Applications of the Sulfinimine-Mediated Asymmetric Strecker Synthesis to the Synthesis of α-Alkyl α-Amino Acids

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Addition of Et_2AlCN and *i*-PrOH to ketosulfinimines (*N*-sulfinyl imines) affords corresponding α-alkyl α-amino nitriles in moderate to good yields. The diastereoselectivity is largely dependent on the *E*/*Z* isomer ratio of the ketosulfinimine. Hydrolysis of the diastereomerically pure amino nitriles affords enantiopure α-alkyl α-amino acids in moderate to good yields.

The high level of interest in α-alkylated α-amino acids[1] stems from their biological stability,[2] their utility in studies of enzyme mechanisms,[3] and their use as enzyme inhibitors.[4] Furthermore, once incorporated into peptides, these amino acids influence the conformation of the protein, thereby altering its properties.[5] One method developed for the enantioselective syntheses of the α-alkylated α-amino acids[1c] is the alkylation of chiral nonracemic enolates derived from β-lactams,[6] bis-lactims,[7] oxazinones,[8] imidazolidinones,[9] oxazaborolidinone,[10] and alanine dianions.[11] Several other methods, such as the ring-opening of aziridine carboxylate esters,[12] have also been used to prepare these amino acids.[13,14]

Application of the asymmetric Strecker synthesis to the synthesis of α-alklylate α-amino acids has generally involved the addition of "HCN" to optically active aryl methyl ketoimines and has had limited success because of the poor de's and problematic removal of the chiral auxiliary (Scheme 1).[15,16] Vachal and Jacobsen recently described the asymmetric hydrocyanation of prochiral ketoimines in a process that utilizes a resin-bound chiral catalyst and which afforded α-amino nitriles with good to excellent ee's.[17] However, even with these encouraging results, the diastereoselective Strecker synthesis, which uses stoichiometric chiral auxiliaries, is still of value when the ee's of the catalytic system are modest and/or cannot be easily upgraded. In this context we report our studies of the application of the sulfinimine (*N*-sulfinyl imine)-mediated asymmetric Strecker synthesis to the preparation of α-alklylate α-amino acids.

The sulfinimine-mediated asymmetric Strecker synthesis involves the addition of ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN] to a sulfinimine **2** (Scheme 2).[18] The [EtAl(O-*i*-Pr)CN] reagent is generated in situ by addition of *i*-PrOH to diethylaluminum cyanide (Et_2-AlCN). With aldimines **2** (R^2 = H), cyanide addition is highly diastereoselective (85−95%), and simple crystal-

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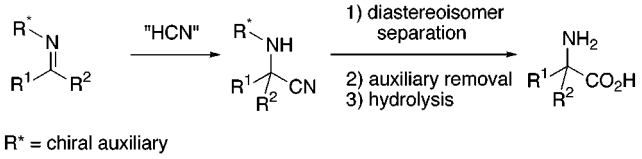
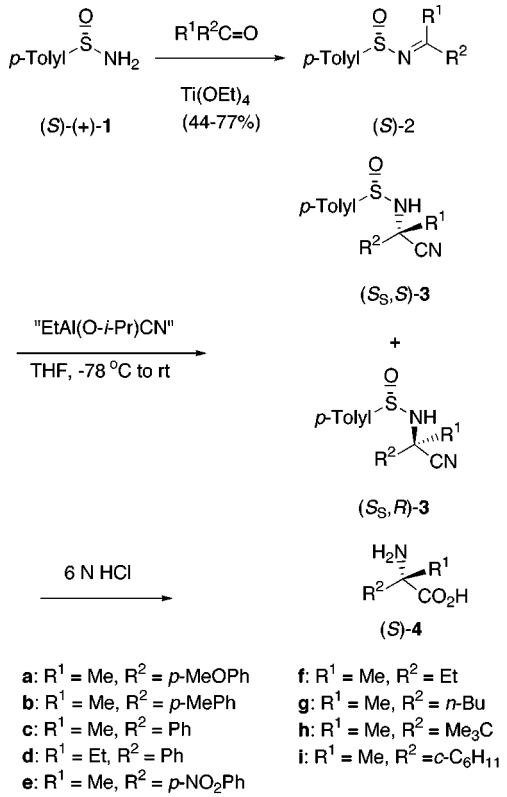
Scheme 1



Scheme 2



lization or chromatography affords the diastereomerically pure α-amino nitriles **3**. Acid-catalyzed hydrolysis of the diastereomerically pure 3 not only removes the sulfinyl auxiliary, but also hydrolyzes the nitrile, which furnishes the enantiomerically pure (>95%) α-amino acids **4**. This methodology has been used in efficient asymmetric syntheses of *β*-fluoro-[19] and *β*-hydroxy α-amino acids,[20] (2*R*,3*S*)-alloisoleucine,[21] the bis(α-amino acids) (2*S*,6*S*)- and *meso*-(2*R*,6*S*)-diaminopimelic acid,[22] and (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine, the central amino acid of vancomycin.[23] Importantly, racemization, even of sensitive aryl glycines, was not detected.

Ketosulfinimines (S_S)-**2** were prepared, as previously described, by condensing commercially available (*S*)-(+)-*p*-toluenesulfinamide (**1**) with the appropriate ketones in the presence of 5 equiv of $Ti(OEt)_4$ for 18 h (Scheme 2).[24,25] Yields were moderate to good (Table 1). The methyl aryl sulfinimines **2a**−**c**, **2e**, and the methyl *tert*-butyl and methyl cyclohexyl sulfinimines **2h** and **2i** were isolated as single *E*-isomers. Sulfinimines derived from propiophenone, 2-butanone, and 2-hexanone, **2d**, **2f**, and **2g**, respectively, were isolated as inseparable mixtures of isomers (Table 1). Generally there is a low barrier to planar inversion in ketone-derived sulfinimines (14−17 kcal/mol), and if the size difference of R^1 versus R^2 in the ketone is not sufficiently large, isomeric mixtures are obtained.[26]

Ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN] was prepared by treatment of 1.5 equiv of diethylaluminum cyanide with 1.0 equiv of *i*-PrOH and added to a −78 °C solution of the sulfinimine **2** (Scheme 1). The reaction mixture was warmed to room temperature, stirred for 10−18 h, and quenched at −78 °C by addition of aqueous NH_4Cl solution. The diastereomerically pure amino nitriles **3** were obtained by flash chromatography (Table 1).

As observed in earlier studies the configuration of the sulfinyl group controls cyanide addition: Re-face addition to (*S*)-**2** gives amino nitrile (S_S,S)-**3** as the major diastereoisomer as was confirmed by conversion to the corresponding amino acids (see below). For sulfinimines derived from methyl aryl **2a**−**c**, **2e**, or methyl alkyl ketones **2h**, **2i** that have exclusively the *E*-geometry, the de's ranged from 60 to 98% (Table 1). No particular pattern was observed for aryl groups having an electron-withdrawing or -donating group (Table 1: compare entries 1 and 5). To eliminate the possibility that the amino nitriles **3** are equilibrating under the reaction conditions diastereomerically pure (+)-**3b** was treated with [EtAl(O-*i*-Pr)CN] for 10 h. The fact that **3b** was isolated in 97% yield with >98% de strongly suggests that cyanide addition to the C−N double bond in sulfinimines is kinetically controlled.

The diastereoselective addition of "CN" to sulfinimines **2d**, **2f,** and **2g**, which exist as mixtures of *E*:*Z* isomers, was low and ranged from 12 to 50% (Table 1: entries 4, 6, and 7). This is because "CN" addition to each of the isomers is expected to give the corresponding amino nitrile with opposite stereochemistry. The de's of 50% for **2f** (derived from 2-butanone) and **2g** (derived from 2-hexanone) are in line with the 4:1 and 3:1 isomer ratios, respectively, for the sulfinimines. The lowest de, 12%, was observed for **2d** (derived from propiophenone) which is undergoing slow *E*/*Z* isomerization at room temperature as indicated by the broad and unresolved protons of the ethyl group (sulfinimine **2d**, Table 1). At −20 °C, ^{1}H NMR indicates **2d** exists as a single *E* isomer. However, when the temperature of "CN" addition to **2d** was held at −30 to −20 °C for 14 h and quenched at this temperature, there was no improvement in the de.

To determine the effect of a bulkier sulfinyl group on the diastereoselectivity, [EtAl(O-*i*-Pr)CN] was added to *tert*-butanesulfinyl ketimines (*R*)-(−)-**5a**[27] and (*R*)-(−)-**5b** (Scheme 3). Sulfinimine (*R*)-(−)-**5a**, which exists as a

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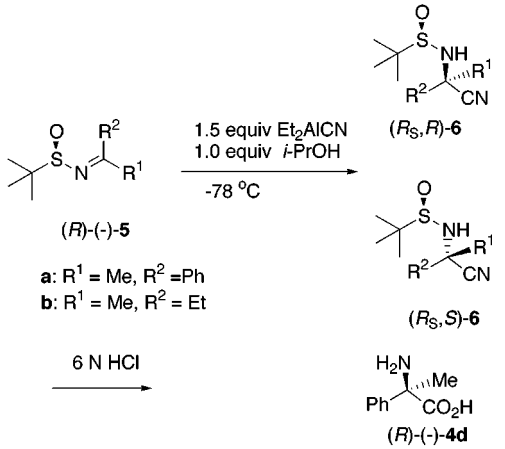
Table 1. Addition of Et_2AlCN/*i*-PrOH to Sulfinimines (*S*)-2 and (*R*)-5

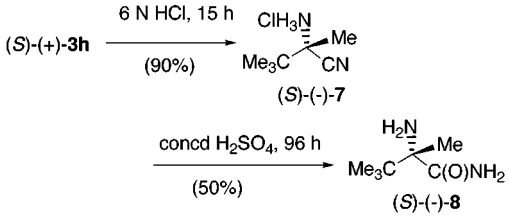
	sulfinimine **2** and **5**				products		
entry		R^1	R^2	(*E*:*Z*)	amino nitriles **3** and **6** (S_S,*S*):(S_S,*R*) (% de)[a]	% yield of major diastereisomer	α-amino acid (*S*)-**4** % isolated yield
1	(*S*)-**2a** (*p*-tolyl)	Me	*p*-MeOPh	(>99:1)	9:1 (80)	60	54
2	**2b**	Me	*p*-MePh	(>99:1)	83:17 (64)	60	64
3	**2c**	Me	Ph	(>99:1)	4:1 (60)	77	67
4	**2d**	Et	Ph	*b*	56:44 (12)	*c*	
5	**2e**	Me	*p*-NO_2Ph	(>99:1)	95:5 (90)	93	53
6	**2f**	Me	Et	(4:1)	3:1 (50)	49	69
7	**2g**	Me	n-Bu	(3:1)	3:1 (50)	50	54
8	**2h**	Me	Me_3C	(>99:1)	99:1 (98)	95	50[d]
9	**2i**	Me	*c*-C_6H_{11}	(>99:1)	85:15 (70)	72	48
10	(*R*)-**5a** (*t*-Bu)	Me	Ph	(>99:1)	(R_S,*R*):(R_S,*S*)-**6** 12:1 (84)	56[e]	(*R*)-**4c** 64
11	(*R*)-**5b**	Me	Et	(6.5:1)	(R_S,*R*):(R_S,*S*)-**6** 83:17 (64)	*c*	

[a] NMR of the crude mixture. [b] Sulfinimine **2d** and **5b** undergo slow *E*/*Z* isomerization at room temperature. [c] Could not be separated by flashchromatography. [d] α-Amino amide (*S*)-**8** was isolated. [e] Obtained by crystallization.

Scheme 3



Scheme 4



single isomer, gave the corresponding amino nitrile **6a** in 84% de (entry 10). A lower de, 64% was observed for (*R*)-(−)-**5b** which is consistent with the 6.5:1 isomer ratio (entry 11). While the diastereomeric amino nitriles of **3** were usually readily separated by flash chromatography, it was not possible to separate **6a**,**b** in a similar manner. However, crystallization of **6a** afforded the major diastereoisomer (R_S*R*)-(−)-**6a** in 57% yield (entry 10), but crystallization was not possible for **6b** which exists as an oil.

Hydrolysis of (S_S,*S*)-**3** and (R_S,*R*)-(−)-**6** was easily accomplished by refluxing with 6 N HCl for 15 h. Extraction with ether, to remove the sulfinic acids, and isolation by ion exchange chromatography (DOWEX 50) afforded the corresponding amino acids in moderate to good yields (Table 1). Because the diastereomeric purity of the amino nitriles was >95% and shown earlier not to undergo epimerization under these conditions enantiomeric purity of the amino acids **4** is also >95%. The enantiomeric purity was further confirmed by comparison of optical rotations with literature values and by making the Mosher amides.

Attempts to hydrolyze the *N*-sulfinyl *tert*-butyl amino nitrile **3h** to the amino acid failed. Under the standard conditions, refluxing with 6 N HCl for 15 h, the sulfinyl group was efficiently removed to give amino nitrile (*S*)-(−)-**7** in 90% yield (Scheme 4). On treating **7** with concd H_2SO_4 for 96 h, α-amino amide (*S*)-(−)-**8** was obtained in 50% yield. All other attempted conditions failed to hydrolyze the amide to the acid. This results is undoubtedly due to steric inhibition of hydrolysis by the bulky *tert*-butyl group.

In summary, the application of the sulfinimine-mediated asymmetric Strecker synthesis, using *N*-sulfinyl ketimines, to the enantioselective synthesis of α-alkyl α-amino acids was demonstrated.

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 μm) 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 argon from a purple solution of sodium and benzophenone.

Unless otherwise stated, all reagents were purchased from commercial sources and used without additional purification. Sulfinimines (*S*)-**2c**,[24a] (*S*)-**2g**,[24a] and (*R*)-**5a**[27] were prepared according to literature procedures.

(*S*)-(+)-*N*-α-Methyl-(4-methylbenzylidene)-*p*-toluenesulfinamide (2a). Typical Procedure. In an oven-dried 25 mL single-necked round-bottom flask equipped with a magnetic stirring bar and a condenser were placed (*S*)-(+)-*p*-toluenesulfinamide (**1**)[24] (0.16 g, 1.0 mmol) and 4′-methylacetophenone (0.67 g, 5.0 mmol) in CH_2Cl_2 (10 mL). Titanium(IV) ethoxide (2.1 mL, 10 mmol) was added, and the reaction mixture was refluxed for 18 h and cooled to 0 °C, H_2O (10 mL) was added, and the solution was filtered through Celite. The phases were separated, and the organic phase was washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc:hexane, 20:80) afforded 0.18 g (65%) of (+)-**2**: mp 104−105 °C; $[\alpha]^{20}_D$ 117 (*c* 1.2, $CHCl_3$); IR (KBr) 3033, 1589, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.40 (s, 3H), 2.72 (s, 3H), 7.20 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.0, 21.3, 125.1, 127.4, 129.0, 129.7, 135.3, 141.6, 142.4, 143.4, 173.8. Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16. Found: C, 70.75; H, 6.39; N, 5.12.

(*S*)-(+)-*N*-α-Methyl-(4-methoxybenzylidene)-*p*-toluenesulfinamide (2a): yield 53%, flash chromatography (EtOAc:hexane, 20:80); mp 91.5−92.5 °C; $[\alpha]^{20}_D$ 145.0 (*c* 1.0, $CHCl_3$); IR (KBr) 1588, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.73 (s, 3H), 3.83 (s, 3H), 6.88 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 7.7 Hz, 2H), 7.89 (d, J = 8.4 Hz,

2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.9, 54.9, 113.3, 124.7, 129.1, 129.3, 130.1, 142.2, 143.4, 162.3, 173.0. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 67.27; H, 5.98; N, 4.71.

[*S*-(*E*/*Z*)]-(+)-*N*-α-Ethylbenzylidene-*p*-toluenesulfinamide (2d): yield 54%, flash chromatography (EtOAc:hexane, 20:80); yellow oil (1:1 mixture of *E*/*Z* isomers); $[\alpha]^{20}_D$ 28.8 (*c* 1.0, $CHCl_3$); IR (neat) 3057, 2977, 1591, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 3H), 2.41 (s, 3H), 3.25 (b, 2H), 7.32 (m, 2H), 7.41 (m, 2H), 7.47 (m, 1H), 7.74 (b, 2H), 7.86 (b, 2H); ^{13}C NMR ($CDCl_3$) δ 13.5, 22.1, 27.0, 32.6, 126.0, 128.5, 130.1, 132.3, 142.5, 144.4, 173.6. Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16. Found: C, 70.89; H, 6.65; N, 4.89.

(*S*)-(+)-*N*-α-Methyl-(4-nitrobenzylidene)-*p*-toluenesulfinamide (2e): yield 51%; flash chromatography (EtOAc:hexane, 20:80); mp 122−123 °C; $[\alpha]^{20}_D$ 72.4 (*c* 1.0, $CHCl_3$); IR (KBr) 1582, 1517, 1347, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.84 (s, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.1, 124.2, 125.8, 129.1, 130.7, 142.9, 143.3, 144.2, 150.1, 172.0. Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.29; H, 4.60; N, 9.15.

(*S*)-(+)-*N*-(*sec*-Butylidene)-*p*-toluenesulfinamide (2f): (4:1, inseparable *E*:*Z* mixture favoring the *E* isomer, yield 74%; flash chromatography (EtOAc: hexane, 15:85), oil: $[\alpha]^{20}_D$ 7.5 (*c* 2.4, $CHCl_3$); IR (neat) 3221, 2975, 1616, 1456, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) (*E* isomer) δ 1.08 (t, J = 7.5 Hz, 3H), 2.32 (s, 3H), 2.33 (m, 2H), 2.38 (s, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); (*Z* isomer) δ 1.19 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.33 (m, 2H), 2.38 (s, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) (*E* isomer) δ 9.8, 21.8, 22.2, 36.9, 125.6, 130.7, 142.1, 144.1, 183.8; (*Z* isomer) δ 11.8, 21.8, 27.5, 31.3, 125.7, 130.6, 141.9, 144.1, 185.1. Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.01; H, 7.11; N, 6.55.

(*S*)-(+)-(1,2,2-trimethyl-propylidene)-*p*-toluenesulfinamide (2h): yield 42%, flash chromatography (EtOAc:hexane, 20:80), oil; $[\alpha]^{20}_D$ 29.0 (*c* 1.0 $CHCl_3$); IR (neat) 2969, 1606, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9H), 2.32 (s, 3H), 2.41 (s, 3H), 7.30 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.3, 21.2, 27.2, 42.3, 125.1, 129.5, 141.3, 143.4, 187.8. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90. Found: C, 66.05; H, 7.85; N, 5.67.

(*S*)-(+)-*N*-(1-Cyclohexyl-ethylidene)-*p*-toluenesulfinamide (2i): yield 51%, flash chromatography (EtOAc:hexane, 20:80), oil; $[\alpha]^{20}_D$ 15.0 (*c* 1.0 $CHCl_3$); IR (neat) 2928, 1612, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6H), 1.79 (m, 4H), 2.25 (m, 1H), 2.31 (s, 3H), 2.40 (s, 3H), 7.29 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.0, 26.4, 30.3, 30.4, 51.5, 125.7, 130.3, 142.2, 144.2, 186.7. Anal. Calcd for $C_{14}H_{19}NOS$: C, 68.40; H, 8.04; N, 5.32. Found: C, 68.21; H, 8.13; N, 5.04.

(*R*)-(−)-*N*-(*sec*-Butylidene)-2-methylpropanesulfinamide (5b). Typical Procedure. Sulfinimine **5b** was prepared from (*R*)-*tert*-butylsulfinamide[27] (0.12 g, 1.0 mmol), methyl ethyl ketone (0.43 mL, 4.8 mmol), and titanium (IV) ethoxide (3.1 mL, 15 mmol) in CH_2Cl_2 (5 mL) according to the procedure reported by Ellman.[27] Flash chromatography (EtOAc:hexane, 30:70) afforded 0.12 g (64%) of (−)-**5b** as an inseparable *E*:*Z* mixture; oil; $[\alpha]^{20}_D$ −203.0 (*c* 1.0 $CHCl_3$); IR (neat) 2973, 1635, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$) (*E* isomer) δ 1.11 (t, J = 7.3 Hz, 3H), 1.23 (s, 9H), 2.31 (s, 3H), 2.43 (m, 2H); (*Z* isomer) δ 1.11 (t, J = 7.3 Hz, 3H), 1.22 (s, 9H), 2.16 (s, 3H), 2.71 (m, 2H); ^{13}C NMR ($CDCl_3$) (*E* isomer) δ 10.5, 22.6, 22.7, 37.3, 56.9, 186.6; (*Z* isomer) δ 12.3, 22.6, 23.4, 30.9, 56.9, 186.6. LRMS Calcd for $C_8H_{17}NOS$: (M + H) 176. Found (M + H) 176.

(2*S*)-(+)-[(S)-*N*-*p*-Toluenesulfinyl]-2-amino-2-*p*-tolylpropionitrile (3b). Typical Procedure. In an oven-dried 50 mL two-necked round-bottom flask fitted with a rubber septum and magnetic stirring bar under an argon balloon was placed a solution of sulfinimine (+)-**2b** (0.27 g, 1.0 mmol) in THF (15 mL) and cooled to −78 °C. In a separate 25 mL single-necked round-bottom flask fitted with a magnetic stir bar and a rubber septum under an argon balloon was added a solution of diethylaluminum cyanide (1.5 mL, 1.5 mmol) in THF (5 mL). The solution was cooled to −78 °C, and *i*-PrOH (0.070 mL, 1.0 mmol) was added. The mixture was brought to room temperature, stirred for 30 min, and cannulated to the solution of (+)-**2b** at −78 °C. After the reaction mixture was brought to room temperature and stirred for 15 h, it was cooled to −78 °C and quenched with sat. NH_4Cl solution (5 mL). The suspension was filtered through Celite, extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$), and concentrated to give a mixture of the amino nitriles **3b** (dr 83:17). Preparative TLC (Et_2O:CH_2Cl_2, 5:95) afforded 0.18 g (60%) of (+)-**3b** as a gel; $[\alpha]^{20}_D$ 62.1 (*c* 1.0 $CHCl_3$); IR (neat) 2250, 1192 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 4.62 (s, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.3, 29.3, 57.1, 120.9, 125.1, 125.7, 129.7, 135.4, 139.4, 141.8, 141.9. Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.81; H, 6.0.9; N, 9.55.

(2*S*)-(+)-[(*S*)-*N*-(*p*-Toluenesulfinyl]-2-amino-2-(4-methoxyphenyl)propionitrile (3a): dr 9:1; preparative TLC (Et_2O:CH_2Cl_2, 5:95), yield 60%, gel; $[\alpha]^{20}_D$ 46.7 (*c* 1.0 $CHCl_3$); IR (neat) 3153, 2361, 1254, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.42 (s, 3H), 3.83 (s, 3H), 4.58 (s, 1H), 6.97 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 29.3, 56.3, 56.8, 114.3, 121.0, 125.0, 127.2, 127.4, 130.0, 130.1, 141.7, 160.2. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.04; H, 5.81; N, 8.59.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-phenylpropionitrile (3c): dr 4:1; flash chromatography (Et_2O:CH_2Cl_2, 5:95), yield 77%, oil; $[\alpha]^{20}_D$ 69.3 (*c* 0.5, $CHCl_3$); IR (neat), 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.41 (s, 3H), 4.69 (s, 1H), 7.34 (d, 2H, J = 7.7 Hz), 7.44 (m, 3H), 7.65 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 29.9, 22.1, 57.9, 121.5, 125.7, 126.4, 129.9, 130.2, 130.6, 139.1, 142.4, 142.8. Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.55; H, 5.77; N, 9.74.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-phenylbutyronitirle (3d): yield 95%; dr 56:44, attempts to separate the diastereoisomers by chromatography failed. Oil, $[\alpha]^{20}_D$ 45.7 (*c* 1.0 $CHCl_3$); IR (neat), 3149, 2361, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$) (major) δ 0.98 (m, 3H), 2.21−2.38 (m, 2H), 2.41 (s, 3H), 4.62 (s, 1H), 7.31−7.71 (m, 9H), (minor) δ 0.98 (m, 3H), 2.21 (m, 1H), 2.40 (s, 3H), 2.49 (m, 1H), 4.64 (s, 1H), 7.31−7.71 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 8.7, 21.2, 35.1, 36.1, 62.8, 63.0, 119.7, 119.9, 124.9, 125.0, 126.5, 126.8, 128.9, 129.0, 129.2, 129.3, 129.6, 129.7, 135.9, 136.5, 141.7, 141.8, 142.1. Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.72; H, 5.99; N, 9.75.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-(4-nitrophenyl)propionitrile (3e): dr 95:5; flash chromatography (EtOAc:hexane = 1:4), yield 93%, gel; $[\alpha]^{20}_D$ 36.7 (*c* 0.8 $CHCl_3$); IR (neat) 3118, 2361, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.43 (s, 3H), 4.75 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 29.6, 57.0, 119.9, 124.2, 125.0, 127.1, 129.8, 140.9, 142.3, 145.3, 148.2. Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.54; H, 4.69; N, 12.96.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-methylbutyronitrile (3f): dr 3:1; preparative TLC (EtOAc:DCM: hexane, 30:30:40), yield 49%, oil; $[\alpha]^{20}_D$ 129.0 (*c* 1.0 $CHCl_3$); IR (KBr) 3211, 2259, 1099 cm^{-1}; ^{1}H NMR δ 1.16 (t, J = 7.5 Hz, 3H), 1.76 (s, 3H), 1.95 (m, 1H), 2.09 (m, 1H), 2.42 (s, 3H), 4.39 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 9.24, 22.0, 26.1, 35.2, 55.4, 121.6, 125.9, 130.4, 142.3, 142.7. Anal. Calcd for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.82; N, 11.85. Found C, 60.87; H, 6.79; N, 11.66.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-methylhexanenitrile (3g): dr 3:1; flash chromatography (EtOAc: hexane, 5:95), yield 50%; mp 79−79.5 °C; $[\alpha]^{20}_D$ 128 (*c* 1.0 $CHCl_3$); IR (KBr) 3421, 3154, 2238, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.41 (m, 2H), 1.53 (m, 2H), 1.77 (s, 3H), 1.91 (m, 1H), 2.04 (m, 1H), 2.42 (s, 3H), 4.23 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 21.3, 22.3, 26.0, 26.2, 41.0, 54.1, 121.2,

125.2, 130.0, 141.7, 141.9. Anal. Calcd for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.62; N, 10.60. Found: C, 63.98; H, 7.82; N, 10.51.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2,3,3-trimethylbutyronitrile (3h): dr 99:1; flash chromatography (EtOAc:hexane, 10:90), yield 95%; mp 135−136 °C, $[\alpha]^{20}_D$ 185 (*c* 1.0 $CHCl_3$); IR (KBr) 3433, 2223, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.85 (s, 3H), 2.43 (s, 3H), 4.27 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 21.2, 24.5, 38.2, 60.0, 120.8, 125.2, 129.7, 141.7, 141.8. Anal. Calcd for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.62; N, 10.60. Found: C, 63.89; H, 7.79; N, 10.61.

(2*S*)-(+)-[(*S*)-*N*-*p*-Toluenesulfinyl]-2-amino-2-cyclohexylpropionitrile (3i): dr 85:15, prep. TLC (EtOAc:hexane, 30:70), yield 72%, mp 103−104 °C, $[\alpha]^{20}_D$ 116 (*c* 1.0 $CHCl_3$); IR (KBr) 3158, 2382, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (m, 6H), 1.73 (s, 3H), 1.86 (m, 4H), 2.01 (m, 1H), 2.42 (s, 3H), 4.24 (s, 1H), 7.32 (d, J = 8.1, 2H), 7.58 (d, J = 8.4, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.2, 25.8, 26.4, 27.5, 46.7, 57.6, 120.9, 125.2, 129.6, 141.7, 141.8. Anal. Calcd for $C_{15}H_{20}N_2SO$: C, 66.17; H, 7.64; N, 9.65. Found: C, 65.91; H, 7.91; N, 9.70.

(2*R*)-(−)-[(R)-*N*-*tert*-Butanesulfinyl]-2-amino-2-phenylpropionitrile (6a): dr 12:1, crystallization (EtOAc:hexane, 25:75) gave 0.16 g (56%) of (−)-**6a**, mp 88−89 °C; $[\alpha]^{20}_D$ −22.4 (*c* 0.8 $CHCl_3$); IR (KBr) 3150, 2363, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.96 (s, 3H), 3.88 (s, 1H), 7.42 (m, 3H), 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.4, 29.7, 56.9, 57.1, 120.6, 125.6, 129.2, 129.4, 139.0. Anal. Calcd for $C_{13}H_{18}N_2OS$: C, 62.37; H, 7.25; N, 11.19. Found: 62.55; H, 7.41; N, 10.96.

(2*R*)-(−)-[(*R*)-*N*-*tert*-Butanesulfinyl]-2-amino-2-methylbutyronitrile (6b): yield 93%, dr 4.5:1, attempts to separate the diastereoisomers by chromatography failed; oil; $[\alpha]^{20}_D$ −69.2 (*c* 0.5 $CHCl_3$); IR (neat) 3432, 2350, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) (major) δ 1.12 (m, 3H), 1.27 (s, 9H), 1.62 (s, 3H), 1.89−2.08 (m, 2H), 3.44 (s, 1H), (minor) δ 1.12 (m, 3H), 1.25 (s, 9H), 1.78 (s, 3H), 1.89−2.08 (m, 2H), 3.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.2, 9.4, 23.0, 26.3, 27.3, 35.1, 35.3, 55.3, 56.4, 57.3, 57.4, 121.4, 121.8. Anal. Calcd for $C_9H_{18}N_2OS$: C, 53.43; H, 8.97; N, 13.85. Found: C, 53.03; H, 9.20; N, 13.67.

(*S*)-(+)-2-Methyl-(2-(*p*-tolyl)glycine (4b). Typical Procedure. In a 25 mL single necked round-bottom flask fitted with a magnetic stirring bar and condenser was placed (+)-**3b** (0.20 g, 0.67 mmol) in 6 N HCl (15 mL). After the solution was refluxed for 15 h, it was cooled to room temperature and extracted with ether (3 × 15 mL). The aqueous layer was passed through 6−8 g of DOWEX 50 ion exchange column eluting with 1.4 N NH_4OH (30 mL). Concentration afforded 0.078 g (64%) of **4b**, mp 245 (dec) °C; $[\alpha]^{20}_D$ 63.7 (*c* 0.7 1, N HCl); IR (KBr) 3156 (b), 1698 cm^{-1}; ^1H NMR (D_2O) δ 1.89 (s, 3H), 2.34 (s, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CD_3OD) δ 21.0, 22.8, 63.9, 127.0, 130.3, 137.7, 139.5, 175.7; HRMS Calcd for $C_{10}H_{13}NO_2$ (M + H) 180.1025; found (M + H) 180.1021.

(*S*)-(+)-2-Methyl-2-(4-methoxyphenyl)glycine, hydrochloride salt (4a): yield 54%, mp > 260 °C, [lit.,[28] mp > 260 °C]; $[\alpha]^{20}_D$ 74.0 (*c* 0.66, 1 N HCl), [lit.[28] $[\alpha]^{20}_D$ 70.4 (*c* 1.0 1 N HCl)]; ^1H NMR (D_2O) δ 1.89 (s, 3H), 3.84 (s, 3H), 7.05 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H).

(*S*)-(+)-2-Methyl-2-phenylglycine (4c): yield 67%; mp 294 °C [lit.[29b] mp >294]; $[\alpha]^{20}_D$ 79.2 (*c* 0.5, 1 N HCl), [lit.[29b] $[\alpha]^{20}_D$ 86.5 (*c* 0.52, 1 N HCl)]. Spectral properties were in agreement with literature values.[29a]

(*S*)-(+)-2-Methyl-2-(4-nitrophenyl)glycine (4e): yield 53%; mp 152−153 °C; $[\alpha]^{20}_D$ 72.1 (*c* 0.6 1 N HCl); IR (KBr) 3613−2363, 1521, 1513, 1361 cm^{-1}; ^1H NMR (D_2O) δ 1.96 (s, 3H), 7.74 (d, J = 8.4 Hz, 2H), 8.31 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDOD_3$) δ 22.4, 63.2, 123.9, 127.8, 146.9, 148.4, 173.4. Anal. Calcd for $C_9H_{10}N_2O_4 \cdot 1/2H_2O$: C, 49.32; H, 5.06; N, 12.78. Found: C, 49.64; H, 4.74; N, 12.86.

(*S*)-(+)-2-Amino-2-methylbutanoic acid (isovaline) (4f): yield 69%; mp>260 °C, [lit.[30] mp 300 °C (sub)]; $[\alpha]^{20}_D$ 10.2 (*c* 0.8, H_2O); [lit.[30] $[\alpha]^{20}_D$ 10.9 (*c* 1.0, H_2O)]; ^1H NMR (D_2O) δ 0.88 (t, J = 8.5 Hz, 3H) 1.41 (s, 3H), 1.7 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (D_2O + CD_3OD) δ 181.2, 66.3, 31.9, 22.5, 6.9.

(*S*)-(+)-2-Amino-2-methylhexanoic acid (4g): yield 54%, mp > 260 °C (dec) (HCl salt); [lit.[31] mp 304 °C (dec)], $[\alpha]^{20}_D$ 10.5 (*c* 1.0 H_2O), [lit.[32] $[\alpha]^{20}_D$ 8.1 (*c* 2.0 H_2O)]; ^1H NMR (D_2O) 0.82 (t, J = 7.6, 3H), 1.13 (m, 2H), 1.28 (m, 2H), 1.41 (s, 3H), 1.67 (m, 1H), 1.81 (m, 1H).

(*S*)-(+)-2-Amino-2-cyclohexyl-propionic acid (4i): yield 48%, mp > 260 °C (dec); [lit.[33] mp 326 °C (dec)], $[\alpha]^{20}_D$ 12.4 (*c* 1.0 5 N HCl), [lit.[33], $[\alpha]^{20}_D$ 10.85 ± 1.0 (*c* 1.0 5 N HCl)]; ^1H NMR (D_2O) δ 0.98 (m, 2H), 1.13 (m, 2H), 1.25 (m, 2H), 1.47 (s, 3H), 1.64 (m, 2H), 1.76 (m, 2H), 1.82 (m, 1H).

(*R*)-(−)-2-Methyl-2-phenylglycine (4c): yield 64%, mp >260 °C (dec), [lit.[29b] mp >240 °C (dec)]; $[\alpha]^{20}_D$ −85.0 (*c* 0.7 1 N HCl), [lit.[30] $[\alpha]^{20}_D$ −86.9 (*c* 0.33 1 N HCl)]; ^1H NMR (D_2O) δ 1.91 (s, 3H), 7.49 (m, 5H).

(*S*)-(−)-2-Amino-2,3,3-trimethyl-butyronitrile Hydrochloride Salt (7). In a 25 mL single-necked round-bottom flask equipped with a magnetic stir bar were placed **3h** (0.26 g, 1.0 mmol) and 6 N HCl (15 mL). After the reaction mixture was refluxed for 15 h, it was extracted with ether (4 × 10 mL). The aqueous phase was concentrated to afford 0.15 g (90%) of (−)-**7**; mp 165−166 °C, $[\alpha]^{20}_D$ −9.0 (*c* 0.7 H_2O); IR (KBr) 3426, 2338 cm^{-1}; ^1H NMR (D_2O) δ 1.11 (s, 9H), 1.66 (s, 3H); ^{13}C NMR ($CDOD_3$) δ 20.6, 25.1, 38.0, 60.2, 118.7. Anal. Calcd for $C_7H_{15}ClN_2$: C, 51.69; H, 9.29; N, 17.22. Found: C, 51.77; H, 9.65; N 16.89.

(*S*)-(−)-2-Amino-2,3,3-trimethyl-butyramide (8). In a 25 mL single-necked round-bottom flask equipped with a magnetic stirring bar was placed concd H_2SO_4 (10 mL), it was cooled to 0 °C, and **7** (0.10 g, 0.61 mmol) was added slowly.[34] The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 96 h. The solution was poured onto crushed ice (25 g) and filtered. The filtrate was slowly adjusted to pH 8 with concentrated NH_4OH at 0 °C and extracted with ether (5 × 10 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated to afford 0.044 g (50%) of (−)-**8**; mp 162−3 °C, $[\alpha]^{20}_D$ −68.0 (*c* 0.2 $CHCl_3$); IR (KBr) 3510, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9H), 1.31 (s, 3H), 5.58 (b, 2H), 7.36 (b, 2H); ^{13}C NMR (CD_3OD) δ 23.2, 25.7, 37.2, 62.1, 179.8. Anal. Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.42. Found: C, 58.44; H, 11.20; N, 19.79.

General Procedure for Preparation of Mosher Amides. Under an argon balloon, in an oven-dried 5 mL two-necked round-bottom flask fitted with a magnetic stir bar and condenser, were placed the appropriate amino acid **4** (0.10 mmol), Mosher's chloride (0.025 g, 0.10 mmol), and propylene oxide (30 μL, 0.51 mmol) in THF (2 mL). The suspension was refluxed for 3 h, cooled to room temperature, and concentrated. Preparative TLC (EtOAc:hexane, 25:75) afforded the Mosher amide of **4**. ^{19}F and ^1H NMR was used to evaluate the enantiomeric purity of the acids.

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Supporting Information Available: IR, ^1H NMR, and ^{13}C NMR spectra for sulfinimine **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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