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Vinylaluminum Addition to Sulfinimines (*N*-Sulfinyl Imines). Asymmetric Synthesis of *anti*- α -Alkyl β -Amino Esters

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Abstract

Addition of vinyl aluminum-NMO reagents to *N*-(*p*-toluenesulfinyl)- and *N*-(2-methylpropanesulfinyl)-derived sulfinimines gives *N*-sulfinyl *aza*-Morita-Baylis-Hillman products (d.r. 7:1 to 12:1) that result from addition of the reagent from the least hindered direction. Hydrogenation of the *aza*-MBH adducts with a Rh(I) catalyst affords *anti*- α -substituted *N*-sulfinyl- β -amino esters in good yield and high dr (10:1 to 21:1).

Introduction

The development of new and improved methodologies for the asymmetric synthesis of β -amino acids continues to be an important objective because of their valuable biological properties, their utility as chiral building blocks, and as precursors of β -lactams.^{1,2} Substitution of β -amino acids for α -amino acids results in β -peptides with novel activity and increased enzyme stability.³ For these reasons many methods have been devised for the synthesis of β -amino acids,^{1,2} including the diastereoselective addition of enolates to enantiopure sulfinimines (*N*-sulfinyl imines).⁴ However, only a few methods have been reported for the enantioselective synthesis of acyclic α -substituted β -amino acids.^{1,5}

As part of a program aimed at the asymmetric synthesis of *N*-sulfinyl α -substituted β -amino esters and ketones, we have been exploring the addition of prochiral Weinreb amide enolates to sulfinimines.^{5a} Another way to access these compounds is the stereoselective reduction of sulfinimine-derived α -(aminoalkyl)acrylates (*aza*-Morita-Baylis-Hillman) adducts (Figure 1).⁶ However, sulfinimines have rarely been employed in the *aza*-Morita-Baylis-Hillman (*aza*-MBH) reaction.⁷ Aggarwal et al. reported the seven-day reaction of methyl acrylate with sulfinimines to give *aza*-MBH adducts with modest diastereoselectivity and yield.⁸ In the presence of PhPMe₂, cyclopent-2-ene-one reacts with aromatic aldehyde-derived sulfinimines to give *aza*-MBH adducts with poor to good diastereoselectivity.⁹ More recently Scheidt and co-workers described the addition of lithium allenolates, in the presence of HMPA, to sulfinimines affording β -substituted *aza*-MBH products in good yield and high selectivity.¹⁰

In a series of papers, Li and co-workers explored the addition of vinylcuprates, prepared by Michael addition of R₂CuLi to α -acetylenic esters, to sulfinimines at -23 °C to give novel branched *aza*-MBH adducts.¹¹ For the addition to occur, stoichiometric amounts of Et₂AlCl or 40 mol% of Yb(OTf)₃ were required. Careful control of the reaction conditions was also necessary for good yields.¹¹ These workers also reported that vinylaluminum reagents were unreactive.^{11c} Ramachandran and co-workers described a new procedure for the synthesis of

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Supporting Information Available. Spectroscopic data for all new compounds are provided. This material is available free of charge via the World Wide Web at <http://pubs.acs.org>.

vinylaluminum reagents from DIBAL-H, α -acetylenic esters and 4-methylmorpholine *N*-oxide (NMO).¹² These workers demonstrated that their vinylaluminum reagents gave good yields of MBH adducts on reaction with aldehydes and ketones. Inspired by these studies we describe the application of this protocol to the asymmetric syntheses of *N*-sulfinyl α -(aminoalkyl) acrylates (aza-Morita Baylis-Hillman products) and their stereoselective reduction to *N*-sulfinyl- α -substituted β -amino esters.

Results and Discussion

Following the Ramachandran procedure, an NMO (2.0 equiv) THF solution was added to a THF solution of DIBAL-H (1.5 equiv) at 0 °C to give a clear solution. After 1 h, to this solution was added 1.0 equiv of ethyl propiolate (**1**) and 1.0 equiv of (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**3**) (Scheme 1). (*S*,*R*)-(-)-Ethyl-2-[phenyl-(*p*-toluenesulfinylamino) methyl]acrylate (**4**) was formed as a 9:1 mixture of diastereoisomers, but the isolated yield of the major diastereoisomer was low (Table 1, entry 1). When the amount of the vinylaluminum reagent **2** was increased three-fold the yield of (+)-**4** improved to 65%. Use of Zn(OTf)₂ in these reactions had little or no effect on the yield or diastereoselectivity. These results are summarized in Table 1.

In the sulfinimine-mediated *aza*-MBH reaction,^{8,9} *Re*-face addition of the vinyl anion species to (*S*)-(+)-**3** gave the *aza*-MBH product having the *S*-configuration at the new C-N stereogenic center.^{8,9,11} However, the ¹H NMR of these products and (+)-**4** were significantly different suggesting that they were different compounds. For example, the vinyl protons in (+)-**4** appear at δ 6.02 and 6.48 ppm whereas in the (*S*,*S*) *aza*-MBH adduct reported by Aggarwal these protons appear at 5.8 and 6.4 ppm, respectively.⁸

Because (+)-**4** is an oil it was not possible to determine its absolute configuration by X-ray analysis and therefore it was necessary to convert it into products of known absolute stereochemistry. This requires the stereoselective reduction of the α -methylene group in (+)-**4** to a methyl group. The homogenous hydrogenation of Baylis-Hillman adducts has been reported and generally gives *anti*-products.^{6,13} Hydrogenation of *N*-acyl β -amino- α -methylene esters using Rh(II) and Rh(I) catalysts at high pressure (30 atm) gives the corresponding *anti*- α -substituted β -amino esters.¹⁴ However, there are no reports of the reduction of *N*-sulfinyl β -amino- α -methylene esters.

Hydrogenation of (+)-**4** at rt using 7.5 mol% of cationic rhodium complex **A** for 48 h gave a 22:1 mixture of diastereoisomers with isolation of the major diastereoisomer (*S*,*2R,3S*)-(+)-**5** in 88% yield (Scheme 2). Oxidation with *m*-CPBA gave (*2R,3S*)-(-)-**7** and hydrolysis afforded the known acid (*2R,3S*)-(-)-**8** in 87% yield.¹⁵ To further confirm the trans stereochemistry, the acid was treated with DCC/4-pyrrolidino-pyridine to give β -lactam (*3R,4S*)-(-)-**9**, also a known compound (Scheme 2).^{15a} In (-)-**9** the $J_{3,4}$ coupling constant was 3.2 Hz and similar to the reported value of 3.0 Hz (*cis* = $J_{3,4}$ = 6 Hz).^{15a} These results indicate that the vinylaluminum reagent adds to the *Si*-face in sulfinimine (*S*)-(+)-**3**. Formation of the *anti*-product (+)-**5** is consistent with coordination of the Rh-catalyst **A** with the sulfinyl nitrogen atom and addition of hydrogen from the more hindered face of the C-C double bond.^{13,14}

Structures resulting from the addition of organometallic reagents to the C-N double bond of sulfinimines can generally be predicted by assuming chelated, chair-like transition states resulting from coordination of the metal ion with the sulfinyl oxygen. The sulfinimine-mediated *aza*-MBH reaction⁹ and the addition of vinylcuprates¹¹ to sulfinimines are in agreement with this transition state hypothesis. However, there are exceptions where the organometallic reagent adds to the C-N double bond from the least hindered direction, away from the bulky sulfinyl group.¹⁶ As previously suggested by us, a Yamamoto-type model **TS-A** (Figure 2), where the vinyl aluminum reagent adds to the *Si*-face of the CN double bond

explains our results.^{16b} We suggest that the added NMO, which acts as a ligand to aluminum to suppress the tendency of DIBAL-H to reduce C=O and C=N groups,¹⁷ also prevents complexation of aluminum with the sulfinyl group. In the presence of HMPA lithium allenolates also add to the *Si*-face of sulfinimines.¹⁰

The addition of β -substituted vinyl aluminum reagents to sulfinimines was next examined. Addition of [α -(ethoxycarbonyl)- β -methylvinyl]diisobutylaluminum, prepared from propargylic ester **10**, afforded **13** as a 5:1 mixture of inseparable diastereoisomers (Table 2, entry 1). In the past we have solved this separation problem by changing the *N*-sulfinyl auxiliary.¹⁸ However, reaction of **2** with (*R_S*)-(-)-*N*-(benzylidene)-2-methylpropanesulfinamide (**12a**) at rt resulted in no reaction (Table 2, entry 2). When the temperature was increased to 70 °C for 15 h, compound (*R_{S,S}*)-(-)-**14a** was obtained as a 12:1 mixture of diastereoisomers with isolation of the major diastereoisomer in 65% yield (Table 2, entry 5).¹⁹ Under these conditions addition of [α -(ethoxycarbonyl)- β -methylvinyl]diisobutylaluminum and [α -(ethoxycarbonyl)- β -phenylvinyl]diisobutylaluminum to (-)-**12a** gave (*R_{S,S}*)-(-)-**14b** and (*R_{S,S}*)-(-)-**14c**, respectively, as 7:1 mixtures of diastereoisomers. The major diastereoisomers were isolated in 71% and 73% yields (Table 2, entries 6 and 7). Similar results were observed for addition of the β -substituted vinylaluminum reagents to (*R_S*)-(-)-*N*-(ethylidene)-2-methylpropanesulfinamide (**12b**), to give **14d** (R = H), **14e** (R = Me), and **14f** (R = Ph). However, the diastereoisomers of **14d** (13:1) and **14e** (11:1) could not be separated (Scheme Table 2, entries 8-10). Based on earlier studies, the stereochemistry **14**, is expected to be *Z*.^{12,20} Upon irradiation of the C-3 vinyl proton at δ 6.28 ppm in (-)-**14b**, a positive NOE was observed on the C-2 amine proton at δ 5.28 (8.3%) consistent with *Z* olefin geometry.

Hydrogenation of **14** as before gave **15** in good yield (Table 3). When R was hydrogen, reduction was complete within 48 h at rt and 1 atm of H₂ (Table 3, entries 1 and 4). When R in **14** was Me or Ph, longer times (72 h) and higher pressures of H₂ (25 atm) were necessary. β -Amino ester **15e** was formed as a mixture of inseparable diastereoisomers contaminated with starting material (Scheme 4). Prolonged hydrogenation (> 90 h) resulted in decomposition.

In summary, reaction of vinylaluminum-NMO reagents with sulfinimines gives *N*-sulfinyl *aza*-Morita-Baylis-Hillman products that result from addition of the reagent from the least hindered direction via a non-chelation control mechanism. Hydrogenation of the *aza*-MBH adducts affords *anti*- α -substituted *N*-sulfinyl- β -amino esters and is a useful new method for their preparation.^{21,22}

Experimental Section

Sulfinimines (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**3**),²³ (*R*)-(-)-*N*-(benzylidene)-2-methylpropanesulfinamide (**12a**),²⁴ and (*R*)-(-)-*N*-(propylidene)-2-methylpropanesulfinamide (**12b**)²⁴ were prepared as previously described. Catalyst (bicyclo [2.2.1]hepta-2,5-diene)[1,4-bisdiphenylphosphino]butanerhodium(I) tetrafluoroborate **A** was purchased from Aldrich.

(*S_S,2R*)-(+)-Ethyl 2-[phenyl(*p*-toluenesulfinylamino)methyl]acrylate (**4**)

In a 50 mL, dry, single-necked round bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed NMO (0.696 g, 5.92 mmol) in THF (8 mL) and the solution was cooled to 0 °C. To the solution was added DIBAL-H (4.48 mL, 1.0 M in THF) at 0 °C and the mixture was stirred at this temperature for 0.5 h before ethyl propiolate (**1**) (0.304 mL, 2.96 mmol) was added. The mixture was stirred for 1 h at 0 °C, and a solution of (*S*)-(+)-**3** (0.240g, 0.984 mmol) in THF (8 mL) was added. The mixture was warmed to rt, stirred for 4 h, quenched with Rochelle salt (NaKC₄H₄O₆·H₂O) (10 mL), diluted with EtOAc (15 mL), and vigorously stirred for 30 min. At this time the solution was extracted with EtOAc

(3 X 15 mL), the combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (50% EtOAc/hexanes) provided 0.220 g (65%) of a colorless oil; $[\alpha]_D^{20} +30.0$ (c 0.28, CHCl₃); IR (neat) 3204, 1711, 1053 cm⁻¹; ¹H NMR (CDCl₃) δ 7.61(d, *J* = 6.4 Hz, 2H), 7.24 (m, 7H), 6.47 (s, 1H), 6.03 (d, *J* = 0.8 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 2H), 4.93 (d, *J* = 7.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.20 (t, *J* = 6.8 Hz, 3H); ¹³C NMR δ 166.0, 141.8, 141.6, 140.5, 129.9, 128.9, 128.0, 127.4, 127.2, 126.0, 61.3, 58.4, 21.7, 14.5 (one carbon could not be identified due to overlap). HRMS calcd for C₁₉H₂₂NO₃S(M+H) 344.1320. Found 344.1327.

Ethyl (*R_s*,2*S*)-(-)-2-[phenyl(2-methylpropanesulfinylamino)methyl]acrylate (14a)

In a 50 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, a reflux condenser, and argon balloon was placed NMO (0.606 g, 5.16 mmol) in THF (6 mL). To the solution was added DIBAL-H (3.9 mL, 1.0 M solution in THF) at 0 °C and the mixture was stirred for 30 min. Ethyl propiolate (**1**) (0.264 mL, 2.59 mmol) was added via syringe, and the mixture was stirred for 1 h at 0 °C, and (*R*)-(-)-**12a** (0.180 g, 0.864 mmol) in anhydrous THF (6 mL) was added. The mixture was heated to 70 °C and stirred for 15 h, cooled to rt, quenched by addition of sat. aqueous Rochelle salt (10 mL), diluted with EtOAc (15 mL), and stirred vigorously for 0.5 h. The organic phase was washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (25% EtOAc/hexanes) provided 0.174 g (65%) of a colorless oil; $[\alpha]_D^{20} -1.40$ (c 0.93, CHCl₃); IR (KBr) 3233, 2980, 1717, 1061 cm⁻¹; ¹H NMR (CDCl₃) δ 7.26 (m, 5H), 6.45 (s, 1H), 5.99 (s, 1H), 5.49 (d, *J* = 4.8 Hz, 1H), 4.12 (m, 2H), 3.76 (d, *J* = 4.8 Hz, 1H), 1.25 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.0, 141.6, 140.7, 129.1, 128.3, 127.9, 126.8, 61.3, 59.8, 56.5, 23.0, 14.4. HRMS calcd. for C₁₆H₂₄NO₃S (M+H) 310.1477. Found 310.1472.

(*Z*)-Ethyl (*R_s*,2*S*)-(-)-2-[phenyl(2-methylpropanesulfinylamino)methyl] but-2-enoate (14b). General procedure

In a 50 mL, flame-dried, single-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, a reflux condenser, and argon balloon was placed NMO (0.606 g, 5.16 mmol) in THF (6 mL). The solution was cooled to 0 °C, DIBAL-H (3.9 mL, 1.0 M solution in THF) was added, and the reaction mixture was stirred for 30 min at which time ethyl but-2-ynoate (**10**) (0.300 mL, 2.59 mmol) was added via syringe. After stirring for 4 h at rt (*R*)-(-)-**12a** (0.180 g, 0.864 mmol) in THF (6 mL) was added. The reaction mixture was heated to 70 °C, stirred for 15 h, cooled to rt and quenched by addition of sat. aqueous Rochelle salt (10 mL). The solution was diluted with EtOAc (15 mL), vigorously stirred, and the organic phase was washed with brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (33% EtOAc/hexanes) provided 0.329 g (71%) of a colorless oil; $[\alpha]_D^{20} -24.8$ (c 0.29, CHCl₃); IR (KBr) 3214, 3030, 2959, 2869, 1717 cm⁻¹; ¹H NMR (CDCl₃) major isomer δ 7.25 (m, 5H), 6.35 (q, *J* = 7.2 Hz, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 4.09 (m, 2H), 3.85 (d, *J* = 6.4 Hz, 1H), 2.05 (dd, *J* = 0.8, 7.2 Hz, 3H), 1.23 (s, 9H), 1.15 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.7, 141.0, 138.8, 133.8, 128.7, 127.8, 127.4, 61.9, 60.5, 56.2, 22.8, 15.7, 14.2. HRMS calcd for C₁₇H₂₆NO₃S (M+H) 324.1633. Found 324.1649.

(*Z*)-Ethyl (*R_s*,2*R*)-(-)-2-[phenyl(2-methylpropanesulfinylamino)methyl]-3-phenylacrylate (14c)

Flash chromatography (25% EtOAc/hexanes) provided 73% of a colorless oil; $[\alpha]_D^{20} -41.0$ (c 1.05, CHCl₃); IR (KBr) 3211, 1734, 1225 cm⁻¹; ¹H NMR (CDCl₃) δ 7.46 (m, 2H), 7.36 (m, 3H), 7.28 (m, 5H), 6.94 (s, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 4.00 (m, 2H), 3.91 (d, *J* = 6.0 Hz, 1H), 1.27 (s, 9H), 0.97 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃) δ 168.1, 139.9, 135.7, 135.4, 134.9, 128.8, 128.6, 128.5, 128.3, 128.2, 127.7, 62.7, 60.9, 56.4, 22.8 (3C), 13.7. HRMS calcd for C₂₂H₂₈NO₃S (M+H) 386.1790. Found 386.1805.

(R_S,3S)-(-)-Ethyl 3-(1,1-dimethylethylsulfinamido)-2-methylenepentanoate (14d)

Flash chromatography (40% EtOAc/hexanes) provided 55% of a colorless oil; IR (neat) 3212, 1718 cm⁻¹; [α]_D²⁰ -39.6 (c 1.26, CHCl₃); ¹H NMR (CDCl₃) δ 6.26 (s, 1H), 5.27 (s, 1H), 4.22 (m, 2H), 4.04 (dt, *J* = 6.8 Hz, 1H), 3.68 (d, *J* = 6.8 Hz, 1H), 1.86 (m, 2H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.19 (s, 9H), 0.93 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.4, 141.3, 126.3, 61.2, 60.1, 56.1, 29.1, 22.9, 14.5, 11.3. HRMS calcd for C₁₂H₂₄NO₃S (M+H) 262.1477. Found 262.1455.

(Z)-(R_S,3S)-(-)-Ethyl 3-(1,1-dimethylethylsulfinamido)-2-ethylidenepentanoate (14e)

Flash chromatography (40% EtOAc/hexanes) provided 50% of a colorless oil; [α]_D²⁰ -51.5 (c 1.20, CHCl₃); IR (neat) 3224, 1714, 1454, cm⁻¹; ¹H NMR (CDCl₃) δ 6.11 (m, 1H), 4.21 (m, 2H), 3.87 (q, *J* = 6.8 Hz, 1H), 3.58 (d, *J* = 6.0 Hz, 1H), 1.97 (d, *J* = 6.8 Hz, 3H), 1.79 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.5, 137.7, 133.8, 62.6, 60.7, 55.9, 29.4, 22.9, 15.8, 14.6, 11.3. HRMS calcd for C₁₃H₂₆NO₃S (M+H) 276.1633. Found 276.1635.

Ethyl (Z)-(R_S,2S)-(-)-2-[ethyl(2-methylpropanesulfinylamino)methyl]-3-phenylacrylate (14f)

Flash chromatography (50% EtOAc/hexanes) provided 35% of a colorless oil; [α]_D²⁰ -36.3 (c 0.84, CHCl₃); IR (KBr) 3211, 1722, 1225, 1061 cm⁻¹; ¹H NMR (CDCl₃) δ 7.22 (m, 5H), 6.77 (s, 1H), 4.07 (m, 3H), 3.47 (d, *J* = 5.2 Hz, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.20 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 168.7, 135.7, 135.3, 134.8, 128.7, 128.6, 128.5, 62.7, 61.1, 56.1, 29.3, 22.9, 14.0, 11.4. HRMS calcd for C₁₈H₂₈NO₃S (M+H) 338.1790. Found 338.1781.

(S_S,2R,3S)-(+)-Ethyl 2-methyl-3-(4-methylphenylsulfinamido)-3-phenyl-propanoate (5)

In an oven-dried, 25 mL one neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and an H₂ balloon was placed (+)-**4** (0.200 g, 0.585 mmol) and rhodium complex **A** (0.031 g, 0.044 mmol) in anhydrous DCM (5.0 mL). The solution was evacuated and filled with H₂, and this sequence was repeated 5 times. The reaction mixture was stirred for 48 h at rt, and concentrated. Flash chromatography (50% EtOAc/hexanes) afforded 0.180 g (88%) of a colorless oil; [α]_D²⁰ +33.6 (c 0.65, CHCl₃); IR (neat) 3206, 1730, 1090, 1053 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 3H), 7.11 (m, 4H), 5.06 (d, *J* = 7.2 Hz, 1H), 4.50 (dd, *J* = 7.2, 8.0 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.88 (dq, *J* = 6.8, 8.0 Hz, 1H), 2.32 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.46 (d, *J* = 6.8 Hz, 3H); ¹³C NMR δ 175.0, 142.0, 141.4, 141.1, 129.5, 129.0, 127.9, 127.3, 126.1, 61.1, 60.4, 46.9, 21.6, 15.8, 14.5. HRMS calcd for C₁₉H₂₃NO₃SNa (M+Na) 368.1296. Found 368.1304.

(R_S,2S,3R)-(-)-Ethyl 2-methyl-3-(4-methylphenylsulfinamido)-3-phenyl propanoate (15a)

Flash chromatography (50% EtOAc/hexanes) afforded 83% of a colorless oil; [α]_D²⁰ -20.6 (c 0.18, CHCl₃); IR (neat) 3584, 3256, 1734 cm⁻¹; ¹H NMR (CDCl₃) δ 7.32 (m, 5H), 4.46 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.12 (q, *J* = 7.3 Hz, 2H), 3.96 (d, *J* = 8.4 Hz, 1H), 2.92 (dq, *J* = 7.2, 8.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 174.9, 140.4, 128.9, 128.2, 127.4, 63.1, 60.8, 56.4, 46.8, 22.7, 15.2, 14.3. HRMS calcd for C₁₆H₂₆NO₃S (M+H) 312.1633. Found 312.1625.

(R_S,S)-(-)-Ethyl 2-[(R)-(1,1-dimethylethylsulfinamido)(phenyl)methyl]butanoate (15b)

In an oven-dried, 25 mL one necked, round-bottomed flask equipped with a magnetic stirring bar was placed (-)-**14b** (0.0302 g, 0.093 mmol) and rhodium complex **A** (0.005 g, 0.007 mmol) in 1,2-dichloroethane (4.5 mL). The solution was placed in a high-pressure vessel (Series 4650 2.50 Inch Inside Diameter HP/HT from Parr Instrument Company). The vessel was tightly closed and was filled with H₂ until the inner pressure reached 25 atm at which time it was

evacuated and refilled with H₂ to 25 atm. This sequence was repeated 3 times. The reaction mixture was stirred at 25 atm of H₂ for 72 h at rt, at which time the solution was concentrated. Preparative TLC (50% EtOAc/hexanes) afforded 0.0241 g (81%) of a colorless oil; $[\alpha]_D^{20}$ -44.4 (*c* 0.41, CHCl₃); IR (neat): 3216, 1732, 1052 cm⁻¹; ¹H NMR (CDCl₃) δ 7.30 (m, 5H), 4.60 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.66 (d, *J* = 7.6 Hz, 1H), 2.80 (m, 1H), 1.63 (m, 2H), 1.20 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 173.0, 140.6, 128.6, 128.0, 127.3, 61.7, 60.4, 56.5, 54.2, 22.7, 22.1, 14.0, 11.9. HRMS calcd for C₁₇H₂₈NO₃S (M+H) 326.1790. Found 326.1782.

(R_S,2S,3R)-(-)-Ethyl 2-benzyl-3-(1,1-dimethylethylsulfinamido)-3-phenyl-propanoate (15c)

Preparative TLC (50% EtOAc/hexanes) afforded 79% of a colorless oil; $[\alpha]_D^{20}$ -19.5 (*c* 0.57, CHCl₃); IR (neat) 3221, 1730, 1052 cm⁻¹; ¹H NMR (CDCl₃) δ 7.30 (m, 10H), 4.66 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.81 (m, 3H), 3.20 (m, 1H), 3.06 (m, 1H), 2.92 (m, 1H), 1.23 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 172.3, 140.0, 138.8, 128.8, 128.6, 128.4, 128.1, 127.3, 126.4, 61.9, 60.3, 56.5, 54.6, 35.0, 22.6, 13.7. HRMS calcd for C₂₂H₂₉NO₃SNa (M+Na) 410.1765. Found 410.1766.

(R_S,2S,3S)-(-)-Ethyl-2-methyl-3-(*tert*-butylsulfinylamino)pentanoate (15d)

In a 50 mL, dry, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and an H₂ balloon was placed (-)-**14d** (0.05 g, 0.17 mmol) and rhodium complex **A** (0.009 g, 0.013 mmol) in anhydrous DCM (5 mL). The solution was evacuated and filled with H₂, and this sequence was repeated 5 times. The reaction mixture was stirred at rt for 48 h. Preparative TLC (50% EtOAc/hexane) afforded 0.0255 g (55%) of a colorless oil; $[\alpha]_D^{20}$ -31.46 (*c* 0.06, CHCl₃); IR (neat) 3280, 1732, 1462, cm⁻¹; ¹H NMR (CDCl₃) TM 4.06 (m, 2H), 3.62 (d, *J* = 12 Hz, 1H), 3.29 (m, 1H), 2.69 (m, 1H), 1.72 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H) 1.23 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H) 0.99 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃) TM 174.9, 61.3, 60.4, 56.2, 43.4, 27.37, 22.7, 14.7, 14.2, 10.0. HRMS calcd for C₁₂H₂₆NO₃S (M+H) 264.1633. Found 264.1613.

(R_S,2S,3S)-(-)-Ethyl 2-benzyl-3-(1,1-dimethylethylsulfinamido)pentanoate (15f)

Preparative TLC (50% EtOAc/hexanes) afforded 77% of a colorless oil; $[\alpha]_D^{20}$ -27.7 (*c* 0.51, CHCl₃); IR (neat) 3228, 1731, 1053 cm⁻¹; ¹H NMR (CDCl₃) major isomer δ 7.19 (m, 5H), 4.00 (q, *J* = 7.6 Hz, 2H), 3.66 (m, 1H), 3.23 (d, *J* = 7.6 Hz, 1H), 2.96 (m, 2H), 2.85 (m, 1H), 1.77 (m, 1H), 1.62 (m, 1H), 1.20 (s, 9H), 1.10 (t, *J* = 8.1 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 173.2, 139.2, 128.8, 128.5, 126.4, 60.4, 59.8, 56.2, 52.0, 34.1, 26.8, 22.9, 14.1, 10.4. HRMS calcd for C₁₈H₂₉NO₃SNa (M+Na) 362.1766. Found 362.1761.

(2R,3S)-(-)-Ethyl 2-methyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoate (7) from (+)-5

In an oven-dried, 10 mL one neck, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**5** (0.168 g, 0.486 mmol) in DCM (18.0 mL). The solution was cooled to 0 °C, *m*-CPBA (0.336 g, 1.458 mmol, 75% wt) was added in one portion, the reaction mixture was warmed to rt, stirred for 1.5 h, and quenched by addition of sat. Na₂S₂O₃ solution (10 mL). The solution was extracted with DCM (2 × 5 mL), the combined organic phases were washed with sat. NaHCO₃ solution (2 × 5 mL), brine (5 mL), dried (MgSO₄), and concentrated. Flash chromatography (50% EtOAc/hexanes) afforded 0.145 g (88%) of a colorless oil; $[\alpha]_D^{20}$ -43.0 (*c* 1.09, CHCl₃); IR (neat) 3279, 1733, 1161 cm⁻¹; ¹H NMR (CDCl₃) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.12 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.00 (m, 2H), 5.96 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.79 (quint, *J* = 6.4 Hz, 1H), 2.31 (s, 3H), 1.13 (m, 6H); ¹³C NMR δ 174.9, 143.1, 139.4, 138.4, 129.5, 128.6, 127.7, 127.3, 126.9, 61.2, 60.5, 46.3, 21.7, 15.8, 14.3. Spectral properties were consistent with literature values.²⁵

(2*S*,3*R*)-(+)-Ethyl 2-methyl-3-(4-methylphenylsulfonamido)-3-phenyl-propanoate the enantiomer of (-)-7** from (*R_S*,2*S*)-(-)-**15a****

In an oven-dried, 50 mL one necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed (-)-**15a** (0.110 g, 0.354 mmol) in anhydrous MeOH (13 mL). The solution was cooled to 0 °C, HCl (0.7 mL, 2.0 M in Et₂O) was added dropwise, warmed up to rt, stirred for 3 h, and quenched by addition of 1 N NaOH solution adjusting the pH to 9. The solution was extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), dried (MgSO₄), and concentrated. The residue was placed in a 15 mL single necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon in DCM (5.2 mL). TsCl (0.067 g, 0.531 mmol) was added, the solution was cooled to 0 °C, and Et₃N (0.1 mL, 0.708 mmol) and DMAP (2.1 mg, 0.0177 mmol) were added. The reaction mixture was warmed to rt, stirred for 12 h, and quenched with H₂O (3 mL). The solution was extracted with DCM (3 × 5 mL), the combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (25% EtOAc/hexanes) afforded 0.101 g (79%) of colorless oil; [α]_D²⁰ +45.0 (*c* 0.21, CHCl₃), [α]_D²⁰ -43.0 (*c* 1.09, CHCl₃) for the enantiomer of (-)-**7**; IR (neat) 3279, 1733, 1161 cm⁻¹; ¹H NMR (CDCl₃) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.12 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.0 (m, 2H), 5.96 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.79 (quint, *J* = 6.4 Hz, 1H), 2.31 (s, 3H), 1.13 (m, 6H); ¹³C NMR δ 174.9, 143.1, 139.4, 138.4, 129.5, 128.6, 127.7, 127.3, 126.9, 61.2, 60.5, 46.3, 21.7, 15.8, 14.3. HRMS calcd for C₁₉H₂₂NO₄S(M+H) 362.1426. Found 362.1419.

(2*R*,3*S*)-(-)-2-Methyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoic acid (8**)**

In an oven-dried, 10 mL one necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and rubber septum was placed (-)-**7** (0.0435 g, 0.120 mmol) and LiOH monohydrate (0.0435 g, 0.120 mmol) in THF (9 mL) and H₂O (0.33 mL). The reaction mixture was refluxed for 16 h at 67 °C, cooled to rt, and concentrated. The residue was diluted with DCM (10 mL), and 1 N HCl was added until the solution reached pH >2. The solution was stirred for 10 min, extracted with DCM (3 × 5 mL), the combined organic phases were washed with brine (4 mL), dried (MgSO₄), and concentrated. Preparative TLC (50% EtOAc/hexanes) afforded 0.0363 g (91%) of white solid, mp 131-133 °C; [lit^{15b} mp 135-136 °C]; [α]_D²⁰ -23.6 (*c* 0.49, EtOAc), [lit^{15b} [α]_D²⁰ -25.6 (*c* 0.06, EtOAc), lit^{15a} [α]_D²⁰ -28.1 (*c* 1.0, EtOAc)]; IR (neat) 3263, 1712, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 7.47 (m, 2H), 7.11 (m, 3H), 7.02 (m, 4H), 6.20 (d, *J* = 9.2 Hz, 1H), 4.50 (dd, *J* = 7.2, 8.8 Hz, 1H), 2.87 (quint, *J* = 6.8 Hz, 1H), 2.29 (s, 3H), 1.17 (d, *J* = 6.8 Hz, 3H); ¹³C NMR δ 178.6, 143.3, 138.9, 138.0, 129.5, 128.7, 127.9, 127.3, 127.1, 60.5, 46.1, 21.7, 15.7. HRMS calcd for C₁₇H₂₀NO₄S(M+H) 334.1113. Found 334.1126. Spectral properties were consistent with literature values.¹⁵

(3*R*,4*S*)-(-)-3-Methyl-4-phenyl-1-tosylazetidin-2-one (9**)**

In an oven-dried, 10 mL one necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (-)-**8** (0.0224 g, 0.067 mmol), DCC (0.017 mg, 0.0804 mmol), and 4-pyrrolidinopyridine (3.7 mg) in DCM (2.5 mL). The reaction mixture was stirred for 16 h at rt, filtered through celite and the filtrate was washed with water (3.0 mL), 5% aqueous HOAc (3 mL), and water (3 mL). The combined organic phases were washed with brine (3.5 mL), dried (MgSO₄), and concentrated. Preparative TLC (25% EtOAc/hexanes) afforded 0.0165 g (80%) of a white solid, mp 133-135 °C [lit^{15a} mp 134-135 °C]; [α]_D²⁰ -103 (*c* 0.58, EtOAc), lit^{15a} [α]_D²⁰ -114 (*c* 1.05, EtOAc)]; IR (neat) 1794, 1361, 1168 cm⁻¹; ¹H NMR (CDCl₃) δ 7.62 (dd, *J* = 3.2, 6.4 Hz, 2H), 7.26 (m, 7H), 4.60 (d, *J* = 3.2 Hz, 1H), 3.16 (m, 1H), 2.42 (s, 3H), 1.34 (d, *J* = 7.6 Hz, 3H); ¹³C NMR δ 167.9, 145.4, 136.5, 136.1, 130.1, 129.3, 129.2, 127.8, 126.9, 65.4, 55.0, 22.0, 12.8. HRMS calcd for C₁₇H₁₈NO₃S [M+H] 316.1007. Found 316.1013. Spectra properties were consistent with literature values.¹⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Retrosynthetic approach to α -substituted N -sulfinyl β -amino esters.

Scheme 1.

Scheme 2.

Figure 2.
Model for the addition of vinylaluminum to the *si*-face of (*S*)-(+)-**3**.

Scheme 3.

Scheme 4.

Table 1

Reaction of (*S*)-(+)-**3** with [α -(ethoxycarbonyl)vinyl]diisobutylaluminum (**2**) at 0 °C in THF for 6 h.

Entry	Conditions (equiv) ^a 1:DIBAL-H:NMO	d.r. ^b	(+)- 4 % isolated yield ^c
1	1:1.5:2.0	9:1	17
2	3.0:4.5:6.0	7:1	65
3	3.0:4.5:6.0 [3 Zn(OTf) ₂]	8:1	63

^a) Equivalents based on sulfinamide (+)-**3**.

^b) Determined by ¹H NMR on the crude reaction mixture.

^c) Isolated yield of major diastereoisomer.

Table 2Reaction of propargylic esters **1**, **10**, and **11** with sulfinimines (+)-(*S*)-**3** and (-)-(*R*)-**12**.

entry	sulfinamide	1 , 10 , or 11 :DIBAL-H:NMO (equiv)	°C (h)	Products % yield ^a (dr) ^b
1	(+)- 3	(10 : R = Me) 3.0:4.5:6.0	25 (16)	13 , 61 (5:1) ^c
2	(-)- 12a (R' = Ph)	(1 : R = H) 3.0:4.5:6.0	25 (6)	No reaction
3		(1 : R = H) 3.0:4.5:6.0	25 (23)	14a , 41 (3:1)
4		(1 : R = H) 3.0:4.5:6.0	45 (15)	14a , 38 (12:1)
5		(1 : R = H) 3.0:4.5:6.0	70 (15)	14a , 65 (12:1)
6		(10 : R = Me) 3.0:4.5:6.0	70 (15)	14b 71 (7:1)
7		(11 : R = Ph) 3.0:4.5:6.0	70 (15)	14c , 73 (7:1)
8	(-)- 12b (R' = Et)	(1 : R = H) 3.0:4.5:6.0	70 (15)	14d , 58 (13:1) ^{c,d}
9		(10 : R = Me) 3.0:4.5:6.0	70 (15)	14e , 50 (11:1) ^{c,d}
10		(11 : R = Ph) 3.0:4.5:6.0	70 (15)	14f , 35 (6.2:1)

^a) Isolated yield of major diastereoisomer.^b) Determined by ¹H NMR on the crude reaction mixture.^c) Inseparable isomers.^d) Determined by ¹H NMR on the mixture after purification.

Table 3Hydrogenation of *aza*-Morita-Baylis-Hillman adducts with catalysts **A**.

entry	14 (R', R =)	Conditions Time (h), atm of H ₂	solvent	15 dr (% yield) ^a
1	14a (Ph, H)	48, 1	CH ₂ Cl ₂	15a , 21:1 (83%)
2	14b (Ph, Me)	72, 25	ClCH ₂ CH ₂ Cl	15b , 20:1 (81%)
3	14c (Ph, Ph)	72, 25	ClCH ₂ CH ₂ Cl	15c , 20:1 (79%)
4	14d (Et, H)	48, 1	CH ₂ Cl ₂	15d , 10:1 (55%)
5	14e (Et, Me)	72, 25	ClCH ₂ CH ₂ Cl	15e , decomposition
6	14f (Et, Ph)	72, 25	ClCH ₂ CH ₂ Cl	15d , 17:1 (79%)

^a) Isolated yield of major diastereoisomer.