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Asymmetric Synthesis of α-Amino Acids by Reduction of *N-tert*-Butanesulfinyl Ketimine Esters

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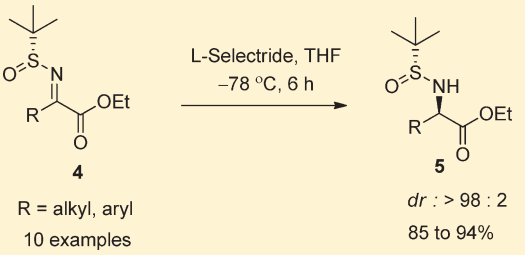
Supporting Information

ABSTRACT: A highly regio- and diastereoselective reduction of various *N-tert*-butanesulfinyl ketimine esters with L-Selectride resulting in the formation of α-amino acids is reported. This method is quite general and also practical for the preparation of both enantiomers of aryl or aliphatic α-amino acids in high yields.

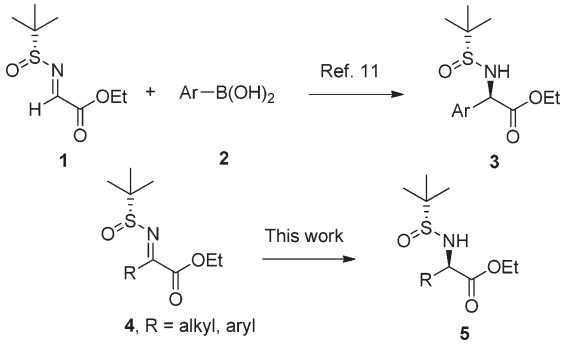


INTRODUCTION

Natural and unnatural α-amino acids are components of a number of significant drugs, including glycopeptide antibiotics, β-lactam antibiotics such as vancomycin,[1] cefprozil,[2] amoxicillin,[3] ampicillin,[4] antihypertensive drugs such as enalapril,[5] a GnRH hormone such as nafarelin,[6] and the cardiovascular agent Plavix.[7] The asymmetric synthesis of unnatural α-amino acids is a fundamental challenge in organic chemistry.[8] Therefore, intense research has been focused on the preparation of enantiomerically enriched α-amino acids.[9]

The classical approach to obtain enantiomerically pure α-amino acids is by resolution of the racemate via diastereoselective salt formation and also enzyme-catalyzed kinetic resolution even used on an industrial scale.[10a] However, the maximum theoretical yield for resolution is only 50%.[10] The commercially available *N-tert*-butanesulfinamides have been widely used as highly efficient chiral auxiliaries in the synthesis of a variety of optically active amines by virtue of their excellent diastereocontrol and mild conditions for their cleavage.[11] Recently, Ellman has reported[12] an elegant method for the asymmetric synthesis of α-amino acids by the rhodium-catalyzed addition of arylboronic acids to *N-tert*-butanesulfinyl aldimine esters (**1**), which proceeds in high yield with high diastereoselectivity for both electron-rich and electron-poor arylboronic acids (**2**); but this method has some limitations: it is limited to the synthesis of only arylglycine derivatives. We reasoned that a direct method to access enantioenriched α-amino acids would be an asymmetric reduction of *N-tert*-butanesulfinyl ketimine esters (**4**), which has not been described to the best of our knowledge.[10] Herein, we report a versatile and practical method for highly regio- and diastereoselective reduction of *N-tert*-butanesulfinyl ketimine esters (**4**) to give α-amino acids (**5**) with high yields (Scheme 1). The *tert*-butanesulfinyl group not only induces excellent diastereoselectivity but also serves as an efficient low molecular weight protecting group for the nitrogen for future modifications of the carboxylic acid of the α-amino acids, if needed.

Scheme 1. Approaches to α-Amino Acids



RESULTS AND DISCUSSION

N-tert-Butanesulfinyl ketimine esters (R_S)-**4a**–**k**[13] were synthesized in high yield via condensation of readily available corresponding α-ketoesters (1.0 equiv)[14] with (R_S)-*N-tert*-butanesulfinamide (1.1 equiv)[15] in the presence of 1.5 equiv of $Ti(OEt)_4$[16] in THF at reflux temperature for 6 h. In the same way, the *N-tert*-butanesulfinyl ketimine esters (S_S)-**4a**,**g** were synthesized via condensation of corresponding α-ketoesters with (S_S)-*N-tert*-butanesulfinamide.

Treatment of *N-tert*-butanesulfinyl ketimine esters (R_S)-**4a** (1 equiv) with L-Selectride (1.05 equiv, slow addition by syringe pump for 1 h) at −78 °C in THF for 6 h afforded α-amino acid derivative **5a** (Table 1, entry 1) in high yield (93%) and with a high diastereomeric ratio (dr ≥ 98:2). The diastereoselectivity of the reaction was determined to be ≥98:2 by ^{1}H NMR analysis of the crude product.[17] The structure and absolute configuration of

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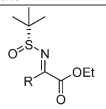
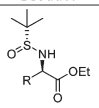
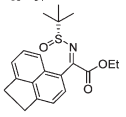
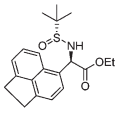
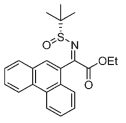
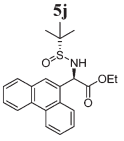
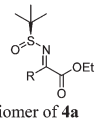
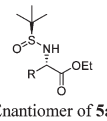
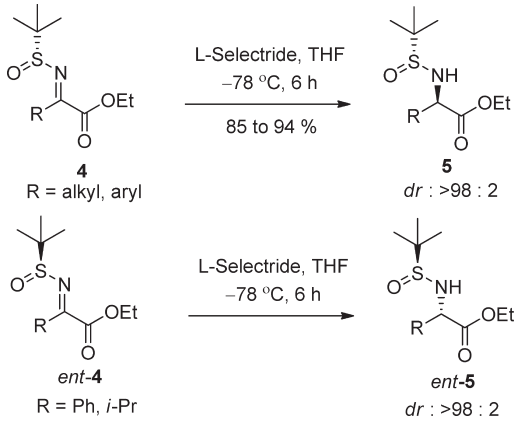
Table 1. Asymmtric Reduction of *N-tert*-Butanesulfinyl Ketimine Esters with L-Selectride

Entry	Substrate	Product	Yield (%)[a]	dr[b]
				
1	**4a** = Ph	**5a**	93	≥98 : 2
2	**4b** = 4-Cl-Ph	**5b**	88	≥98 : 2
3	**4c** = 3,5-di-F-Ph	**5c**	85	≥98 : 2
4	**4d** = 4-OMe-Ph	**5d**	86	≥98 : 2
5	**4e** = 4-*t*-Bu-Ph	**5e**	90	≥98 : 2
6	**4f** = 4-*n*-Bu-Ph	**5f**	89	≥98 : 2
7	**4g** = Me	**5g**	88	≥98 : 2
8	**4h** = *i*-Pr	**5h**	86	≥98 : 2
9	**4i** = $C_{18}H_{37}$	**5i**	94	≥98 : 2
				
10	**4j**	**5j**	90	≥98 : 2
				
11	**4k**	**5k**	91	≥98 : 2
				
12	Enantiomer of **4a**	Enantiomer of **5a**	90	≥98 : 2
13	Enantiomer of **4h**	Enantiomer of **5h**	85	≥98 : 2

[a] Isolated yield. [b] The diastereoselectivity was determined by ^{1}H NMR analysis. The "≥ 98:2" dr denotes that signals for only one diastereomer were observed.

Scheme 2. Reduction of Various *N-tert*-Butanesulfinyl Ketimine Esters with L-Selectride



(R_s,*R*)-**5a** were confirmed by comparing the ^{1}H NMR, ^{13}C NMR, and specific rotation with literature data.[12] The reduction of *N-tert*-butanesulfinyl ketimine ester (S_S)-*ent*-**4a** (Table 1, entry 12) with L-Selectride at −78 °C in THF for 6 h afforded the other enantiomer of the α-amino acid derivative (*ent*-**5a**) in high yield (90%) and with high diastereomeric ratio (dr ≥98:2) (Scheme 2). A series of other metal hydrides (Table 2) were screened to further elaborate this reduction, L-selectride gave the

Table 2. Asymmtric Reduction of *N-tert*-Butanesulfinyl Ketimine Esters 4a with Various Metal Hydrides

entry	reducing agent	conversion (%)	dr[a,c]
1	L-Selectride	100	≥98:2
2	$LiBHEt_3$	100	95:5
3[b]	$NaBH_4$	60	45:55
4	$NaBH_3CN$	82	40:60
5	$LiBH_4$	75[d]	39:61
6	9-BBN	90	38:62

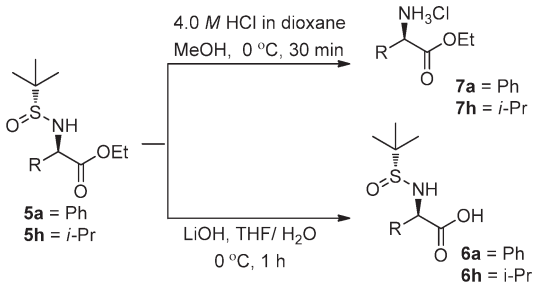
[a] All reactions were performed with 1.1 equiv of reducing agent at −78 °C for 12 h in THF, unless stated otherwise indicated. [b] 10 equiv of MeOH is used. [c] The diastereoselectivity was determined by ^{1}H NMR analysis. The "≥ 98:2" dr denotes that signals for only one diastereomer were observed. [d] 5% alcohol was formed.

Table 3. Asymmtric Reduction of *N-tert*-Butanesulfinyl Ketimine Ester 4a with L-Selectride at Different Temperatures

entry	temp (°C)	conversion (%)	dr[a,b]
1	−78	100	≥98:2
2	−50	100	96:4
3	−20	100[c]	88:12
4	0	100[d]	85:15

[a] All reactions were performed with 1.1 equiv of reducing agent for 6 h in THF, unless otherwise indicated. [b] The diastereoselectivity was determined by ^{1}H NMR analysis. The "≥ 98:2" dr denotes that signals for only one diastereomer were observed. [c] 11% alcohol was formed. [d] 18% alcohol was formed.

Scheme 3. Selective Fuctional Group Tranformations



best results in terms of diastereo- and regioselectivities. We also investigated this readuction at different temparatures (Table 3), and the best results were obtained at −78 °C in THF.

Encouraged by these results, we turned our attention to other substituted aromatic *N-tert*-butanesulfinyl ketimine esters. Interestingly, a large number of substituted aromatic *N-tert*-butanesulfinyl ketimine esters, such as *p*-chloro, *p*-methoxy, *p-tert*-butyl, *p-n*-butyl, and 3,5-difluoro derivatives, reacted cleanly with L-Selectride at −78 °C in THF for 6 h, leading to the corresponding α-amino acid derivatives **5b**−**f** (Table 1, entries 2−6) in excellent yields (85−90%) and with high diastereometric ratios (dr ≥98:2).

Similarly, polyaromatic *N-tert*-butanesulfinyl ketimine esters, such as naphthyl derivative **4j** and anthracenyl *N-tert*-butanesulfinyl ketimine esters **4k**, were smoothly reduced with L-Selectride at −78 °C in THF for 6 h, affording the correspending α-amino

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acid derivative **5j** and **5k** (Table 1, entries 10 and 11) in 90% and 91% yield, respectively, with high diastereomeric ratio (dr ≥98:2). In the same way, reduction of aliphatic N-*tert*-butanesulfinyl ketimine esters, such as methyl ketimine ester **4g** and isopropyl ketimine ester **4h**, with L-Seletride in THF at −78 °C for 6 h afforded **5g** and **5h** in high yields (88% and 86%, respectively) and with high diastereomeric ratio (dr ≥98:2). Similarly, the long chain aliphatic *N*-*tert*-butanesulfinyl ketimine ester **4i** was also reduced with L-Selectride in THF at −78 °C for 6 h to afford **5i** (Table 1, entry 9) in high yield (94%) and with high diastereoselectivity (dr ≥98:2). Referring to the literature,[18] a possible mechanistic model explains the achieved stereoselectivity (R_S,*R*-**5**), which involves a cyclic chair transition state.

A key feature of this α-amino acid synthesis method is the versatility of *N*-sulfinyl-α-amino ester products **5a**,**h** in subsequent transformations. Selective cleavage of the sulfinyl group with 4.0 M HCl in methanol at 0 °C for 30 min,[12] or ester group with LiOH in THF/water at 0 °C for 1 h,[19] can be accomplished in high yields without loss of stereochemical purity (Scheme 3).

CONCLUSION

In conclusion, we have described a practical, highly distereoselective reduction of various *N*-*tert*-butanesulfinyl ketimine esters with L-Selectride affording chiral α-amino acids. This method is quite general for the preparation of both enantiomers of aromatic and aliphatic α-amino acids. Extension of this work is currently under way in our laboratory.

EXPERIMENTAL SECTION

General Information. All the reactions were performed under dry nitrogen gas in glassware that was flame-dried and equipped with a magnetic stirring bar. Tetrahydrofuran (THF) was freshly distilled from the sodium complex of benzophenone before use. Thin-layer chromatography (TLC) was performed with silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed with silica gel (40 μm particle size). All compounds were judged pure by TLC analysis (single spot/two solvent systems), using a UV lamp or PMA for detection purposes. ^{1}H and ^{13}C NMR spectra were recorded on a FT-NMR spectrometer at 500 and 125 MHz, respectively. High-resolution mass spectroscopy (HRMS) was carried out in electrospray mode. All the reagents were purchased from commercial suppliers and used without further purification. Unless indicated otherwise, the reaction temperatures refer to internal reaction temperatures.

General Procedure (GP1) for the Synthesis of *N*-*tert*-Butanesulfinyl Ketimine Esters 4. A 500 mL, three-necked, round-bottomed flask was charged with α-ketoesters (40.0 mmol), THF (100 mL), *tert*-butanesulfinamide (44.0 mmol), and $Ti(OEt)_4$ (60.0 mmol) under nitrogen atm. The reaction mixture was then heated at reflux at 65 °C for 6 h. After completion, the reaction was allowed to cool to rt. Isopropyl acetate (100 mL) and saturated NaCl solution (100 mL) were then added and the mixture was stirred for 1 h. The solids were removed by filtration, and the filtrate was washed with water (2 × 50 mL). The organic phase was evaporated under vacuum to dryness to obtain the crude product. The crude product was purified by flash column chromatography (silica gel, 10% ethyl acetate in heptanes) to afford the pure *N*-*tert*-butanesulfinyl ketimine esters **4**.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate, 4a: Following the general procedure (GP1), the reaction of ethyl 2-oxo-2-phenylacetate (17.8 g, 100.0 mmol) with (R_S)-*tert*-butanesulfinamide (13.3 g, 110.0 mmol) and $Ti(OEt)_4$ (34.5 g, 150.0 mmol) gave 23.6 g (84%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate (**4a**) as a viscous liquid. $[\alpha]^{25}_D$ −114.3 (*c* 0.89, $CHCl_3$). FTIR (ATR) *ν* 2981, 1736, 1571, 1287, 1203, 1180, 1090, 1018, 689 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.34 (s, 9 H), 1.41 (t, *J* = 7.09 Hz, 3 H), 4.45 (dd, *J* = 12.45, 7.09 Hz, 2 H), 7.45 (t, *J* = 7.57 Hz, 2 H), 7.52 (d, *J* = 7.25 Hz, 1 H), 7.73−7.82 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.0, 23.0, 59.5, 62.2, 127.8, 128.8, 132.6, 133.1, 163.3, 165.8. HRMS (EI) calcd for $C_{14}H_{20}NO_3S$ [M + H] 282.1164, found 282.1169.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-chlorophenyl) acetate, 4b: Following the general procedure (GP1), the reaction of ethyl 2-(4-chlorophenyl)-2-oxoacetate (12.1 g, 100.0 mmol) with (R_S)-*tert*-butanesulfinamide (13.3 g, 110.0 mmol) and $Ti(OEt)_4$ (34.5 g, 150.0 mmol) gave 25.2 g (80%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-chlorophenyl)acetate (**4b**) as a viscous liquid. $[\alpha]^{25}_D$ −57.0 (*c* 1.31, $CHCl_3$). FTIR (ATR) *ν* 2979, 1733, 1586, 1564, 1258, 1207, 1168, 1086, 877 cm^{-1}. ^{1}H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 1.34 (s, 9 H), 1.41 (t, *J* = 7.25 Hz, 3 H), 4.34−4.52 (m, 2 H), 7.42 (d, *J* = 8.51 Hz, 2 H), 7.71 (d, *J* = 8.51 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 23.0, 59.6, 62.3, 129.1, 129.2, 131.6, 138.9, 162.2, 165.4. HRMS (EI) calcd for $C_{14}H_{19}NO_3SCl$ [M + H] 316.0774, found 316.0778.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(3,5-difluorophenyl) acetate, 4c: Following the general procedure (GP1), the reaction of ethyl 2-(3, 5-difluorophenyl)-2-oxoacetate (2.14 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.33 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 2.45 g (78%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(3,5-difluorophenyl)acetate (**4c**) as a viscous liquid. $[\alpha]^{25}_D$ −120.1 (*c* 1.10, $CHCl_3$). FTIR (ATR) *ν* 2982, 1736, 1586, 1331, 1255, 1150, 1095, 991, 854 cm^{-1}. ^{1}H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 1.35 (s, 9 H), 1.42 (t, *J* = 7.09 Hz, 3 H), 4.39−4.55 (m, 2 H), 6.94−7.02 (m, 1 H), 7.29 (dd, *J* = 7.88, 2.21 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.8, 22.9, 60.0, 62.6, 107.7 (t, *J* = 25.20 Hz), 107.7, 110.6, 110.8, 136.1, 162.0 (d, *J* = 11.91 Hz), 164. 0 (d, *J* = 11.91 Hz), 164.8. HRMS (EI) calcd for $C_{14}H_{18}NO_3SF_2$ [M + H] 318.975, found 318.970.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-methoxyphenyl)acetate, 4d: Following the general procedure (GP1), the reaction of ethyl 2-(4-methoxyphenyl)-2-oxoacetate (2.08 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.33 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 2.23 g (72%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-methoxyphenyl)acetate (**4d**) as a viscous liquid. $[\alpha]^{25}_D$ −98.2 (*c* 1.02, $CHCl_3$). FTIR (ATR) *ν* 2981, 1731, 1599, 1577, 1229, 1157, 1075, 842 cm^{-1}. ^{1}H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 1.32 (s, 9 H), 1.40 (t, *J* = 7.25 Hz, 3 H), 3.85 (s, 3 H), 4.33−4.55 (m, 2 H), 6.93 (d, *J* = 8.83 Hz, 2 H), 7.73 (d, *J* = 8.83 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.9, 55.5, 59.1, 62.1, 114.2, 125.9, 129.9,162.7, 163.2, 165.9. HRMS (EI) calcd for $C_{15}H_{22}NO_4S$ [M + H] 312.1270, found 312.1273.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-*tert*-butylphenyl) acetate, 4e: Following the general procedure (GP1), the reaction of ethyl 2-(4-*tert*-butylphenyl)-2-oxoacetate (2.34 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.33 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 2.72 g (81%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-*tert*-butylphenyl)acetate (**4e**) as a viscous liquid. $[\alpha]^{25}_D$ −60.4 (*c* 0.9, $CHCl_3$). FTIR (ATR) *ν* 2962, 1739, 1590, 1558, 1211, 1188, 1091, 832 cm^{-1}. ^{1}H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 1.33 (s, 18 H), 1.40 (t, *J* = 7.25 Hz, 3 H), 4.36−4.53 (m, 2 H), 7.42−7.51 (m, 2 H), 7.71 (d, *J* = 8.83 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.9, 31.0, 35.1, 62.1, 125.8, 127.7, 130.5, 156.4, 163.2, 165.9. HRMS (EI) calcd for $C_{18}H_{28}NO_3S$ [M + H] 338.1790, found 338.1795.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-butylphenyl) acetate, 4f: Following the general procedure (GP1), the reaction of ethyl 2-(4-butylphenyl)-2-oxoacetate (2.33 g, 10.0 mmol) with (R_S)-

tert-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 2.91 g (92%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl) imino]-2-(4-butylphenyl)acetate (**4f**) as a viscous liquid. $[\alpha]^{25}_D$ −66.5 (*c* 0.94, $CHCl_3$). FTIR (ATR) *ν* 2958, 2930, 1738, 1590, 1562, 1208, 1179, 1091, 838, 754 cm^{-1}. ^1H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 0.93 (t, *J* = 7.25 Hz, 3 H), 1.27−1.37 (m and s, 11 H), 1.40 (t, *J* = 7.25 Hz, 3 H), 1.55−1.65 (m, 2 H), 2.66 (t, *J* = 7.57 Hz, 2 H), 4.44 (dd, *J* = 12.61, 7.25 Hz, 2 H), 7.19−7.29 (m, 2 H), 7.68 (d, *J* = 8.51 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.8, 13.9, 22.2, 22.9, 33.2, 35.6, 59.3, 62.1, 127.9, 128.9, 130.7, 148.4, 163.3, 165.9. HRMS (EI) calcd for $C_{18}H_{28}NO_3S$ [M + H] 338.1790, found 338.1793.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]propanoate, 4g: Following the general procedure (GP1), the reaction of ethyl 2-oxopropanoate (1.16 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 1.86 g (85%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino)propanoate (**4g**) as a viscous liquid. $[\alpha]^{25}_D$ −125.8 (*c* 1.79, $CHCl_3$). FTIR (ATR) *ν* 2981, 1778, 1734, 1253, 1129, 1019, 859 cm^{-1}. ^1H NMR (501 MHz, $CDCl_3$) *δ* (ppm) 1.32 (t and m, 12 H), 2.46 (s, 3 H), 4.19−4.41 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 18.2, 22.7, 25.1, 59.1, 62.2, 163.3, 166.7, 167.6. HRMS (EI) calcd for $C_9H_{18}NO_3S$ [M + H] 220.1007, found 220.1011.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-3-methylbutanoate, 4h: Following the general procedure (GP1), the reaction of ethyl 3-methyl-2-oxobutanoate (1.16 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 1.86 g (85%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-3-methylbutanoate (**4h**) as a viscous liquid. $[\alpha]^{25}_D$ −154.2 (*c* 1.64, $CHCl_3$). FTIR (ATR) *ν* 2975, 1734, 1626, 1251, 1178, 1089, 847 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.20 (t, *J* = 6.15 Hz, 6 H), 1.25 (s, 9 H), 1.36 (t, *J* = 7.09 Hz, 3 H), 2.79−2.90 (m, 1 H), 4.24−4.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 18.9, 19.3, 22.5, 37.1, 58.1, 61.7, 166.5, 174.2. HRMS (EI) calcd for $C_{11}H_{22}NO_3S$ [M + H] 248.1313, found 248.1317.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]icosanoate, 4i: Following the general procedure (GP1), the reaction of ethyl 2-oxoicosanoate (3.54 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 4.34 g (95%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino] icosanoate (**4i**) as a viscous liquid. $[\alpha]^{25}_D$ −127.7 (*c* 1.22, $CHCl_3$). FTIR (ATR) *ν* 2916, 2849, 1737, 1631, 1471, 1253, 1091, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 0.88 (m, 3 H), 1.18−1.32 (m, 36 H), 1.35 (q, *J* = 7.04 Hz, 6 H), 1.50−1.75 (m, 2 H), 2.46−2.71 (m, 2 H), 4.18−4.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 14.1, 22.6, 22.7, 25.0, 26.9, 29.4, 29.5, 29.7, 31.9, 38.4, 58.0, 61.3, 166.9, 170.3. HRMS (EI) calcd for $C_{26}H_{52}NO_3S$ [M + H] 458.3668, found 458.3666.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(1,2-dihydroacenaphthylen-5-yl)acetate, 4j: Following the general procedure (GP1), the reaction of ethyl 2-(1,2-dihydroacenaphthylen-5-yl)-2-oxoacetate (2.54 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 3.24 g (91%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(1,2-dihydroacenaphthylen-5-yl)acetate (**4j**) as a viscous liquid. $[\alpha]^{25}_D$ −116.1 (*c* 0.88, $CHCl_3$). FTIR (ATR) *ν* 2955, 1733, 1576, 1248, 1177, 1085, 832 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.39 (s, 9 H), 1.41 (t, *J* = 7.09 Hz, 3 H), 3.25−3.40 (m, 4 H), 4.41−4.53 (m, 2 H), 7.25 (d, *J* = 7.25 Hz, 1 H), 7.33 (d, *J* = 6.62 Hz, 1 H), 7.55 (dd, *J* = 8.51, 6.94 Hz, 1 H), 7.75 (d, *J* = 7.25 Hz, 1 H), 8.72 (d, *J* = 8.83 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.0, 22.9, 30.3, 30.4, 53.4, 58.8, 62.2, 118.6, 120.5, 121.9, 125.0, 129.3, 130.2, 132.6, 139.7, 146.7, 153.1, 165.1, 165.9. HRMS (EI) calcd for $C_{20}H_{24}NO_3S$ [M + H] 358.3477, found 358.3479.

(*R*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(phenanthren-9-yl)acetate, 4k: Following the general procedure (GP1), the reaction of ethyl 2-(phenanthren-9-yl)-2-oxoacetate (2.78 g, 10.0 mmol) with (R_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 3.42 g (90%) of pure (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl) imino]-2-(phenanthren-9-yl)acetate (**4k**) as a viscous liquid. $[\alpha]^{25}_D$ −124.8 (*c* 1.10, $CHCl_3$). FTIR (ATR) *ν* 2982, 1729, 1597, 1261, 1204, 1115, 1087, 728 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.28−1.47 (m, 12 H), 4.45 (q, *J* = 6.94 Hz, 2 H), 7.56 (t, *J* = 7.41 Hz, 1 H), 7.59−7.69 (m, 3 H), 7.88 (d, *J* = 7.57 Hz, 1 H), 8.09 (s, 1 H), 8.57 (d, *J* = 8.20 Hz, 1 H), 8.61−8.68 (m, 1 H), 8.77 (d, *J* = 7.57 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.0, 23.0, 59.1, 62.5, 122.6, 123.1, 126.4, 127.2, 127.2, 128.7, 128.9, 129.9, 130.1, 130.4, 130.9, 131.6, 165.6. HRMS (EI) calcd for $C_{22}H_{24}NO_3S$ [M + H] 382.1477, found 382.1481.

(*S*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate, *ent*-4a: Following the general procedure (GP1), the reaction of ethyl 2-oxo-2-phenylacetate (8.9 g, 50.0 mmol) with (R_S)-*tert*-butanesulfinamide (6.65 g, 55.0 mmol) and $Ti(OEt)_4$ (17.25 g, 75.0 mmol) gave 12.3 g (89%) of pure (*S*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate (*ent*-**4a**) as a viscous liquid. $[\alpha]^{25}_D$ +110.2 (*c* 1.08, $CHCl_3$). FTIR (ATR) *ν* 2980, 1736, 1571, 1287, 1203, 1190, 1018, 689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.35 (s, 9 H), 1.41 (t, *J* = 7.25 Hz, 3 H), 4.38−4.53 (m, 2 H), 7.45 (t, *J* = 7.57 Hz, 2 H), 7.53 (d, *J* = 7.25 Hz, 1 H), 7.73−7.84 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.0, 23.0, 59.5, 62.3, 127.8, 128.8, 132.6, 133.1, 163.3, 165.8. HRMS (EI) calcd for $C_{14}H_{20}NO_3S$ [M + H] 282.1164, found 282.1169.

(*S*,*E*)-Ethyl 2-[(*tert*-butylsulfinyl)imino]-3-methylbutanoate, *ent*-4h: Following the general procedure (GP1), the reaction of ethyl 3-methyl-2-oxobutanoate (1.18 g, 10.0 mmol) with (S_S)-*tert*-butanesulfinamide (1.35 g, 11.0 mmol) and $Ti(OEt)_4$ (3.45 g, 15.0 mmol) gave 1.75 g (80%) of pure (*S*,*E*)-ethyl 2-[(*tert*-butylsulfinyl) imino]-3-methylbutanoate (*ent*-**4h**) as a viscous liquid. $[\alpha]^{25}_D$ +152.2 (*c* 1.10, $CHCl_3$). FTIR (ATR) *ν* 2981, 1733, 1624, 1250, 1180, 1088, 848 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.20 (t, *J* = 6.15 Hz, 6 H), 1.25 (s, 9 H), 1.36 (t, *J* = 7.09 Hz, 3 H), 2.75−2.89 (m, 1 H), 4.21−4.41 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 16.3, 21.2, 21.7, 24.9, 39.4, 60.4, 64.1, 168.9, 176.6. HRMS (EI) calcd for $C_{11}H_{22}NO_3S$ [M + H] 248.1313, found 248.1315.

General Procedure (GP2) for the Synthesis of α-Amino Acids 5. L-Selectride (5.25 mL, 5.5 mmol, 1.0 M solution in THF solution) was added to a solution of ketimine ester **4** (5 mmol) in THF (20 mL) at −78 °C under nitrogen (by syringe pump for 1 h). After being stirred for 6 h at −78 °C, the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with water and dried under vacuum to give crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexanes) to afford the pure α-amino acid **5**.

(*R*)-Ethyl 2-[(*R*)-1,1-dimethylethylsulfinamido]-2-phenylacetate, 5a: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate (**4a**) (1.40 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5a** (1.31 g, 93%) as a viscous liquid. $[\alpha]^{25}_D$ −186.4 (*c* 0.98, $CHCl_3$). FTIR (ATR) *ν* 2980, 1733, 1247, 1175, 1066, 847, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.20 (t, *J* = 7.09 Hz, 3 H), 1.24 (s, 9 H), 4.09−4.18 (m, 1 H), 4.23 (dd, *J* = 10.72, 7.25 Hz, 1 H), 4.59 (d, *J* = 4.41 Hz, 1 H), 5.06 (d, *J* = 4.41 Hz, 1 H), 7.26−7.43 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 55.9, 60.4, 62.1, 127.6, 128.6, 137.2, 171.3. HRMS (EI) calcd for $C_{14}H_{22}NO_3S$ [M + H] 284.1320, found 284.1318.

(*R*)-Ethyl 2-(4-chlorophenyl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate, 5b: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-chlorophenyl)acetate (**4b**) (1.57 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5b** (1.39 g, 88%)

as a viscous liquid. $[\alpha]^{25}_{D}$ −66.1 (*c* 1.02, $CHCl_3$). FTIR (ATR) *ν* 2960, 1735, 1491, 1366, 1174, 1073, 1014, 824 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.20 (t, *J* = 7.25 Hz, 3 H), 1.23 (s, 9 H), 4.06−4.28 (m, 2 H), 4.62 (d, *J* = 4.10 Hz) 1 H), 5.04 (d, *J* = 4.10 Hz, 1 H), 7.27−7.37 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 55.9, 59.7, 62.3, 128.6, 129.1, 134.3, 135.8, 170.8. HRMS (EI) calcd for $C_{14}H_{21}NO_3SCl$ [M + H] 318.0931, found 318.0928.

(*R*)-Ethyl 2-(2,5-difluorophenyl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate, 5c: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(2,5-fluorophenyl)acetate (**4c**) (1.58 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5c** (1.35 g, 85%) as a viscous liquid. $[\alpha]^{25}_{D}$ −86.4 (*c* 1.12, $CHCl_3$). FTIR (ATR) *ν* 2981, 1736, 1624, 1598, 1459, 1183, 1119, 1071, 849, 673 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.23 (t, *J* = 7.09 Hz, 3 H), 1.27 (s, 9 H), 4.11−4.29 (m, 2 H), 4.60 (d, *J* = 3.78 Hz, 1 H), 5.03 (d, *J* = 4.10 Hz, 1 H), 6.72−6.81 (m, 1 H), 6.94 (d, *J* = 5.67 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 56.2, 59.5, 62.7, 103.9, (t, *J* = 25.20 Hz) 104.1, 110.6, 110.6, 141.0, 162.0 (d, *J* = 11.91 Hz), 164.0 (d, *J* = 12.81 Hz), 170.2. HRMS (EI) calcd for $C_{14}H_{20}NO_3SF_2$ [M + H] 320.1132, found 320.1125.

(*R*)-Ethyl 2-(4-methoxyphenyl)-2-[(*R*)-1,1-dimethylethylsulfinamido]actate, 5d: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-methoxyphenyl)acetate (**4d**) (1.55 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5d** (1.34 g, 86%) as a viscous liquid. $[\alpha]^{25}_{D}$ −161.1 (*c* 1., $CHCl_3$). FTIR (ATR) *ν* 2959, 1733, 1512, 1245, 1175, 1071, 831 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.20 (t, *J* = 7.09 Hz, 3 H), 1.23 (s, 9 H), 3.81 (s, 3 H), 4.04−4.30 (m, 2 H), 4.54 (d, *J* = 3.78 Hz, 1 H), 5.01 (d, *J* = 4.10 Hz, 1 H), 6.88 (d, *J* = 8.83 Hz, 2 H), 7.28 (d, *J* = 8.83 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 55.2, 55.8, 59.8, 62.0, 114.0, 128.9, 129.2, 159.8, 171.5. HRMS (EI) calcd for $C_{15}H_{24}NO_4S$ [M + H] 314.1426, found 314.1420.

(*R*)-Ethyl 2-(4-*tert*-butylphenyl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate, 5e: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-*tert*-butylphenyl)acetate (**4e**) (1.68 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5e** (1.52 g, 90%) as a viscous liquid. $[\alpha]^{25}_{D}$ −145.9 (*c* 0.98, $CHCl_3$). FTIR (ATR) *ν* 2959, 299, 1735, 1246, 1175, 1074, 849 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.22 (t, *J* = 7.09 Hz, 3 H), 1.24 (s, 9 H), 1.30−1.32 (m, 9 H), 4.07−4.17 (m, 1 H), 4.24 (dd, *J* = 10.72, 7.25 Hz, 1 H), 4.56 (d, *J* = 5.04 Hz, 1 H), 5.03 (d, *J* = 5.04 Hz, 1 H), 7.26−7.31 (m, 2 H), 7.33−7.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 31.2, 34.5, 55.9, 60.2, 62.0, 125.5, 127.1, 134.1, 151.2, 171.5. HRMS (EI) calcd for $C_{18}H_{30}NO_3S$ [M + H] 340.1946, found 340.1941.

(*R*)-Ethyl 2-(4-butylphenyl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate, 5f: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(4-butylphenyl)acetate (**4f**) (1.66 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5f** (1.50 g, 89%) as a viscous liquid. $[\alpha]^{25}_{D}$ −128.2 (*c* 1.16, $CDCl_3$). FTIR (ATR) *ν* 2960, 1734, 1249, 1174, 1077, 1018, 825 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 0.92 (t, *J* = 7.41 Hz, 3 H), 1.20 (t, *J* = 7.09 Hz, 3 H), 1.23 (s, 9 H), 1.32−1.41 (m, 2 H), 1.50−1.64 (m, 2 H), 2.54−2.64 (m, 2 H), 4.07−4.17 (m, 1 H), 4.17−4.28 (m, 1 H), 4.58 (d, *J* = 4.73 Hz, 1 H), 5.02 (d, *J* = 4.73 Hz, 1 H), 7.15 (d, *J* = 8.20 Hz, 2 H), 7.26 (d, *J* = 7.88 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.3, 22.5, 33.3, 35.2, 55.9, 60.3, 62.0, 127.4, 128.6, 134.4, 143.1, 171.5. HRMS (EI) calcd for $C_{18}H_{30}NO_3S$ [M + H] 340.1930, found 340.1921.

(*R*)-Ethyl 2-[(*R*)-1,1-dimethylethylsulfinamido]propanoate, 5g: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]propanoate (**4g**) (1.1 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5g** (0.96 g, 88%) as a viscous liquid. $[\alpha]^{25}_{D}$ −60.2 (*c* 1.04, $CDCl_3$). FTIR (ATR) *ν* 2981, 1733, 1286, 1194, 1131, 1053, 853 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.24 (s, 9 H), 1.27−1.32 (m, 3 H), 1.41 (d, *J* = 6.94 Hz, 3 H), 3.96−4.06 (m, 1 H), 4.16 (br s, 1 H), 4.22 (q, *J* = 7.25 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.1, 19.7, 22.5, 52.6, 55.7, 61.7, 173.4. HRMS (EI) calcd for $C_9H_{20}NO_3S$ [M + H] 222.1164, found 222.1156.

(*R*)-Ethyl 2-[(*R*)-1,1-dimethylethylsulfinamido]-3-methylbutanoate, 5h: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-3-methylbutanoate (**4h**) (1.2 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5h** (1.07 g, 86%) as a viscous liquid. $[\alpha]^{25}_{D}$ −100.8 (*c* 0.98, $CDCl_3$). FTIR (ATR) *ν* 2969, 1732, 1467, 1198, 1064, 724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 0.90 (d, *J* = 6.94 Hz, 3 H), 0.97 (d, *J* = 6.94 Hz, 3 H), 1.27 (s, 9 H), 1.29 (t, *J* = 7.09 Hz, 3 H), 2.00−2.18 (m, 1 H), 3.71 (dd, *J* = 7.88, 5.04 Hz, 1 H), 4.10 (d, *J* = 7.88 Hz, 1 H), 4.15−4.29 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.1, 17.3, 19.1, 22.7, 32.3, 56.2, 61.5, 63.1, 173.0. HRMS (EI) calcd for $C_{11}H_{24}NO_3S$ [M + H] 250.1477, found 250.1479.

(*R*)-Ethyl 2-[(*R*)-1,1-dimethylethylsulfinamido]icosanoate, 5i: Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]icosanoate (**4i**) (2.28 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5i** (2.15 g, 94%) as a viscous liquid. $[\alpha]^{25}_{D}$ −134.2 (*c* 1.14, $CHCl_3$). FTIR (ATR) *ν* 2915, 2850, 1740, 1470, 1180, 1072, 716 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 0.88 (t, *J* = 6.94 Hz, 3 H), 1.12−1.45 (m, 44 H), 1.62−1.86 (m, 2 H), 3.84−3.95 (m, 1 H), 4.08 (d, *J* = 7.25 Hz, 1 H), 4.22 (q, *J* = 7.25 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 14.1, 22.6, 24.9, 29.1, 29.3, 29.6, 29.7, 31.9, 33.9, 55.9, 57.4, 61.5, 173.4. HRMS (EI) calcd for $C_{26}H_{54}NO_3S$ [M + H] 460.3824, found 460.3820.

(*R*)-Ethyl 2-(1,2-dihydroacenaphthylen-5-yl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate 5j. Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-(1,2-dihydroacenaphthylen-5-yl)acetate (**4j**) (1.75 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5j** (1.61 g, 90%) as a viscous liquid. $[\alpha]^{25}_{D}$ −124.8 (*c* 1.10, $CHCl_3$). FTIR (ATR) *ν* 2959, 1729, 1215, 1178, 1068, 838 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.10 (t, *J* = 7.09 Hz, 3 H), 1.15 (s, 9 H), 3.27−3.43 (m, 4 H), 4.08 (dd, *J* = 10.88, 7.09 Hz, 1 H), 4.21 (dd, *J* = 10.88, 7.09 Hz, 1 H), 4.71 (d, *J* = 3.47 Hz, 1 H), 5.56 (d, *J* = 3.78 Hz, 1 H), 7.25 (dd, *J* = 21.75, 6.94 Hz, 2 H), 7.40−7.50 (m, 2 H), 7.76 (d, *J* = 8.51 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 30.0, 30.5, 55.7, 58.5, 62.1, 118.7, 119.5, 128.1, 129.5, 138.8, 146.4, 147.3, 172.0. HRMS (EI) calcd for $C_{20}H_{26}NO_3S$ [M + H] 360.1633, found 360.1630.

(*R*)-Ethyl 2-(phenanthren-9-yl)-2-[(*R*)-1,1-dimethylethylsulfinamido]acetate 5k. Following the general procedure (GP2), the reaction of (*R*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-(phenanthren-9-yl)acetate (**4k**) (1.90 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid **5k** (1.74 g, 91%) as a viscous liquid. $[\alpha]^{25}_{D}$ −134.4 (*c* 1.19, $CHCl_3$). FTIR (ATR) *ν* 2959, 1728, 1219, 1115, 1068, 728 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 1.04 (t, *J* = 7.09 Hz, 3 H), 1.12 (s, 9 H), 4.05−4.23 (m, 2 H), 5.64 (d, *J* = 3.15 Hz, 1 H), 7.50−7.65 (m, 4 H), 7.82 (s, 1 H), 7.86 (d, *J* = 7.57 Hz, 1 H), 8.09−8.16 (m, 1 H), 8.60 (d, *J* = 8.20 Hz, 1 H), 8.67 (d, *J* = 7.88 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* (ppm) 13.9, 22.5, 55.7, 60.0, 62.3, 122.5, 123.3, 124.8, 126.6, 126.9, 127.4, 128.9, 129.6, 130.7, 130.7, 131.0, 131.2, 171.9. HRMS (EI) calcd for $C_{22}H_{26}NO_3S$ [M + H] 384.1633, found 384.1638.

(*S*)-Ethyl 2-[(*S*)-1,1-dimethylethylsulfinamido]-2-phenylacetate, *ent*-5a: Following the general procedure (GP2), the reaction of (*S*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]-2-phenylacetate (*ent*-**4a**)

(1.38 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid *ent*-**5a** (1.26 g, 90%) as a viscous liquid. $[\alpha]^{25}_{D}$ +184.2 (*c* 1.06, $CHCl_3$). FTIR (ATR) ν 2981, 1737, 1585, 1292, 1178, 1090, 834 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.13 (t, *J* = 7.09 Hz, 3 H), 1.19 (s, 9 H), 4.00−4.12 (m, 1 H), 4.12−4.22 (m, 1 H), 4.62 (d, *J* = 4.10 Hz, 1 H), 5.02 (d, *J* = 4.41 Hz, 1 H), 7.21−7.37 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 13.9, 22.5, 55.9, 60.4, 62.0, 127.6, 128.6, 137.1, 171.3. HRMS (EI) calcd for $C_{14}H_{22}NO_3S$ [M + H] 284.1320, found 284.1317.

(*S*)-Ethyl 2-[(*S*)-1,1-dimethylethylsulfinamido]-3-methylbutanoate, *ent*-5h: Following the general procedure (GP2), the reaction of (*S*,*E*)-ethyl 2-[(*tert*-butylsulfinyl)imino]propanoate (*ent*-**4h**) (1.15 g, 5.0 mmol) with L-Selectride (5.25 mL, 5.25 mmol, 1.0 M in THF) afforded α-amino acid *ent*-**5h** (0.91 g, 85%) as a viscous liquid. $[\alpha]^{25}_{D}$ +104.2 (*c* 1.10, $CHCl_3$). FTIR (ATR) ν 2969, 1732, 1467, 1198, 1063, 724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.90 (d, *J* = 6.94 Hz, 3 H), 0.97 (d, *J* = 6.94 Hz, 3 H), 1.27 (s, 9 H), 1.29 (t, *J* = 7.09 Hz, 3 H), 1.97−2.15 (m, 1 H), 3.71 (dd, *J* = 7.88, 5.04 Hz, 1 H), 4.10 (d, *J* = 7.88 Hz, 1 H), 4.17−4.32 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 14.0, 17.2, 19.1, 22.6, 32.2, 56.1, 61.4, 63.0, 172.9. HRMS (EI) calcd for $C_9H_{20}NO_3S$ [M + H] 222.1164, found 222.1160.

General Procedure (GP3) for the Hydrolysis of Ester 5. To a round-bottomed flask containing LiOH (1.2 g, 50 mmol, 10 equiv) was added distilled H_2O (50.0 mL), and the resulting solution was cooled to 0 °C. A solution of **5** (5.0 mmol, 1.0 equiv) in THF (50.0 mL) was added into the reaction flask. The resulting solution was stirred at 0 °C for 1 h. The reaction mixture was then concentrated to remove the THF, and the remaining material was diluted with distilled H_2O (50 mL) and EtOAc (50 mL). The reaction mixture was neutralized with saturated $NaHSO_4$ solution to pH ∼2 and the organic layer was separated and washed with water (2 × 50 mL). The organic layer were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product **6** was isolated as a white solid with no further purification.

(*R*)-2-[(*R*)-1,1-Dimethylsulfinamido]-2-phenylacetic acid, 6a: Following the general procedure (GP3), hydrolysis of (*R*)-ethyl 2-[(*R*)-1, 1-dimethylethylsulfinamido]-2-phenylacetate (**5a**) (1.41 g, 5.0 mmol) with LiOH (1.2 g, 50 mmol) afforded compound (*R*)-2-[(*R*)-1,1-dimethylsulfinamido]-2-phenylacetic acid (**6a**) (1.16 g, 96%) as a white solid. Mp 141−142 °C. $[\alpha]^{25}_{D}$ −86.2 (*c* 1.08, $CHCl_3$). FTIR (ATR) ν 2967, 1715, 1184, 1060, 1013, 722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.27 (s, 9 H), 5.10 (br s, 2 H), 7.25−7.55 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 22.6, 56.6, 61.3, 127.4, 128.4, 128.7, 137.1, 172.5. HRMS (EI) calcd for $C_{12}H_{16}NO_3S$ [M − H] 254.0851, found 254.0853.

(*R*)-2-[(*R*)-1,1-Dimethylsulfinamido]-3-methylbutanoic acid, 6h: Following the general procedure (GP3), hydrolysis of (*R*)-ethyl 2-[(*R*)-1,1-dimethylethylsulfinamido]-3-methylbutanoate (**5h**) (1.24 g, 5.0 mmol) with LiOH (1.2 g, 50 mmol) afforded compound (*R*)-2-[(*R*)-1,1-dimethylsulfinamido]-3-methylbutanoic acid (**6h**) (1.02 g, 92%) as a white solid. Mp 124−126 °C. $[\alpha]^{25}_{D}$ −98.2 (*c* 1.12, $CHCl_3$). FTIR (ATR) ν 2958, 1722, 1258, 1178, 1025, 1014, 876, 663 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.90 (d, *J* = 6.94 Hz, 3 H), 0.98 (d, *J* = 6.94 Hz, 3 H), 1.28 (s, 9 H), 1.99−2.12 (m, 1 H), 3.71 (dd, *J* = 7.88, 5.04 Hz, 1 H), 4.42 (d, *J* = 7.57 Hz, 1 H), 11.36 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 17.2, 19.3, 22.9, 32.2, 56.9, 64.1, 173.6. HRMS (EI) calcd for $C_9H_{18}NO_3S$ [M − H] 220.1007, found 220.1010.

General Procedure (GP4) for Deprotection of the *tert*-Butanesulfinyl Group from 5. To a solution of **5** (2 mmol) in MeOH (10 mL) was added a 4 M HCl solution (in dioxane, 2 mL). After the mixture was stirred at room temperature for 30 min, it was concentrated to dryness and diethyl ether (40 mL) was added. The solid was collected by filtration and washed with diethyl ether (20 mL) and dried at room temperature for 2 h under vacuum to obtain the pure hydrochloride salt of **7**.

(*R*)-2-Phenylglycine ethyl ester hydrochloride, 7a: Following the general procedure (GP4), the reaction of **5a** (565 mg, 2.0 mmol) with a 4 M HCl solution (in dioxane, 2 mL) gives the (*R*)-2-phenylglycine ethyl ester hydrochloride (**7a**) (418 mg, 97%) as a white solid. Mp 189−190 °C. $[\alpha]^{25}_{D}$ −98.2 (*c* 1.22, $CHCl_3$). FTIR (ATR) ν 2842, 1737, 1494, 1232, 1185, 1044, 857 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ (ppm) 1.13 (t, *J* = 7.09 Hz, 3 H), 4.04−4.28 (m, 2 H), 5.19 (s, 1 H), 7.35−7.49 (m, 3 H), 7.54 (dd, *J* = 7.57, 1.89 Hz, 2 H), 9.28 (br s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 13.7, 55.2, 61.9, 128.2, 128.8, 129.3, 132.6, 168.2. HRMS (EI) calcd for $C_{10}H_{14}NO_2$ [M + H] 180.1025, found 180.1027.

(*R*)-Valine ethyl ester hydrochloride, 7h: Following the general procedure (GP4), the reaction of **5h** (498 mg, 2.0 mmol) with a 4 M HCl solution (in dioxane, 2 mL) gives the (*R*)-valine ethyl ester hydrochloride (**7h**) (360 mg, 98%) as a white solid. Mp 98−100 °C. $[\alpha]^{25}_{D}$ −38.2 (*c* 1.10, $CHCl_3$). FTIR (ATR) ν 2863, 1742, 1522, 1263, 1097, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1 1.15 (t, *J* = 7.41 Hz, 6 H), 1.32 (t, *J* = 7.09 Hz, 3 H), 2.37−2.57 (m, 1 H), 3.93 (d, *J* = 3.47 Hz, 1 H), 4.19−4.41 (m, 2 H), 8.85 (br s, 3 H). ^{13}C NMR (125 MHz, $CDCL_3$) δ (ppm) 14.1, 18.2, 18.3, 29.9, 58.5, 62.3, 168.1. HRMS (EI) calcd for $C_7H_{16}NO_2$ [M + H] 146.1181, found 146.1184.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Van Bambeke, F.; Van Laethem, Y.; Courvalin, P.; Tulkens, P. M. *Drugs* **2004**, *64*, 913.
(2) Wiseman, L. R.; Benfield, P. *Drugs* **1993**, *45*, 295.
(3) Imming, P; Sinning, C; Meyer, A. *Nat. Rev. Drug Discovery* **2006**, *5*, 821.
(4) Campoli-Richards, D. M.; Brogden, R. N. *Drugs* **1987**, *33*, 577.
(5) Todd, P. A.; Goa, K. L. *Drugs* **1992**, *43*, 346.
(6) Chrisp, P.; Goa, K. L. *Drugs* **1990**, *39*, 523.
(7) Jarvis, B.; Simpson, K. *Drugs* **2000**, *60*, 347.
(8) (a) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (d) Saaby, S.; Fang, X.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (e) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
(9) For selected reviews see: (a) Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Pergamon: Oxford, UK, 1989. (b) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (e) Nájera, C.; Sansano, M. J. *Chem. Rev.* **2007**, *107*, 4584–4671.
(10) (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Chemistry*; VCH: Weinheim, Germany, 2002. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.(c) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: Oxford, UK, 1989. (d) Barnett, G. C.; Elmore, D. T. *Amino Acids and Peptides*; Cambridge

University Press, 1998. (e) Scott, J. W. *Topics in Stereochemistry*; John Wiley & Sons Inc.: New York, 2007; Vol. 19, pp 209−226.

(11) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *N-tert*-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Ellman, J. A. Application of *tert*-Butanesulfinamide in the Asymmetric Synthesis of Amines. *Pure Appl. Chem.* **2003**, *75*, 39–46. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. Enantiopure Sulfoxides and Sulfinamides: Recent Developments in Their Stereoselective Synthesis and Application to Asymmetric Synthesis. *Aldrichim. Acta* **2005**, *38*, 93–103. (d) Daniel, M.; Stockman, R. A. Chiral Non-racemic Sulfinimines: Versatile Reagents for Asymmetric Synthesis. *Tetrahedron* **2006**, *62*, 8869–8905. (e) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. An Advance on Exploring *N-tert*-Butanesulfinyl Imines in Asymmetric Synthesis of Chiral Amines. *Acc. Chem. Res.* **2008**, *41*, 831–840. (f) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.

(12) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304–6305.

(13) (a) Reddy, L. R.; Das, S. G.; Liu, Y.; Prashad, M. *J. Org. Chem.* **2010**, *75*, 2236–2246. (b) Reddy, L. R.; Prashad, M. *Chem. Commun.* **2010**, *46*, 222–224. (c) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Org. Lett.* **2008**, *14*, 3109–3312.

(14) α-Ketoesters are commercially available from various companies.

(15) (*RS*)-*N-tert*-Butanesulfinamide and (*SS*)-*N-tert*-butanesulfinamide are readily available from various companies.

(16) Titanium(IV) ethoxide (purum) was purchased from Aldrich, and it contains ∼3% of tetraisopropyl orthotitanate.

(17) We have seen less than 1% of amino alcohol in the ^{1}H NMR analysis of the crude product.

(18) Donolf, B.; Leemans, E.; Kimpe, N. D. *J. Org. Chem.* **2007**, *72*, 3211–3217.

(19) For reviews on methyl ester cleavage, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.