Subtilisin-Catalyzed Resolution of *N*-Acyl Arylsulfinamides

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Supporting Information

Synthesis of Racemic Sulfinamides. Racemic sulfinamides were prepared using literature procedures.¹ Analytical data are given below.

***p*-Toluenesulfinamide (1).** Obtained as white crystals (6.51 g, 56% overall yield): mp 115-117 °C (lit.¹ 117-118 °C); ¹H NMR δ 2.42 (s, 3H, PhCH₃), 4.30 (br s, 2H, -NH₂), 7.30 (d, *J* = 8.1, 2H, phenyl), 7.62 (d, *J* = 8.1, 2H, phenyl); ¹³C NMR δ 21.7 (PhCH₃), 125.6, 129.7, 141.5, 143.6 (phenyl). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1**, *t*_R = 21.0 min; (*S*)-**1**, *t*_R = 27.5 min).

Benzenesulfinamide (2). Obtained as white crystals (3.06 g, 59% overall yield): mp 104-106 °C; ¹H NMR δ 4.38 (br s, 2H, NH₂), 7.51 (m, 3H, phenyl), 7.75 (m, 2H, phenyl); ¹³C NMR (101 MHz) δ 125.6, 129.1, 131.3, 146.6 (phenyl). The enantiomers were separated by HPLC

(Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**2**, t_R = 22.6 min; (*S*)-**2**, t_R = 26.2 min).

***p*-Chlorobenzenesulfinamide (3).** Obtained as amber crystals (9.91 g, 53% overall yield): mp 130-132 °C; ^1H NMR (DMSO- d_6) δ 4.39 (br s, 2H, NH_2), 7.48 (d, J = 8.7, 2H, phenyl), 7.68 (d, J = 9.0, 2H, phenyl); ^{13}C NMR (101 MHz) δ 127.3, 129.4, 137.8, 145.1 (phenyl). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**3**, t_R = 24.7 min; (*S*)-**3**, t_R = 43.0 min).

***p*-Methoxybenzenesulfinamide (4).** Obtained as white crystals (2.90 g, 35% overall yield): mp 129-131 °C (lit.² 135-136); ^1H NMR δ 3.86 (s, 3H, $-\text{OCH}_3$), 4.29 (br s, 2H, NH_2), 7.00 (d, J = 9.0, 2H, phenyl), 7.66 (d, J = 9.0, 2H, phenyl); ^{13}C NMR (DMSO- d_6) δ 56.2 ($-\text{OCH}_3$), 114.7, 127.7, 140.2, 161.4 (phenyl). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**4**, t_R = 28.8 min; (*S*)-**4**, t_R = 41.4 min).

2,4,6-Trimethylbenzenesulfinamide (5). Obtained as a white crystals (6.03 g, 33% overall yield): mp 116-118 °C (lit.² 115-118 °C); ^1H NMR δ 2.29 (s, 3H, PhCH_3), 2.61 (s, 6H, 2 x PhCH_3), 4.41 (br s, 2H, NH_2), 6.86 (s, 2H, phenyl); ^{13}C NMR (DMSO- d_6) δ 19.8 (2 x PhCH_3), 21.3 (PhCH_3), 130.8, 136.2, 139.8, 140.9 (phenyl). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**5**, t_R = 26.8 min; (*S*)-**5**, t_R = 25.0 min).

1-Naphthylsulfonamide (6). Obtained as amber crystals (2.20 g, 55% overall yield): mp 166-168 °C; ^1H NMR (DMSO- d_6) δ 6.26 (br s, 2H, NH_2), 7.58-7.70 (m, 3H, phenyl), 8.01-8.08 (m, 3H, phenyl), 8.18-8.21 (m, 1H, phenyl); ^{13}C NMR (DMSO- d_6) δ 122.9, 123.8, 125.8, 127.0, 127.4, 129.2, 129.3, 131.6, 133.9, 143.8 (phenyl). The enantiomers were separated by

HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**6**, t_R = 32.9 min; (*S*)-**6**, t_R = 39.5 min).

2,4,6-Triisopropylbenzenesulfinamide (7). Obtained as a white solid (2.51 g, 21% overall yield): mp (decomp.) 183-185 °C (lit.¹ 99-102 °C)³; ¹H NMR δ 1.24 (d, J = 6.9, 6H, 2 x CH₃), 1.27 (d, J = 6.6, 6H, 2 x CH₃), 1.32 (d, J = 7.2, 6H, 2 x CH₃), 2.88 (sept, J = 6.6, 1H, CH(CH₃)), 4.03 (sept, J = 6.7, 2H, 2 x CH(CH₃)), 4.48 (br s, 2H, NH₂) 7.07 (s, 2H, phenyl); ¹³C NMR (DMSO-d₆) δ 24.6, 24.7, 25.1, 25.7, 28.7, 34.3, (*i*-Pr), 122.5, 141.5, 147.3, 149.5. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R* or *S*)-**7**, t_R = 8.5 min; (*R* or *S*)-**7**, t_R = 10.5 min).

***tert*-Butylsulfinamide (8).** *m*-CPBA (14 g, 62 mmol) in CH₂Cl₂ (100 mL) was added dropwise to a stirred solution of *tert*-butyldisulfide (10 g, 56 mmol) in CH₂Cl₂ (25 mL) at 0 °C over 15 min. The solution was stirred for 30 min at 0 °C and RT until the reaction was complete by TLC (3 h). The reaction mixture was poured into a separatory funnel containing CH₂Cl₂ (100 mL) and sat. NaHCO₃ (100 mL) and further extracted with CH₂Cl₂ (2 x 100 mL). The organic layer was removed and washed with sat. NaHCO₃ (3 x 100 mL), sat. NaCl (100 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give 10.34 g (95%) of *tert*-butylthiosulfinate⁴; ¹H NMR (200 MHz) δ 1.32 (sulfide) 1.39 (s, 9H, (CH₃)₃S), 1.57 (s, 9H, (CH₃)₃S=O). This intermediate was dissolved in CH₂Cl₂ (25 mL) and a solution of SO₂Cl₂ (7.2 g, 53 mmol) in CH₂Cl₂ (10 mL) was added dropwise at 0 °C. The resulting yellow solution was stirred for 1 h allowing it to gradually reach RT.⁵ Excess SO₂Cl₂ was removed under vacuum and the resulting product, *tert*-butylsulfinyl chloride, was diluted in CH₂Cl₂ (100 mL) and added dropwise to NH₄OH (200 mL) at 0 °C over 30 min. After stirring for 30 min at RT, the reaction mixture was saturated with NaCl and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with

sat. NaCl (150 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give the crude sulfinamide. Purification using flash chromatography (12:1 CHCl₃/MeOH) gave the title compound (1.41 g, 22%) as a white solid: mp 98-100 °C (lit.⁶ 101-102 °C (*R*-enantiomer)); ¹H NMR (200 MHz) δ 1.23 (s, 9H, -(CH₃)₃), 3.72 (br s, 2 H, NH₂); ¹³C NMR δ 22.6 (-(CH₃)₃), 55.4 (C(CH₃)₃). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 222 nm; (*R*)-**8**, *t*_R = 12.6 min; (*S*)-**8**, *t*_R = 15.2 min).

***N*-Acylsulfinamides.** *N*-Acylsulfinamides of **1-8** were prepared by treating sulfinamides **1-8** with two equivalents of *n*-BuLi in THF¹, followed by rapid addition of the symmetrical anhydride of the appropriate carboxylic acid.⁷ The relevant analytical data are given below:

***N*-Acetyl-*p*-toluenesulfinamide (1a).** Obtained as white solid (95 mg, 30%): mp 125-127 °C; ¹H NMR δ 2.21 (s, 3H, C(O)CH₃), 2.45 (s, 3H, PhCH₃), 7.35 (d, *J* = 8.4, 2H, phenyl), 7.59 (d, *J* = 8.1, 2H, phenyl); ¹³C NMR δ 21.8 (C(O)CH₃), 21.9 (PhCH₃), 124.9, 130.3, 140.3, 142.9 (phenyl), 171.3 (C=O); HRMS calcd for C₉H₁₂NO₂S (M+H⁺) 198.0589. Found: 198.0582. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R* or *S*)-**1a**, *t*_R = 24.6 min; (*R* or *S*)-**1a**, *t*_R = 36.6 min).

***N*-Butanoyl-*p*-toluenesulfinamide (1b).** Obtained as white solid (780 mg, 90%): mp 95-97 °C; ¹H NMR δ 1.0 (t, *J* = 7.0, 3H, -CH₂CH₃), 1.72 (m, 2H, -CH₂CH₃), 2.20 (m, 2H, C(O)CH₂), 2.43 (s, 3H, PhCH₃), 7.32 (d, *J* = 8, 2H, phenyl), 7.57 (d, *J* = 8, 2H, phenyl); ¹³C NMR δ 13.9 (-CH₂CH₃), 18.7 (-CH₂CH₃), 21.8 (PhCH₃), 37.2 (C(O)CH₂), 124.9, 130.1, 139.9, 142.5 (phenyl), 174.7 (C=O); HRMS calcd for C₁₁H₁₆NO₂S (M+H⁺) 226.0902. Found: 226.0897. The enantiomers were separated by HPLC (Diacel Chiracel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R* or *S*)-**1b**, *t*_R = 12.9 min; (*R* or *S*)-**1b**, *t*_R = 17.4 min).

***N*-Bromoacetyl-*p*-toluenesulfinamide (1d).** Obtained as white solid (175 mg, 20%): mp 83-85 °C; ^1H NMR δ 2.46 (s, 3H, PhCH_3), 3.94 (s, 2H, $\text{C}(\text{O})\text{CH}_2\text{Br}$), 7.37 (d, $J = 8.1$, 2H, phenyl), 7.62 (d, $J = 8.1$, 2H, phenyl); ^{13}C NMR δ 21.8 (PhCH_3), 29.6 ($\text{C}(\text{O})\text{CH}_2\text{Br}$), 125.5, 130.4, 140.7, 142.6 (phenyl), 168.4 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_9\text{H}_{11}^{79}\text{BrNO}_2\text{S}$ ($\text{M}+\text{H}^+$) 275.9694. Found: 275.9698. The enantiomers were separated HPLC (Diacel Chiralcel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1d**, $t_{\text{R}} = 19.8$ min; (*S*)-**1d**, $t_{\text{R}} = 48.9$ min).

***N*-Methoxyacetyl-*p*-toluenesulfinamide (1e).** Obtained as white solid (304 mg, 42%): mp 57-59 °C; ^1H NMR δ 2.42 (s, 3H, PhCH_3), 3.37 (s, 3H, OCH_3), 4.00 (s, 2H, $\text{C}(\text{O})\text{CH}_2$), 7.37 (d, $J = 8.4$, 2H, phenyl), 7.63 (d, $J = 8.4$, 2H), 8.29 (br s, 1H, NH); ^{13}C NMR δ 21.9 (PhCH_3), 59.6 (OCH_3), 71.9 ($\text{C}(\text{O})\text{CH}_2$), 124.8, 130.3, 140.4, 142.9 (phenyl), 170.7 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_{10}\text{H}_{14}\text{NO}_3\text{S}$ ($\text{M}+\text{H}^+$) 228.0694. Found: 228.0689. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1e**, $t_{\text{R}} = 24.6$ min; (*S*)-**1e**, $t_{\text{R}} = 31.7$ min).

***N*-[*N*-(*tert*-Butoxycarbonyl)-glycine]-*p*-toluenesulfinamide (1f).** Obtained as white solid (290 mg, 29%): mp 128-130 °C; ^1H NMR δ 1.39 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 2.43 (s, 3H, PhCH_3), 3.88 (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 5.29 (br s, 1H, NH), 7.32 (d, $J = 7.8$, 2H, phenyl), 7.57 (d, $J = 8.1$, 2H, phenyl), 8.65 (br s, 1H, NH); ^{13}C NMR δ 21.8 (PhCH_3), 28.6 ($\text{C}(\text{CH}_3)_3$), 44.7 ($\text{C}(\text{O})\text{CH}_2$), 80.6 ($\text{C}(\text{CH}_3)_3$), 124.9, 130.2, 139.8, 142.7 (phenyl), 156.4 ($\text{C}=\text{O}$, carbamate), 171.4 ($\text{C}=\text{O}$, amide); HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ ($\text{M}+\text{H}^+$) 313.1222. Found: 313.1218. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1f**, $t_{\text{R}} = 17.8$ min; (*S*)-**1f**, $t_{\text{R}} = 30.9$ min).

***N*-[*N*-(*tert*-Butoxycarbonyl)-phenylalanine]-*p*-toluenesulfinamide (1g).** Obtained as white solid (660 mg, 51%): mp 111-113 °C; ^1H NMR δ 1.33-1.46 (m, 9H, $(\text{CH}_3)_3$), 2.42 (s, 3H,

PhCH₃), 3.11 (m, 2H, CH₂Ph), 4.38 (bs s, 1H, NH), 4.99 (m, 1H, C(O)CH), 7.12-7.53 (m, 9H, phenyl), 8.33 (br s, 1H, NH); ¹³C NMR δ 21.8 (PhCH₃), 28.6 (C(CH₃)₃), 38.7 (CH₂Ph), 60.8 (C(O)CH), 80.6 (C(CH₃)₃), 125.0, 127.1, 128.8, 129.7, 130.2, 136.3, 139.8, 142.5, 155.8 (C=O, carbamate), 173.2 (C=O, amide); HRMS calcd for C₂₁H₂₇N₂O₄S (M+H⁺) 403.1691. Found: 403.1683. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*S,S*)-**1g**, *t*_R = 11.9 min; (*R,S*)-**1g**, *t*_R = 13.4 min).

***N*-Phenoxyacetyl-*p*-toluenesulfinamide (1i).** Obtained as white solid (391 mg, 42%): mp 107-109 °C; ¹H NMR δ 2.45 (s, 3H, PhCH₃), 4.60 (s, 2H, C(O)CH₂), 6.83-7.06 (m, 3H, phenyl), 7.27-7.36 (m, 4H, phenyl), 7.58 (d, *J* = 8.1, 2H); ¹³C NMR δ 21.9 (PhCH₃), 67.5 (C(O)CH₂), 114.9, 122.7, 124.9, 130.0, 130.4, 140.2, 143.1, 156.8 (phenyl), 169.6 (C=O); HRMS calcd for C₁₅H₁₆NO₃S (M+H⁺) 290.0851. Found: 290.0843. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R* or *S*)-**1i**, *t*_R = 31.4 min; (*R* or *S*)-**1i**, *t*_R = 43.8 min).

***N*-4-Methylvaleroyl-*p*-toluenesulfinamide (1j).** Obtained as white solid (160 mg, 20%): mp 123-125 °C; ¹H NMR δ 0.90 (s, 3H, CH₃), 0.93 (s, 3H, CH₃), 1.56-1.62 (m, 3H, CH₂CH(CH₃)₂), 2.40 (m, 2H, C(O)CH₂), 2.45 (s, 3H, PhCH₃), 7.35 (d, *J* = 8.6, 2H, phenyl), 7.59 (d, *J* = 8.2, 2H); ¹³C NMR δ 21.9 (PhCH₃), 22.6 ((CH₃)₂), 28.0 (CH(CH₃)₂), 33.9 (CH₂CH) or (C(O)CH₂), 34.4 (CH₂CH) or (C(O)CH₂), 124.9, 130.1, 140.4, 142.5 (phenyl), 174.6 (C=O); HRMS calcd for C₁₃H₂₀NO₂S (M+H⁺) 254.1215. Found: 254.1209. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1j**, *t*_R = 11.9 min; (*S*)-**1j**, *t*_R = 13.7 min).

***N*-Levulinoyl-*p*-toluenesulfinamide (1k).** Obtained as white solid (399 mg, 49%): mp 74-76 °C; ¹H NMR δ 2.20 (s, 3H, C(O)CH₃), 2.44 (s, 3H, PhCH₃), 2.61 (m, 2H, C(O)CH₂), 2.86

(m, 2H, $\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 7.33 (d, $J = 8.6$, 2H, phenyl), 7.60 (d, $J = 8.2$, 2H, phenyl), 8.08 (br s, 1H, NH); ^{13}C NMR δ 21.8 (PhCH_3), 30.1 ($\text{C}(\text{O})\text{CH}_3$), 30.2 ($\text{C}(\text{O})\text{CH}_2$), 38.0 ($\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 125.0, 130.1, 140.2, 142.5 (phenyl), 173.4 ($\text{C}=\text{O}$, amide), 207.6 ($\text{C}=\text{O}$, ketone); HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{S}$ ($\text{M}+\text{H}^+$) 254.0851. Found: 254.0857. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1k**, $t_R = 30.4$ min; (*S*)-**1k**, $t_R = 42.9$ min).

***N*-Isopropoxyacetyl-*p*-toluenesulfinamide (1l).** Obtained as white solid (289 mg, 35%): mp 68-70 °C; ^1H NMR (200 MHz) δ 1.13 (t, $J = 6.0$, 3H, CH_3), 1.23 (t, $J = 5.8$, 3H, CH_3), 2.46 (s, 3H, PhCH_3), 3.63 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 4.03 (s, 2H, $\text{C}(\text{O})\text{CH}_2$), 7.36 (d, $J = 7.8$, 2H, phenyl), 7.64 (d, $J = 8.2$, 2H, phenyl) 8.34 (br s, 1H, NH); ^{13}C NMR δ 21.9 (PhCH_3), 22.1 ($(\text{CH}_3)_2$), 22.2 ($(\text{CH}_3)_2$), 67.8 ($\text{CH}(\text{CH}_3)_2$), 124.8, 130.3, 140.5, 142.9 (phenyl), 171.5 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{S}$ ($\text{M}+\text{H}^+$) 256.1007. Found: 256.1012. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH 0.5 mL/min, 238 nm; (*R* or *S*)-**1l**, $t_R = 18.4$ min; (*R* or *S*)-**1l**, $t_R = 19.7$ min).

***N*-3-(Methoxycarbonyl)propionyl-*p*-toluenesulfinamide (1m).** Obtained as white solid (561 mg, 65%): mp 90-92 °C; ^1H NMR δ 2.43 (s, 3H, tolyl CH_3), 2.61 (m, 2H, $\text{CH}_2\text{C}(\text{O})\text{CH}_3$) or (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 2.70 (m, 2H, $\text{CH}_2\text{C}(\text{O})\text{CH}_3$) or (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 7.32 (d, $J = 8.4$, 2H, phenyl), 7.56 (d, $J = 8.7$, 2H, phenyl), 8.31 (br s, 1H, NH); ^{13}C NMR δ 21.8 (tolyl CH_3), 28.8 ($\text{C}(\text{O})\text{CH}_2$) or ($\text{CH}_2\text{C}(\text{O})\text{OCH}_3$), 29.1 ($\text{C}(\text{O})\text{CH}_2$) or ($\text{CH}_2\text{C}(\text{O})\text{OCH}_3$), 52.3 (OCH_3), 125.0, 130.1, 140.1, 142.6 (phenyl), 172.9 ($\text{C}=\text{O}$, ester), 173.2 ($\text{C}=\text{O}$, amide); HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_4\text{S}$ ($\text{M}+\text{H}^+$) 270.0800. Found: 270.0790. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**1m**, $t_R = 26.5$ min; (*S*)-**1m**, $t_R = 61.9$ min).

***N*-Chloroacetylbenzenesulfinamide (2c).** Obtained as white solid (216 mg, 56%): mp 92-94 °C; ^1H NMR δ 4.15 (s, 2H, $\text{C}(\text{O})\text{CH}_2\text{Cl}$), 7.59 (m, 3H, phenyl), 7.75 (m, 2H, phenyl), 8.41 (br s, 1H, *NH*); ^{13}C NMR δ 42.4 ($\text{C}(\text{O})\text{CH}_2$), 124.9, 129.8, 132.7, 143.0 (phenyl), 167.3 ($\text{C}=\text{O}$); HRMS-EI calcd for $\text{C}_8\text{H}_8^{35}\text{ClNO}_2\text{S}$ (M^+) 216.9964. Found: 216.9972. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**2c**, t_{R} = 21.7 min; (*S*)-**2c**, t_{R} = 43.9 min).

***N*-Dihydrocinnamoylbenzenesulfinamide (2h).** Obtained as white solid (185 mg, 48%): mp 94-96 °C; ^1H NMR δ 2.68 (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 3.02 (t, J = 7.8, 2H, CH_2Ph), 7.18-7.31 (m, 5H, phenyl), 7.49-7.57 (m, 5H, phenyl); ^{13}C NMR (DMSO-d_6) δ 31.1 (CH_2Ph), 37.7 ($\text{C}(\text{O})\text{CH}_2$), 125.6, 126.7, 128.9, 129.0, 129.9, 132.1, 141.2, 144.2 (phenyl), 174.1 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_2\text{S}$ ($\text{M}+\text{H}^+$) 274.0902. Found: 274.0896. The enantiomers were separated by HPLC (Diacel AD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**2h**, t_{R} = 44.9 min; (*S*)-**2h**, t_{R} = 22.2 min).

***N*-Chloroacetyl-*p*-chlorobenzenesulfinamide (3c).** Obtained as white solid (87 mg, 21%): mp 118-120 °C; ^1H NMR 4.16 (s, 2H, $\text{C}(\text{O})\text{CH}_2\text{Cl}$), 7.57 (d, J = 8.4, 2H, phenyl), 7.71 (d, J = 8.4, 2H, phenyl); ^{13}C NMR δ 42.4 ($\text{C}(\text{O})\text{CH}_2\text{Cl}$), 126.3, 130.2, 139.3, 141.5 (phenyl), 167.0 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_8\text{H}_7^{35}\text{Cl}_2\text{NO}_2\text{S}$ (M^+) 250.9574. Found: 250.9577. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**3c**, t_{R} = 28.1 min; (*S*)-**3c**, t_{R} = 63.7 min).

***N*-Dihydrocinnamoyl-*p*-chlorobenzenesulfinamide (3h).** Obtained as white solid (506 mg, 58%): mp 133-135 °C; ^1H NMR δ 2.69 (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 3.02 (t, J = 7.2, 2H, CH_2Ph), 7.18-7.31 (m, 7H, phenyl), 7.46 (s, 2H, phenyl); ^{13}C NMR (DMSO-d_6) δ 31.0 (CH_2Ph), 37.7 ($\text{C}(\text{O})\text{CH}_2$), 126.8, 127.6, 128.9, 129.0, 129.9, 136.9, 141.2, 143.2 (phenyl), 174.1 ($\text{C}=\text{O}$); HRMS

calcd for $C_{15}H_{15}^{35}ClNO_2S$ ($M+H^+$) 308.0512. Found: 308.0505. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**3h**, t_R = 25.1 min; (*S*)-**3h**, t_R = 27.9 min).

***N*-Chloroacetyl-*p*-methoxybenzenesulfinamide (4c).** Obtained as white solid (152 mg, 42%): 91-93 °C; ^1H NMR δ 3.89 (s, 3H, OCH_3), 4.14 (s, 2H, $C(O)CH_2Cl$), 7.06 (d, J = 8.7, 2H, phenyl), 7.68 (d, J = 9.3, 2H, phenyl), 8.28 (s, 1H, NH); ^{13}C NMR δ 42.4 ($C(O)CH_2$), 55.9 (OCH_3), 115.2, 126.6, 133.9, 163.1 (phenyl), 167.2 ($C=O$); HRMS calcd for $C_9H_{11}^{35}ClNO_3S$ ($M+H^+$) 248.0148. Found: 248.0142. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**4c**, t_R = 31.6 min; (*S*)-**4c**, t_R = 90.3 min).

***N*-Dihydrocinnamoyl-*p*-methoxybenzenesulfinamide (4h).** Obtained as white solid (589 mg, 66%): mp 60-62 °C; ^1H NMR δ 2.67 (m, 2H, $C(O)CH_2$), 3.01 (t, J = 7.5, 2H, CH_2Ph), 3.86 (s, 3H, OCH_3), 6.98 (d, J = 8.7, 2H, phenyl), 7.18-7.31 (m, 5H, phenyl), 7.47 (d, J = 9.0, 2H, phenyl); ^{13}C NMR (DMSO- d_6) δ 31.1 (CH_2Ph), 37.7 ($C(O)CH_2$), 56.4 (OCH_3), 115.3, 126.7, 127.3, 128.9, 129.0, 135.2, 141.3, 162.4 (phenyl), 174.0 ($C=O$); HRMS calcd for $C_{16}H_{18}NO_3S$ ($M+H^+$) 304.1007. Found: 304.1014. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH; 0.5 mL/min, 238 nm; (*R*)-**4h**, t_R = 40.0 min; (*S*)-**4h**, t_R = 42.4 min).

***N*-Chloroacetyl-2,4,6-trimethylbenzenesulfinamide (5c).** Obtained as white solid (195 mg, 28%): mp 89-91 °C; ^1H NMR δ 2.33 (s, 3H, $PhCH_3$), 2.62 (s, 6H, 2 x $PhCH_3$), 4.15 (m, 2H, $C(O)CH_2Cl$), 6.92 (s, 2H, phenyl); ^{13}C NMR δ 19.4 (2 x $PhCH_3$), 21.4 ($PhCH_3$), 42.6 ($C(O)CH_2Cl$), 131.5, 135.8, 138.1, 143.0 (phenyl), 166.7 ($C=O$); HRMS calcd for $C_{11}H_{14}^{35}ClNO_2S$ 259.0433 (M^+). Found: 259.0430. The enantiomers were separated by HPLC

(Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**5c**, t_R = 19.3 min; (*S*)-**5c**, t_R = 21.0 min).

***N*-Dihydrocinnamoyl-2,4,6-trimethylbenzenesulfinamide (5h).** Obtained as white solid (529 mg, 36%): mp 125-127 °C (lit.¹ 126-127 °C); ¹H NMR δ 2.31 (s, 3H, PhCH₃), 2.50 (s, 6H, 2 x PhCH₃), 2.68 (m, 2H, C(O)CH₂), 2.99 (t, J = 6.9, 2H, PhCH₂), 6.87 (s, 2H, phenyl), 7.16-7.29 (m, 5H, phenyl), 7.62 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 19.6 (2 x PhCH₃), 21.4 (PhCH₃), 31.2 (CH₂Ph), 37.4 (C(O)CH₂), 126.7, 128.9, 128.9, 131.1, 136.2, 138.2, 141.4, 141.6 (phenyl), 174.1 (C=O). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**5h**, t_R = 17.6 min; (*S*)-**5h**, t_R = 21.2 min).

***N*-Chloroacetyl-1-naphthylenesulfinamide (6c).** Obtained as white solid (92 mg, 22%): mp 117-119 °C; ¹H NMR δ 4.13 (d, J = 4.8, 2H, C(O)CH₂Cl), 7.61-7.72 (m, 3H, phenyl), 7.98 (m, 2H, phenyl), 8.08 (d, J = 8.1, 1H, phenyl), 8.28 (m, 1H, phenyl); ¹³C NMR δ 43.2 (C(O)CH₂Cl), 122.4, 124.3, 126.0, 127.7, 128.5, 128.8, 129.6, 132.9, 133.9, 138.6 (phenyl), 168.4 (C=O); HRMS calcd for C₁₂H₁₁³⁵ClNO₂S (M+H⁺) 268.0199. Found: 268.0192. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**6c**, t_R = 23.9 min; (*S*)-**6c**, t_R = 90.2min).

***N*-Dihydrocinnamoyl-1-naphthylenesulfinamide (6h).** Obtained as white solid (302 mg, 36%): mp 113-115 °C; ¹H NMR δ 2.67 (t, J = 7.5, 2H, C(O)CH₂), 2.99 (m, 2H, CH₂Ph), 7.12-7.28 (m, 5H, phenyl), 7.54-7.65 (m, 3H, phenyl), 7.87-8.18 (m, 4H, phenyl); ¹³C NMR δ 31.0 (CH₂Ph), 37.5 (C(O)CH₂), 122.4, 124.2, 126.0, 126.7, 127.5, 128.4, 128.9, 128.9, 129.6, 132.7, 133.9, 139.1, 141.2 (phenyl), 174.0 (C=O); HRMS calcd for C₁₉H₁₈NO₂S (M+H⁺) 324.1058. Found: 324.1053. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**6h**, t_R = 24.2 min; (*S*)-**6h**, t_R = 37.4 min).

***N*-Chloroacetyl-2,4,6-triisopropylbenzenesulfinamide (7c).** Obtained as white solid (140 mg, 15%): mp 119-121 °C; ^1H NMR δ 1.27 (d, J = 6.9, 12H, 2 x $\text{CH}(\text{CH}_3)_2$), 1.37 (d, J = 6.9, 6H, $\text{CH}(\text{CH}_3)_2$), 2.92 (sept, J = 6.9, 1H, $\text{CH}(\text{CH}_3)_2$), 3.93 (m, 2H, 2 x $\text{CH}(\text{CH}_3)_2$), 4.18 (s, 2H, $\text{C}(\text{O})\text{CH}_2\text{Cl}$), 7.14 (s, 2H, phenyl), 8.74 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 24.3, 24.4, 24.5, 25.4, 28.8, 34.5, 39.5 (3 x *i*-Pr), 43.1 ($\text{C}(\text{O})\text{CH}_2\text{Cl}$), 123.5, 135.2, 149.6, 153.3 (phenyl); HRMS calcd for $\text{C}_{17}\text{H}_{27}^{35}\text{ClNO}_2\text{S}$ ($\text{M}+\text{H}^+$) 344.1451. Found: 344.1443. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R* or *S*)-**7c**, t_{R} = 8.7 min; (*R* or *S*)-**7c**, t_{R} = 9.1 min).

***N*-Chloroacetyl-*tert*-butanesulfinamide (8c).** Obtained as white solid (191 mg, 29%): mp 56-58 °C; ^1H NMR (200 MHz) δ 1.32 (s, 9H, $(\text{CH}_3)_3$), 4.15 (m, 2H, CH_2Cl), 7.94 (br s, 1H, NH); ^{13}C NMR δ 22.3 ($(\text{CH}_3)_3$), 42.9 ($\text{C}(\text{O})\text{CH}_2\text{Cl}$), 58.1, ($\text{C}(\text{CH}_3)_3$), 167.3 ($\text{C}=\text{O}$); HRMS calcd for $\text{C}_6\text{H}_{13}^{35}\text{ClNO}_2\text{S}$ (MH^+) 198.0355. Found: 198.0360. The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 222 nm; (*R* or *S*)-**8c**, t_{R} = 13.6 min; (*R* or *S*)-**8c**, t_{R} = 16.9 min).

***N*-Dihydrocinnamoyl-*tert*-butanesulfinamide (8h).** Obtained as white solid (450 mg, 71%): mp 63-65 °C; ^1H NMR (200 MHz) δ 1.17 (s, 9H, $(\text{CH}_3)_3$), 2.72 (m, 2H, $\text{C}(\text{O})\text{CH}_2$), 2.99 (t, J = 7.4, 2H, $\text{C}(\text{O})\text{Ph}$), 7.22-7.28 (m, 5H, phenyl), 7.62 (br s, 1H, NH); ^{13}C NMR δ 22.3 ($(\text{CH}_3)_3$), 31.3 (CH_2Ph), 37.1 ($\text{C}(\text{O})\text{CH}_2$), 57.7 ($\text{C}(\text{CH}_3)_3$), 126.6, 128.6, 128.8, 140.3 (phenyl), 173.6 ($\text{C}=\text{O}$). The enantiomers were separated by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 222 nm; (*R* or *S*)-**8h**, t_{R} = 13.6 min; (*R* or *S*)-**8h**, t_{R} = 16.9 min).

Synthesis of enantiopure sulfinamide standards. Enantiopure sulfinamides were prepared using literature procedures.^{8,9} These compounds of known absolute stereochemical

configuration were used as HPLC standards to determine the enantioselectivity of enzymatic resolutions. Their relevant analytical data are given below:

(*S*)-*p*-Toluenesulfinamide ((*S*)-1). Prepared from (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate as previously described.⁸ This was obtained as a white solid (620 mg, 59% overall yield): mp 111-113 °C; ¹H NMR (400 MHz) δ 2.42 (s, 3H, PhCH₃), 4.35 (br s, 2H, -NH₂), 7.30 (d, *J* = 8.0, 2H, phenyl), 7.61 (d, *J* = 8.4, 2H, phenyl); ¹³C NMR δ 21.8 (PhCH₃), 125.6, 129.8, 141.7, 143.6 (phenyl). The ee was determined to be 97% by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 1.0 mL/min, 238 nm; (*R*)-1, *t*_R = 8.7 min; (*S*)-1, *t*_R = 10.3 min).

(*R*)-Benzenesulfinamide ((*R*)-2). Prepared from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as previously described.⁹ This was obtained as a white solid (180 mg, 37% overall yield): mp 91-93 °C; ¹H NMR (400 MHz) δ 4.38 (br s, 2H, NH₂), 7.50 (m, 3H, phenyl), 7.74 (m, 2H, phenyl); ¹³C NMR δ 125.6, 129.1, 131.3, 146.6 (phenyl). The ee was determined to be 96% by HPLC (Diacel AD column, 90:10 hexanes/EtOH, 1.0 mL/min, 238 nm; (*R*)-2, *t*_R = 20.4min; (*S*)-2, *t*_R = 23.0min).

(*R*)-*p*-Chlorobenzenesulfinamide ((*R*)-3). Prepared from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as previously described.⁹ This was obtained as a white solid (100 mg, 16% overall yield): mp 135-137 °C; ¹H NMR (400 MHz) δ 4.41 (s, 2H, NH₂), 7.47 (d, *J* = 8.8, 2H, phenyl), 7.66 (d, *J* = 8.4, 2H, phenyl); ¹³C NMR δ 127.3, 129.3, 137.7, 145.0. The ee was determined to be 95% by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 1.0 mL/min, 238 nm; (*R*)-3, *t*_R = 22.4 min; (*S*)-3, *t*_R = 37.1 min).

(*R*)-*p*-Methoxybenzenesulfinamide ((*R*)-4). Prepared from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as previously described.⁹ This was obtained as a white solid (80 mg, 14% overall yield): mp 111-113 °C; ¹H NMR (400 MHz) δ 3.85 (s, 3H, -OCH₃), 4.36 (s, 2H, NH₂), 6.98 (d, *J* = 7.6,

2H, phenyl), 7.64 (d, $J = 7.6$, 2H, phenyl); ^{13}C NMR δ 55.9, 114.5, 127.3, 137.9, 161.9. The ee was determined to be 95% by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 1.0 mL/min, 238 nm; (*R*)-**4**, $t_R = 29.4$ min; (*S*)-**4**, $t_R = 43.9$ min).

(*R*)-2,4,6-Trimethylbenzenesulfinamide ((*R*)-5). Prepared from (1*R*,2*S*)-(-)-*cis*-1-amino-2-indanol as previously described.⁹ This was obtained as a white solid (20 mg, 3% overall yield): mp 116-118 °C; ^1H NMR (400 MHz) δ 2.29 (s, 3H, PhCH_3), 2.61 (s, 6H, 2 x PhCH_3), 4.41 (br s, 2H, NH_2), 6.86 (s, 2H, phenyl); ^{13}C NMR δ 19.7 (2 x PhCH_3), 21.4 (PhCH_3), 131.1, 136.4, 139.0, 140.9 (phenyl). The ee was determined to be 68% by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 0.5 mL/min, 238 nm; (*R*)-**5**, $t_R = 13.4$ min; (*S*)-**5**, $t_R = 12.3$ min).

(*R*)-1-Naphthylenesulfinamide ((*R*)-6). Prepared from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as previously described.⁹ This was obtained as a white solid (160 mg, 25% overall yield): mp 151-153 °C; ^1H NMR (400 MHz) δ 4.40 (br s, 2H, NH_2), 7.56-7.64 (m, 3H, phenyl), 7.89-8.01 (m, 3H, phenyl), 8.22 (d, $J = 8.0$, 1H, phenyl); ^{13}C NMR (DMSO-d_6) δ 122.9, 123.8, 125.8, 127.0, 127.4, 129.2, 129.3, 131.6, 133.9, 143.8 (phenyl). The ee was determined to be 93% by HPLC (Diacel OD column, 90:10 hexanes/EtOH, 1.0 mL/min, 238 nm; (*R*)-**6**, $t_R = 52.2$ min; (*S*)-**6**, $t_R = 49.9$ min).

Cultivation and Purification of Subtilisin E. Protease deficient *B. subtilis* DB104 was transformed with vector pBE3, as previously described.^{10,11} Transformed cells were grown in 2XSG¹¹ media (500 mL) with shaking for 10 h at 37 °C. This culture was used to inoculate 14 L of 2XSG¹¹ media in a 20 L fermentor. After 42 hours ($\text{OD}_{600} = 9.1$), the culture was cooled and centrifuged. The cell pellet was discarded and the supernatant was concentrated using a 0.45 μm cartridge (8,000 MW cutoff) equipped with a 1.2 μm prefilter. The concentrate was brought to 70% saturation with NH_4SO_4 (472 g/L), stirred overnight and then centrifuged at 8,000 rpm for

1.5 h. The precipitate was resuspended and dialyzed for 48 h against 8 L of 10 mM HEPES (pH 7.5, 1 mM CaCl_2). The sample was passed through a bed of DE-52 anion exchange cellulose with vacuum. The clarified solution was then concentrated by passage through an 8,000 MW ultra filtration cartridge. The retentate was brought to 1.8 M NH_4SO_4 , centrifuged and the supernatant was passed through a 0.45 μm filter.

Subtilisin E was purified on a BioCad purification system (Applied Biosystems, Foster, USA) using a Poros 20HP2 (10 x 100) column.¹² The sample was loaded and washed with 1.8 M NH_4SO_4 in 20 mM HEPES (pH 7.0) and then eluted with a linear gradient of 1.8 M to 0 M NH_4SO_3 in 20 mM HEPES (pH 7.0). The enzyme activity was monitored by adding 90 μL of assay solution [0.2 mM succinyl-AAPF-*p*-nitroanilide (suc-AAPF-*p*NA) / 100 mM Tris pH 8.0 / 10 mM CaCl_2] to 10 μL of eluent and following the reaction at 410 nm at 37 °C for 15 min. The specific activity toward suc-AAPF-*p*NA was 21 U/mg (lit.¹⁰ 17.2 U/mg). Fractions containing protein were concentrated by passage through an 8,000 MW cutoff ultrafiltration cartridge and diafiltered in 10 mM HEPES (pH 7.5, 1 mM CaCl_2). The final retentate was frozen and lyophilized to give ca. 300 mg of subtilisin E.

Figure S1. SDS-polyacrylamide gel electrophoresis of subtilisin E from *B. subtilis* DB104 carrying pBE3. The gel was stained by Coomassie Blue. To prevent autolysis, subtilisin E was treated with PMSF (phenylmethylsulfonylfluoride) before denaturation. PMSF (phenylmethylsulfonylfluoride) inhibited subtilisin E prepared from culture medium of *B. subtilis* DB104 carrying pBE3 is shown in *lane 1*. Subtilisin E prepared from culture medium of *B. subtilis* DB104 carrying pBE3 is shown in *lane 2*. Purified PMSF-inhibited subtilisin E is shown in *lane 3*. Purified subtilisin E is shown in *lane 4*.

Table S1. Enantioselectivity of *Bacillus subtilis* var. biotecnus A with **2c-5c**

		R	%c _{app} ^a	ee _s (%) ^b	ee _p (%) ^b	E _{app}	E _{true} ^c
2c			47	81	90	48	>150 ^d
3c			45	77	96	103	>150 ^e
4c			49	87	90	53	>150 ^d
5c			41	66	94	64	97 ^e

^a% Conversion: amount of sulfonamide formed in 6 h. ^b% Enantiomeric excess. Enantiomeric excess of substrate and product were determined by HPLC analysis on Daicel Chiralcel OD or

AD columns at 238 nm or 222 nm. ^eEnantiomeric Ratio: the enantiomeric ratio *E* measures the relative rate of hydrolysis of the fast enantiomer as compared to the slow enantiomer as defined by Sih (Chen, C.S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299). ^dCorrected for ca. 4% chemical hydrolysis. ^eCorrected for ca. 1% chemical hydrolysis.

Molecular Modeling Details for (*R*)-1h and (*S*)-1h tetrahedral intermediates bound to Subtilisin E. Modeling **1h** with subtilisin E gave one productive conformation for each enantiomer. The two other plausible conformations encountered severe steric clash with the protein.

Productive Conformer of (*R*)-1h. The productive complex of (*R*)-**1h** had its *p*-tolyl group in the S₁' pocket and sulfoxide oxygen exposed to solvent (water). All hydrogen bond angles were >120° and all five hydrogen bond lengths were <3.1 Å. The *p*-tolyl group appears to just fit in the S₁' pocket. Met222 in the bottom of the S₁' pocket (C_{ortho}-C_ε distance = 3.74 Å)¹³, Tyr217 at the back of the S₁' pocket (C_{para} - C_{meta}(Tyr217) distance = 3.93 Å, C_{meta} - C_{para}(Tyr217) distance = 3.94 Å, *p*-CH₃ - C_{meta}(Tyr217) distance = 3.64 Å and *p*-CH₃ - C_{para}(Tyr217) distance = 3.93 Å)¹³ and catalytic His64 (C_{ortho} - C_{δ2} distance = 3.72 Å and C_{meta} - C_{δ2} distance = 3.83 Å)¹³ bumped the *p*-tolyl group. This tight fit suggests a favorable hydrophobic interaction between the *p*-tolyl group and the S₁' residues.

Non-productive Conformer of (*R*)-1h. The *p*-tolyl group of non-productive (*R*)-**1h** encounters steric clash with Gly 219 (C_{ortho} - C_α distance = 3.43 Å)¹³ and catalytic Asn 155 (C_{ipso} - N_{δ2} distance = 3.41 Å, C_{ortho} - N_{δ2} distance = 3.10 Å, C_{meta} - N_{δ2} distance = 3.37 Å)¹³. This steric clash results in the sulfoxide oxygen being forced out of the S₁' leaving-group pocket.

Productive Conformer of (S)-1h. The productive complex of (S)-1h had its sulfoxide oxygen in the S₁' pocket and *p*-tolyl group exposed to solvent water. All hydrogen bond angles were >120° and all five hydrogen bond lengths were <3.1 Å. The sulfoxide oxygen fits well in the S₁' pocket (O_s - C_e (Met222) distance = 5.64 Å and O_s - C_{δ2} (His64) distance = 3.89 Å)¹³ and the protein does not hinder the *p*-tolyl group. Unlike the favored enantiomer, the smaller oxygen does not make steric contact with S₁' residues. Although the slow-reacting (S)-enantiomer avoids steric hindrances, it also lacks favorable hydrophobic interactions between the *p*-tolyl group and the S₁' residues.

Non-productive Conformer of (S)-1h The tolyl group of non-productive (S)-1h encounters steric clash with catalytic His 64 (C_{ortho} - C_{δ2} distance = 3.58 Å, C_{meta} - C_{δ2} distance = 3.62 Å)¹³. This steric clash results in the *p*-tolyl group being forced out of the S₁' leaving-group pocket.

Molecular Modeling Force Field (AMBER) Parameters for the Sulfinamide Group.

(1) Atom labels: sulfur, SO; oxygen, OX. (2) Bond parameters: SO-OX, bond length = 1.48 Å; $K_r = 680$ kcal/Å; SO-NT, bond length = 1.71 Å, $K_r = 230$ kcal/Å; SO-CA, bond length = 1.78 Å, $K_r = 222$ kcal/Å. (3) Angle parameters: SO-NT-H, $K_\theta = 35$ kcal/rad², $\theta_{eq} = 108.9^\circ$; SO-CA-CA, $K_\theta = 100$ kcal/rad², $\theta_{eq} = 118.8^\circ$; OX-SO-CA, $K_\theta = 74$ kcal/rad², $\theta_{eq} = 107.6^\circ$; NT-SO-OX, $K_\theta = 100$ kcal/rad², $\theta_{eq} = 112.2^\circ$; NT-SO-CA $K_\theta = 100$ kcal/rad², $\theta_{eq} = 97.1^\circ$. (4) Dihedral angles parameters: X-NT-SO-X, $V_n = 5.0$ kcal/rad², $\gamma = 0^\circ$, $n = 3$; NT-SO-CA-CA, $V_n = 0.0$ kcal/rad², $\gamma = 0^\circ$, $n = 2$; OX-SO-CA-CA, $V_n = 0.0$ kcal/rad², $\gamma = 0^\circ$, $n = 2$. (5) Nonbonded parameters: SO, $R^* = 2.00$ Å, $\epsilon = 0.20$ kcal/mol; OX, $R^* = 1.60$ Å, $\epsilon = 0.20$ kcal/mol.

Figure S2. Catalytically productive tetrahedral intermediates for the subtilisin E catalyzed hydrolysis of (*S*)-**7c** (I) and (*S*)-**7c** (II) as identified by molecular modeling. The important active site and substrate atoms (sticks) are colored as follows: grey (carbon), red (oxygen), blue (nitrogen), orange (sulfur) and pink (chlorine). Surrounding atoms (space fill) of subtilisin are shown in blue. For clarity, all hydrogen atoms and water molecules are hidden. Both I and II maintain all catalytically essential hydrogen bonds and the chloroacetyl group binds in the S₁ pocket. The triisopropyl benzene group (Large) or sulfoxide oxygen (Medium) was bound in the leaving-group S₁' pocket. However, both groups were forced out of the S₁' pocket because of steric hindrance between the triisopropyl group and active site residues. The productive orientation of slow-reacting (*S*)-**7c** differs from (*S*)-**1h** because of steric clash between the triisopropyl group and the oxyanion residue Asn155 when the sulfoxide oxygen is bound in the S₁' pocket. This forces the substrate to rotate about the S-N bond, which places the triisopropyl group above the S₁' pocket.-This conformation is similar to the productive orientation of fast-reacting (*R*)-**7c**. Since the aryl group of both (*R*)-**7c** and (*S*)-**7c** bind above the S₁' pocket, there is little difference in their binding conformations and the enantioselectivity is low ($E = 1.2$).

I

II

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3. We are unable to account for the discrepancy with the previously reported mp value. However, the ^1H and ^{13}C NMR spectra correspond to the proposed structure of **7** and agree with the previously reported data.¹

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13. The van der Waals distance for CH-C = 3.99 Å, CH-N = 3.84 Å, CH-S = 4.09 Å and O-HC = 3.81 Å. These were estimated from the van der Waals radii of carbon (1.70 Å), nitrogen (1.55 Å), sulfur (1.80 Å) or oxygen (1.52 Å) and hydrogen (1.20 Å) and the C-H bond length (1.09 Å) or O-H bond length (0.96 Å) from Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441-451.