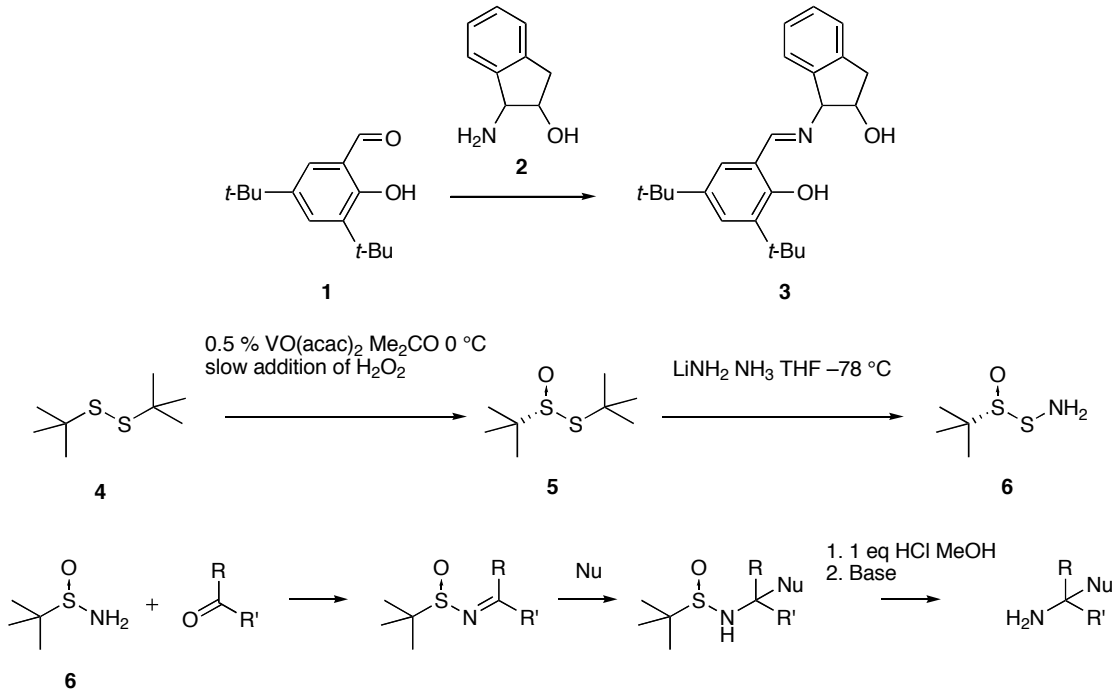
(*SS*)- *tert*-Butanesulfinamide
Stereoselective synthesis of 1,2-Aminoalcohols



General notes
Compounds 4-9 has an extremely intense bad odor. All equipment used, including cooling traps for punps, were collected and soaked overnight in a solution of 30 % H_2O_2 in 2 M aq NaOH (1:5). Then the odor free bath was discarded.

Di -*tert*-butyl disulfide **4** was purchased from Acros, hydrogen peroxide (30% aq., stabilized with sodium stannate) was purchased from Fisher Scientific, ACS grade acetone was purchased from EM Scientific, anhydrous ammonia was purchased from Matheson, lithium bars were purchased from Alfa Aesar and vanadyl acetylacetonate was purchased from Strem.1 All materials were used without purification except for THF, which was distilled from sodium benzophenone ketyl, and **4**, which was distilled (bulb to bulb, 90 ºC/20 torr). The ligand **3** is derived from *cis*-1-amino-indan-2-ol (Strem) and 3,5-di*tert*- butylsalicylaldehyde (Aldrich) and its synthesis has been reported.2 After isolation of the ligand, further purification by chromatography or crystallization is not required. *Note:* (1 *R*, 2 *S*)-(+)- *cis*-aminoindanol gives (*SS*)-thiosulfinate, which leads to (*SS*)-sulfinamide.

(1*S*,2*R*)-1-[(2-Hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol 3
3,5-Di-*tert*butylsalicylaldehyde **1** (4.68 g, 20.0 mmol) was dissolved in 125 mL ethanol. (1*S*,2*R*)-1- Amino-2-indanol **2** (3.13 g, 21.0 mmol) was added in one portion. The solution immediately turned bright yellow. The mixture was stirred for 2 hours, at which time ethanol was removed on the rotary evaporator. The flask was filled three successive times with methylene chloride and evaporated. The resulting solid was dried under vacuum (caution: foaming!) overnight to afford **3** (7.30 g, 99%). [£\]25 D –32.00 (c 0.69, CH2Cl2). IR (KBr disk) 3423, 2959, 2923, 1627, 1476, 1440. 1H NMR (500 MHz, CDCl3) £_ 1.34 (s, 9H), 1.43 (s, 9H), 2.20 (s, 1H), 3.13 (dd, *J*=4.9, 15.6 Hz, 1H), 3.25 (dd, *J*=5.9, 15.6 Hz, 1H), 4.70 (s, 1H), 4.81 (d, *J*=4.9 Hz, 1 H), 7.19-7.34 (m, 5H), 7.44 (d, *J*=2.4 Hz, 1H), 8.6 (s, 1H). 13C NMR (125.8 MHz, CDCl3) £_ 29.6, 31.7, 34.4, 35.3, 39.9, 75.5, 76.0, 118.0, 125.2, 125.7, 126.8, 127.3, 127.9, 128.8, 137.2, 140.7, 141.1, 141.2, 158.2, 168.5.

(*SS*)-(-)- *tert*-Butyl *tert*-Butanethiosulfinate 5

To a two neck 1L round bottom flask fitted with an overhead stirrer was added 1.89 g (5.17 mmol) of ligand **3** and 1.33 g (5.00 mmol) of vanadyl acetylacetonate (STREM). Acetone (250 mL) was added and the reaction mixture was stirred vigorously, while open to the air, for 30 min. To the resulting dark green solution was added 192 mL (1.00 mol) of di- *tert*-butyl disulfide **4** and the resulting mixture was cooled to 0 °C. The reaction mixture was stirred vigorously and 110 mL (1.10 mol) of 30% aq. hydrogen peroxide3 was added over 20 h using a syringe pump. Adding hydrogen peroxide resulted in a color change from dark green to dark purple. After 20 h, the conversion was 98% by NMR and the *ee* was 86% by HPLC. Conversion was monitored using NMR (300 MHz in CDCl3; disulfide 1.31 ppm, thiosulfinate 1.38 and 1.56 ppm; note that the peak at 1.56 ppm can be obscured by the water peak) or HPLC (Daicel AS column, 1mL/min, 97:3 hexanes:iPrOH, £f = 254nm, tdisulfide = 3.3 min, t *S* = 6.6 min, t *R* = 8.4 min) and % *ee* was monitored by HPLC. The reaction was quenched at 0 ºC with 50 mL of sat. aqueous Na2S2O3 added over 30 min via syringe pump.4 The mixture was diluted with hexanes (250 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with hexanes (2 x 250 mL) and the combined organic layers were washed with brine (2 x 50 mL). The combined organic layers were then dried over Na2SO4, filtered, and the solvent removed under reduced pressure at 30 ºC or lower. The resulting yellow to brown oil5 contained <1% acetone by NMR.6 The crude thiosulfinate **5** can be recrystallized from a half volume of hexanes at -20 °C as white crystals in about 70% yield,7 or Kugelrohr distilled8 to obtain pure thiosulfinate. However, the crude material is of sufficient purity to be used directly in the second step. It is essential to store the thiosulfinate at –20 ºC to prevent racemization.

(*SS*)- *tert*-Butanesulfinamide 6 8
A 5 L four-necked round bottom flask equipped with a mechanical stirrer, an NH3 condenser, and a nitrogen inlet was charged with 1000 mL of liquid NH3. Fe(NO3)3·9H2O (500 mg, 1.24 mmol) was then added, followed by lithium bar pieces (17.4 g, 2.50 mol) in 500-700 mg portions.9 A –78 °C bath was periodically raised to the bottom of the flask to slow the refluxing caused by the formation of LiNH2. As portions of Li bar were added, the mixture initially became blue, and then faded to a gray suspension. Once the addition of lithium was complete (about 2.5 h), the flask was submerged in the –78 °C bath. After cooling for 30 min, a solution of crude (*SS*)-thiosulfinate **5** (194 g, 1.00 mol) in 320 mL of THF was slowly added to the vigorously stirred reaction mixture via addition funnel over the course of 1 h. Once the addition was complete, the mixture was stirred for an additional 15 min before 160 g (3.00 mol) of NH4Cl (s) was slowly and carefully added. The cold bath was removed and stirring was continued until the mixture reached ambient temperature.10 The remaining volatile material was removed using a small pump (20 torr).10,11 The residue was diluted with water (165 mL)12 and stirred vigorously to dissolve most of the solids. To this mixture was then added EtOAc (1000 mL) and the resulting mixture was again stirred vigorously. The mixture was transferred to a separatory funnel and the organic layer was separated, washed with 60 mL of salt water (made from 40 mL of brine and 20 mL of water), and dried with with MgSO4.13 The aqueous layer was then repeatedly extracted with EtOAc (1 x 1000 mL, then 2 x 500 mL) and each extract was washed once with the same 60 mL of salt water and then dried with MgSO4. The solvent was removed under vacuum to afford 121 g of crude solid. The crude material was triturated once with hexanes14 (245 mL), filtered, and the solids (91.0 g) were recrystallized from hexanes15 (450 mL) to provide 78.8 g (65% overall) of >99% *ee* (SS)- *tert*butanesulfinamide **6** (HPLC, Daicel Chiralpak AS column, 90:10 hexanes/ethanol; 1.2 mL/min, 222 nm; t *R* = 7.6 min; t *S* = 10.5 min) as a white to off-white crystalline powder: [£\]23 D +4.9º (*c* 1.0, CHCl3); mp 101-102 ºC; IR 1032, 1364, 1474 cm-1; 1H NMR (400 MHz) £_ 1.18 (s, 9H), 3.82 (br s, 2H); 13C NMR (101 MHz) £_ 22.1, 55.3. Anal. Cald for C4H11NOS: C, 39.64; H, 9.15; N, 11.56; S, 26.46. Found: C, 39.50; H, 9.43; N, 11.55; S, 26.66.

1 We had previously found that VO(acac)2 purchased from Aldrich chemical company gave poor conversion and % *ee* for the oxidation of *tert*-butyl disulfide in chloroform.
2 Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882-2883. Prepared exactly as detailed in the supporting information.

3 This mixture of acetone, hydrogen peroxide, and water is considered safe, http://www.ekachem.com/paper/bleaching/1.2.5.asp
4 It is best to quench any remaining H2O2 before allowing the reaction to warm to room temperature since a mild exotherm can occur due to H2O2 decomposition upon warming. When the sat. aqueous Na2S2O3 was added to the reaction mixture in one portion with cooling, an exotherm occurred, which raised the internal temperature of the reaction to 32 ºC; therefore, slow addition is preferred.
5 The thiosulfinate **3** may solidify upon concentration.
6 Any remaining acetone can be removed by azeotroping with hexanes.
7 Schenkel, L. B.; Tang, T. P.; Owens, T. D.; Dragoli, D. R.; Cogan, D. A.; Ellman, J. A. unpublished results.
8 Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011- 8019.
9 Each piece was cut in two immediately prior to dropping it into the reaction mixture.
10 Because of the strong odor of the *tert*-butanethiol liberated in this step, it is best to remove the thiol from the volatiles produced during warming the reaction vessel to room temperature and during concentration of the reaction mixture. We have scrubbed the thiol on a laboratory scale by passing the gas stream through two 1 L bubblers with fritted-glass gas dispersion disks containing 500 mL each of 2.5 M NaOH solution.
11 It is important to remove residual THF, which can complicate the extraction steps.
12 Smaller amounts of water led to contamination of the product with lithium chloride, thereby complicating the recrystallization of **1**. Larger amounts of water will decrease the yield of **1**.
13 The first extraction recovers 84% of the total crude material.
14 Simple trituration with hexanes (breaking up all clumps) provides material that is pure by elemental analysis, and 95% *ee* in 75% yield from di- *tert*-butyl disulfide.
15 Using 10 mL hexanes/gram crude (instead of 5 mL hexanes/g of crude) provided enantiomerically pure material (minor enantiomer not detectable) in 60% overall yield.

General Procedure for the Condensation of Aldehydes with *N*-*tert*-Butanesulfinamide 6
A 0.5 M solution of Ti(OEt)4 (2.5 equiv) and aldehyde (1.0 equiv) in THF was prepared under a nitrogen atmosphere. To the solution was added *tert*-butanesulfinamide **6** (1.1 equiv), and conversion was followed by TLC. Upon reaction completion, the mixture was poured into an equal volume of brine while being stirred rapidly. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel, where the aqueous layer was extracted with EtOAc (3_). The organic layers were combined, washed with brine, dried, and concentrated to afford the crude product.

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(*S*S,2*S*)-2-Methyl-propane-2-sulfinic Acid (2-Benzyloxypropylidene)- amide (1a)
The general procedure was followed with use of 0.51 g (3.1 mmol) of (*S*)-2-benzyloxy propanal for 3 h. Pure **1a** (0.61 g, 75%) was obtained as a clear oil after chromatography (35% EtOAc/hexanes). HPLC (Diacel Chiralpak OD column, 99:01 hexanes/IPA; 1.0 mL/min; 254 nm) *t*R[(*S*S,2*R*)-**1a**]) 8.8 min, *t*R[(*S*S,2*S*)-**1a**]) 12.8 min; [R]21 D +10.53 (*c* 0.70, CH2Cl2); IR 3063, 1626, 1087 cm-1; 1H NMR (400 MHz) ‰ 1.21 (s, 9H), 1.38 (d, 3H, *J*) 6.8), 4.31 (dq, 1H, *J*) 4.8, 6.8), 4.48 (d, 1H, *J*) 11.6), 4.63 (d, 1H, *J*) 11.6), 7.24-7.34 (m, 5H), 8.06 (d, 1H, *J*) 4.8); 13C NMR (100 MHz) ‰ 18.4, 22.3, 56.7, 71.4, 77.5, 127.6, 127.8, 128.4, 137.6, 170.3. Anal. Calcd for C14H21NO2S: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.90; H, 8.23; N, 5.35.

General Procedure for the Grignard Additions to *N*-*tert*-Butanesulfinyl Imines
To a flame-dried flask was added the aldimine (1.0 equiv, 0.10 g) in appropriate solvent (Tables 1-4, 0.20 M), and the solution was cooled. The Grignard reagent (2.0 equiv, 3.0 M in ether) was added dropwise to the solution and conversion was followed by TLC. Upon reaction completion, excess organometallic reagent was quenched with NH4Cl (saturated), and the mixture was warmed to room temperature. The resulting suspension was diluted with

an equal portion of brine and extracted with EtOAc (3_). The organic layers were combined, washed with brine, dried, and concentrated to afford the crude product (for yields and diastereoselectivities, see Tables 1-3). Syn-anti 99:1

General Procedure for the Grignard Additions to *N*-*tert*-Butanesulfinyl Imines with TMEDA

To a flamedried flask was added the aldimine (1.00 equiv, 0.10 g) in THF (0.24 M), and the solution was cooled to -78 °C. In another flask was added the Grignard reagent (2.0 equiv, 3.0 M in ether) to a solution of TMEDA (2.05 equiv) in THF (2.0 M), and this mixture was transferred dropwise via cannula to the cooled aldimine solution. Upon reaction completion as determined by TLC, excess organometallic reagent was quenched with NH4Cl (saturated), and the mixture was warmed to room temperature. The resulting suspension was diluted with an equal portion of brine and extracted with EtOAc (3_). The organic layers were combined, washed with brine, dried, and concentrated to afford the crude product (for yields and diastereoselectivities, see Tables 1 and 3). Syn-anti 5:95

(*S*S,2*S*)-2-Methyl-propane-2-sulfinic Acid (2-Benzyloxy- 1-phenyl-propyl)-amide (3a)

The general procedure was followed with use of 0.081 g (0.30 mmol) of **1a**. A mixture of *syn*- and *anti*-**3a** (0.095 g, 94% yield) was obtained as a clear oil after chromatography (40% EtOAc/hexanes to 55% EtOAc/ hexanes). HPLC-MS (60-95% MeOH/H2O over 15 min at 0.5 mL/min) *t*R(*syn*-**3a**)) 9.2 min, *t*R(*anti*-**3a**)) 8.5 min. *syn*-**3a**: IR 3269, 3063, 1603, 1495, 1068 cm-1; 1H NMR (400 MHz) ‰ 1.04 (d, 3H, *J*) 6.2), 1.13 (s, 9H), 3.66 (dq, 1H, *J*) 6.2, 8.6), 4.29 (d, 1H, *J*) 8.6), 4.42 (d, 1H, *J*) 12.0), 4.52 (s, 1H), 4.71 (d, 1H, *J*) 12.0), 7.27-7.37 (m, 10H); 13C NMR (100 MHz) ‰ 15.8, 22.6, 55.1, 63.0, 70.2, 78.6, 127.7, 127.8, 128.0, 128.36, 128.41, 128.7, 138.0, 138.8. Anal. Calcd for C20H27NO2S: C, 69.53; H, 7.88; N, 4.05. Found: C, 69.46; H, 7.94; N, 3.85.

Representative Procedure for the Sulfinyl Group Cleavage of Sulfinamides (products 1a-c to 8a-c)

To a 0.10 M solution of protected amino alcohol **5a** (0.097 g, 0.28 mmol) in MeOH was added 0.35 mL of 4.00 N HCl/dioxane (5.0 equiv, 1.4 mmol). The solution was stirred for 1 h at room temperature and was then concentrated in vacuo. The amine hydrochloride was obtained as a white solid after precipitation from MeOH with ether, and was used without further purification.

Representative Procedure for the Hydrogenation of Benzyl Protected Amino Alcohols (products 3-8a)

To a solution of the crude amine hydrochloride resulting from the sulfinyl deprotection of **5a** (ca. 0.060 mmol) in 0.60 mL of MeOH (0.10 M) was added dry Pd/C (0.005 g, 5% Pd/C dry) and then 0.10 mL of 4 N HCl/dioxane (5.0 equiv, 0.35 mmol). The mixture was purged with a stream of H2 and stirred overnight under a H2 atmosphere (balloon). The reaction mixture was filtered through Celite, the cake was washed with MeOH (2_), and the solvent was evaporated. Pure amino alcohol **9** (0.009 g, 83% two steps) was obtained as white solid after precipitation from MeOH with ether.

Deprotection and Determination of the Absolute Stereochemistry of 3a

The general procedure for sulfinyl group cleavage was followed with use of 0.070 g (0.21 mmol) of **3a**. After removal of the sulfur impurities in vacuo, the crude HCl salt was hydrogenated by using the general procedure and precipitated from MeOH with ether to afford **9** (0.033 g, 85%) as a white solid. A portion of amino alcohol **9** (0.014 g, 0.072 mmol) was cyclized following the general procedure to afford pure oxazolidone **15** (11 mg, 86%) after column chromatography (90% CHCl3/MeOH). Spectroscopic data are consistent with previously published results. Amino alcohol **9** (free base): 1H NMR (400 MHz) ‰ 1.04 (d, 3H, *J*) 6.0), 3.56 (d, 1H, *J*) 8.0), 3.76 (dq, 1H, *J*) 6.0, 8.0), 7.25-7.36 (m, 5H).25