R*)-α-phenyl ethylamine in $CDCl_3$

(1 mL). After 5 min the % de was determined by integration of the Me proton in the ^{1}H NMR spectra of the imine.

Typical Procedure for the Preparation α-Fluorosulfinimines. (*R*$_S$)-(−)-*N*-(2(*S*)-Fluorophenylacetylidene)-*p*-toluenesulfinamide (9a). In a 100 mL round-bottom flask, fitted with a magnetic stir bar and calcium chloride tube, was placed crude (*S*)-(+)-**7a** (0.276 g, 2 mmol) in CH_2Cl_2 (20 mL). Activated (crushed) 4 Å molecular sieves (1.0 g) and (*R*)-(+)-*p*-toluenesulfinamide (**8**) (0.31 g, 2 mmol) in CH_2Cl_2 (5 mL) were added, and the reaction mixture was stirred at room temperature for 6−8 h. The solution was filtered and concentrated. Chromatography (EtOAc/hexane 10:90) afforded 0.380 g (69%) of (−)-**9a**: mp 91 °C; $[\alpha]^{23}_D$ −331.5 (*c* 0.38, CH_2Cl_2); IR (KBr) 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.68 (s, 3H), 5.50 (dd, J = 4.0, 47.0 Hz, 1H), 6.56−6.67 (m, 7H), 6.78 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 4.0, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 92.8 (d, J = 181 Hz), 124.6, 126.3, 126.4, 128.9, 129.5, 129.8, 134.3, 141.3, 162 (d, J = 30.5 Hz); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −180.6 (dd, J = 9, 45.7 Hz). Anal. Calcd for $C_{15}H_{14}NOSF$: C, 65.31; H, 5.11; N, 5.07. Found: C, 65.30; H, 4.94; N, 4.77.

(*R*s)-(−)-*N*-(2(*R*)-Fluorophenylacetylidene)-*p*-toluenesulfinamide (13). Chromatography (EtOAc/hexane 10:90) afforded 0.400 g (72%) of (−)-**13**: mp 64 °C; $[\alpha]^{23}_D$ −153.2 (*c* 2, $CHCl_3$); IR (KBr) 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39 (s, 3H), 6.11 (dd, J = 4.0, 47.2 Hz, 1H), 7.26−7.39 (m, 7H), 7.48 (d, J = 8 Hz, 2H), 8.31 (dd, J = 4.0, 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1, 93.5 (d, J = 179 Hz), 125.3, 127.0, 127.1, 129.6, 130.2, 130.5, 134.8 (d, J = 20 Hz), 142.8, 162.6 (d, J = 28.5 Hz); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −183.40 (dd, J = 9.2, 45.8 Hz). Anal. Calcd for $C_{15}H_{14}NOSF$: C, 65.31; H, 5.10; N, 5.07. Found: C, 65.29; H, 4.69; N, 4.86.

(*R*$_S$)-(+)-*N*-(2(*S*)-Fluoroisovalerylidene)-*p*-toluenesulfinamide (9b). Chromatography (EtOAc/hexane 3:97) afforded 0.570 g (62%) of (+)-**12**: oil; $[\alpha]^{23}_D$ 209.8 (*c* 0.8, $CHCl_3$); IR (NaCl) 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.0 (2d, J = 7 Hz, 6H), 2.2 (m, 1H), 2.42 (s, 3H), 5.0 (ddd, J = 3.6, 4.8, 49.8 Hz, 1H), 7.3 (d, J = 8.4 Hz, 2H), 7.5 (d, J = 8.4 Hz, 2H), 8.25 (dd, J = 3.7, 11.0 Hz, 1H); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ -(197.35−197.55, m). The compound was found to be unstable and attempts to obtain a satisfactory elemental analysis or HRMS failed.

Typical Procedure for the Addition of EtAlCN/*i*-PrOH to the α-Fluorosulfinimines. (*R*$_S$)-(+)-2-[*N*-(*p*-Toluenesulfinamido)]-3-(*S*)-fluoro-3-phenylpropionitrile (10a). In an oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar and an argon balloon was placed the (*R*$_S$,*S*)-(−)-**9a** (0.275 g, 1.0 mmol) in THF (10 mL) and cooled to −78 °C. In a separate two-neck round-bottom flask equipped with a magnetic stir bar, an argon balloon, was placed diethylaluminum cyanide (1.5 mL, 1.5 mmol) and *i*-PrOH (0.1 mL). The reaction mixture was stirred for 15 min at 10 °C and was cannulated to the solution of **9a**. After being stirred at −78 °C for 15 min, the solution was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (2 × 10 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), concentrated. Chromatography (EtOAc/hexane 12:88) afford 0.235 g (78%) of (+)-**10** as an oil: $[\alpha]^{23}_D$ 14.0 (*c* 0.5, CH_2Cl_2); IR (NaCl) 3445−2733, 2249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.4 (s, 3H), 4.5−4.7 (m, 2H), 5.7 (dd, J = 5.5, 44.7 Hz, 1H), 7.3−7.6 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1, 47.9 (d, J = 34.0 Hz), 92.5 (d, J = 193.6 Hz), 116.2, 126.6, 126.8, 127.6, 129.6, 130.8, 133.6 (d, J = 21.3 Hz), 139.6, 143.3; ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −177.7 (dd, J = 10, 43 Hz). Anal. Calcd for $C_{16}H_{15}FN_2OS$: C, 63.55; H, 5.00; N, 9.26. Found: C, 63.48; H, 4.94; N, 9.05.

(*R*$_S$)-(+)-2-[*N*-(*p*-Toluenesulfinamido)]-3(*S*)-fluoroisohexanonitrile (10b). Chromatography (EtOAc/hexane 10:90) afforded 0.170 g (63%) of (+)-**10b**: mp 126 °C; $[\alpha]^{23}_D$ 67.0 (*c* 0.45, CH_2Cl_2); IR (KBr) 3588−2870, 2167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (d, J = 7.0 Hz, 3H), 1.0 (d, J = 7.0 Hz, 3H), 2.0 (m, 1H), 2.4 (s, 3H), 4.2−4.4 (m, 2H), 5.25 (d, J = 8.8 Hz, 1H), 7.3 (d, J = 8 Hz, 2H), 7.6 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.3, 18.6, 21.4, 30.3 (d, J = 19 Hz), 44.2 (d, J = 20 Hz), 98.9 (d, J = 183 Hz), 115.3, 126.1, 130.2, 139.0, 142.5; ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −(193.14−193.34, m). Anal. Calcd for $C_{13}H_{17}N_2OSF$: C, 58.18; H, 6.38; N, 10.43. Found: C, 57.99; H, 6. 27; N, 10.23.

(*R*$_S$)-(−)-2-[*N*-(*p*-Toluenesulfinamido)]-3*(R)*-fluoro-3-phenylpropionitrile (14). Chromatography (EtOAc/hexane 15:85) afforded 0.242 g (80%) of (−)-**14**: mp 121 °C; $[\alpha]^{23}_D$ −25.29 (*c* 0.85, $CHCl_3$); IR (KBr) 3445−2874, 2249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3H), 4. 20−4.28 (m, 1H), 5.35 (d, J = 9.73 Hz, 1H), 5.8 (dd, J = 2.57, 45 8 Hz, 1H), 7.30−7.41 (m, 7H), 7.60 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 48.5 (d, J = 24.4 Hz), 94.3 (d, J = 183.1 Hz), 114.5, 125.4, 126.2, 128.9, 129.8, 130.2, 133.5 (d, J = 20.4 Hz), 139.0, 142.7. HRMS calcd for $C_{16}H_{15}N_2OSF$ (M + H) 330.30967, found 303.0966 (M + H).

Preparation of (2*S*,3*S*)-(+)-β-Fluorophenylpropionitrile (12). In a 50 mL round-bottom flask equipped with a magnetic stir bar were placed **10a** (0.150 g, 0.5 mmol) in CH_2Cl_2 (5 mL) and 1 N HCl (5 mL). The solution was stirred at room temperature for 2−3 h, the aqueous phase was separated and concentrated, and the resulting solid was treated with *i*-PrOH (2 mL) and propylene oxide (0.058 g, 1 mmol). After being stirred for 5−6 h, the solution was concentrated to give 0.017 g (20%) of (+)-**12**: mp 118 °C; $[\alpha]^{23}_D$ 34.4 (*c* 1.2, $CHCl_3$); IR (KBr) 3750−3000, 2347 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58−1.61 (bs, 2H), 4.17 (dd, J = 5.0, 12.5 Hz, 1H), 5.54 (dd, J = 5.0, 45 Hz, 1H), 7.45 (s, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.6 (d, J = 29 Hz), 93.8 (d, J = 179 Hz), 126.2, 126.3, 128.7, 129.8, 133.8 (d, J = 19 Hz); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −184.5 (dd, J = 12.2, 45.8 Hz).

General Procedure for the Hydrolysis of the α-Amino Nitriles. (2*S*,3*S*)-(+)-3-Fluorophenylalanine (11a). In a single-neck 25 mL round-bottom flask were placed **10a** (0.302 g, 1 mmol) and 6 N HCl (20 mL), and the solution was refluxed for 3−5 h. The aqueous phase was washed with ether (2 × 10 mL), and the aqueous solution was concentrated. The solid was treated with *i*-PrOH (5 mL) and propylene oxide (0.232 g, 4 mmol), and the solution was stirred for 5−6 h. At this time, the reaction mixture was concentrated and the product was crystallized from 2-propanol to give 0.125 g (68%) of **11a**: mp 170 °C (lit.[9a] 168−169 °C); $[\alpha]^{23}_D$ 8.4 (*c* 0.5, H_2O); IR (KBr) 3570−2350 (bs), 1650−1540 cm^{-1}; ^{1}H NMR (D_2O, 500 MHz) δ 5.1 (dd, J = 6.6, 14.3 Hz), 6.1 (dd, J = 6.9, 45.5 Hz, 1H), 7.5 (s, 5H); ^{19}F NMR ($CFCl_3$ in D_2O) −179.5 (dd, J = 13.7, 45.8 Hz).

(2*S*,3*R*)-(−)-3-Fluorophenylalanine (15): yield 0.06 g (55%); mp 149−150 °C (lit.[9a] mp 150−152 °C); $[\alpha]^{23}_D$ −14.5 (*c* 0.4, MeOH); IR (KBr) 3570−2350 (bs), 1650−1540 (3s) cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 5.1 (dd, J = 3.0, 26.4 Hz, 1H), 6.0 (dd, J = 2.6, 46 Hz, 1H), 7.5 (s, 5H); ^{19}F NMR ($CFCl_3$ in CD_3OD) δ −184.5 (dd, J = 27.4, 48.5 Hz).

(2*S*,3*R*)-(+)-3-Fluoroleucine (11b): yield 0.055 g (58%); mp 160−161 °C (dec) (lit.[10b] 162−163 °C (dec)); $[\alpha]^{23}_D$ 10.4 (*c* 1, H_2O); IR (KBr) 3650−2600, 1639, 1508 cm $^{-1}$; ^{1}H NMR (D_2O, 500 MHz) δ 0.9 (d, J = 6.9 Hz, 3H), 1.1 (d, J = 6.6 Hz, 3H), 2.28 (m, 1H), 4.55 (ddd, J = 1.8, 9.5, 47.6 Hz, 1H), 4.93 (dd, J = 2.2, 28.2 Hz, 1H); ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −(189.58−189.76, m).

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Supporting Information Available: IR and ^{1}H and ^{13}C NMR spectra of **5b**, **6b**, **7a**,**b**, **12**, and **14** and X-ray crystal data for (+)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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