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Communications to the Editor

A New and Direct Asymmetric Synthesis of a Hindered Chiral Amine via a Novel Sulfinate Ketimine Derived from *N*-Tosyl-1,2,3-oxathiazolidine-2-oxide: Practical Asymmetric Synthesis of (*R*)-Sibutramine

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Abstract:

A novel and direct approach for the asymmetric synthesis of (*R*)-sibutramine via chiral amine 5 using *N*-tosyl-1,2,3-oxathiazolidine-2-oxide (13) as a recyclable chiral auxiliary is described. Chiral sulfinate imine 16e was obtained by treatment of 13e with the imine intermediate formed from the reaction of a nitrile 1 and ^{i}BuMgCl that, upon reduction, provides an optically active amine 5 with high enantiopurity.

During the past few decades, many synthetic drug groups have been engaged in the development of single enantiomeric drug targets that exhibit an amine functionality at the chiral center.[1] Despite the fact that these chiral amines are regarded as an important class for the development of active pharmaceutical ingredients, their practical asymmetric synthesis poses significant challenges for synthetic organic chemists. In this context, we recently reported an asymmetric synthesis of **5** (a precursor for the anti-obesity drug sibutramine) in excellent ee using ^{i}BuLi addition to Ellman's *tert*-butanesulfinamide ((*R*)-TBSA) derived aldimine **3** (Scheme 1).[2] Although the use of ^{i}BuLi gave excellent results, this route suffers from poor cost-effectiveness due to the use of nonrecyclable (*R*)-TBSA and from the low stability of ^{i}BuLi at ambient temperature, which limits the use of this method on large scale. To circumvent the use of ^{i}BuLi, the diastereoselective reduction of a ketimine derived from ketone **6** and (*R*)-TBSA was envisioned (Scheme 2). Treatment of nitrile **1** with ^{i}BuMgCl followed by acidic hydrolysis provided hindered ketone **6** in good yield. Although preparation of *tert*-butanesulfinyl imines from ketones has been reported with high yield, preparation of ketimine **7** from sterically hindered ketone **6** using the known procedure[3] resulted in only 5% yield.

Nevertheless, ketimine **7** could be reduced at elevated temperature, followed by hydrolysis of sulfinamide **4**, which provided **5** in 70% ee. However, both routes (Schemes 1 and 2) suffered from the use of nonrecyclable chiral auxiliary (*R*)-TBSA, and other practical limitations for larger-scale production of (*R*)-sibutramine.

We identified the following objectives in devising our new synthetic strategy: (1) the N atom of the nitrile should become the amine N atom in the product, (2) the chiral imine should be formed in high yield even for sterically challenging substrates, (3) high diastereoselectivity with high yield should be obtained in the asymmetric reduction process, and (4) the chiral auxiliary should be readily recycled. As reported,[1] chiral amine can be prepared in excellent stereoselectivity by reduction of chiral sulfinyl ketimines derived from sulfinamide and ketone. The drawback of this method is that the auxiliary, sulfinamide, is destroyed during hydrolysis with acid and the auxiliary cannot be recycled and reused. Our plan was to construct the chiral ketimine with a recyclable chiral auxiliary using a Grignard addition to nitrile **8** followed by trapping the resulting magnesium imine **9** with a suitable electrophilic chiral auxiliary Xc-Y (Scheme 3). Stereoselective reduction of imine **10** would provide **11**, which would then be subjected to mild cleavage conditions to provide chiral amine **12** and chiral auxiliary precursor Xc-Z. The direct formation of chiral ketimine **10** from nitrile **8** using a suitable electrophilic chiral auxiliary and diastereoselective reduction of imine **10** to **11** plays a vital role in our reaction design.

We envisioned that, due to the unique reactivity (S−O vs S−N bond) of our recently reported activated oxathiazolidine-2-oxide derivatives (**13**, ASOO, Scheme 4) towards nucleophiles,[4] which also proved useful in the preparation of chiral sulfinamides[4a] and chiral sulfoxides,[4b] we may be

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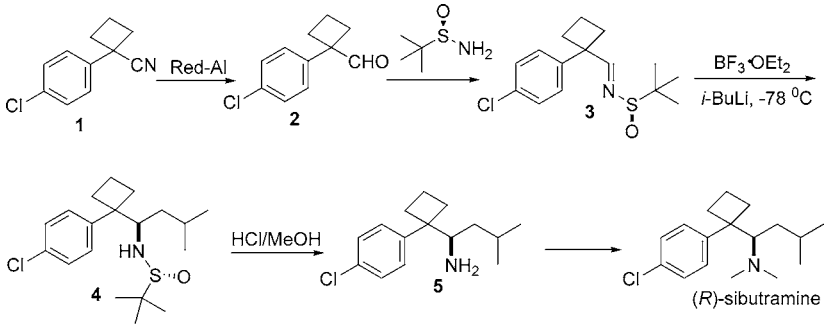
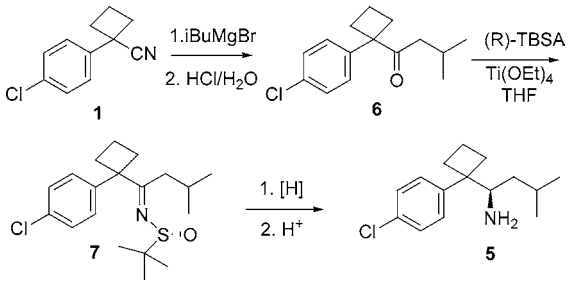
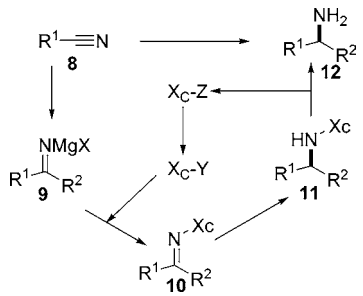
Scheme 1. **Asymmetric synthesis of (*R*)-sibutramine using (*R*)-TBSA**



Scheme 2. **Synthesis of 5 using diastereoselective reduction of 7**



Scheme 3. **New synthetic strategy for conversion of nitriles to chiral amines**



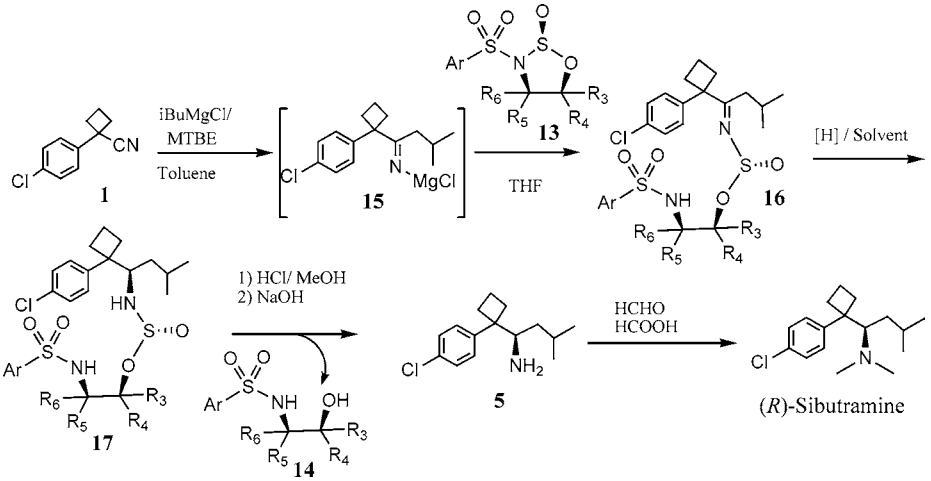
able to use this chiral auxiliary for the formation of various structurally diverse imines. Furthermore, a range of oxathiazolidine-2-oxide derivatives can be accessed from the corresponding amino alcohols. Here we disclose the first preparation and characterization of sulfinate ketimines from activated chiral oxathiazolidine-2-oxide derivatives and the utilization of these sulfinyl ketimines for the practical asymmetric synthesis of (*R*)-sibutramine (Scheme 4).

To verify the hypothesis shown in Scheme 3, our initial effort focused on the preparation of diastereopure sulfinate imines **16a**−**c** from readily available oxathiazolidine-2-oxides **13a**−**c** (Figure 1)[4] followed by finding proper stereoselective reduction conditions for the corresponding sulfinate imines. The strategy for using ketimines **16a** and **16b** in our primary study was to investigate the effect of the auxiliary framework (open chain **16a** vs rigid cyclic system **16b**) on the stereoselective reduction process. In addition, the comparison of **16b** and **16c** would demonstrate the effect of different aryl sulfonyl groups on the stereoselectivity.

With this strategy in mind, we first prepared ketimine **16**. After a number of experiments, it was found that both norephedrine- and amino indanol-derived sulfinate ketimines **16a**−**c** (Figure 1) could be prepared in >95% yield by slow addition of imine **15** in toluene to oxathiazolidine-2-oxide **13** in THF at −45 °C. It should be noted that, like the reaction of carbon nucleophiles with **13**,[4] reaction of this nitrogen nucleophile provided the corresponding sulfinyl ketimine **16** with inversion of configuration at the sulfur atom (Scheme 4).[5]

With the sulfinate ketimines in hand, next we chose **16a** as the representative substrate for the identification of reaction conditions for the stereoselective reduction of ketimines (Table 1, entries 1−13). Addition of $NaBH_4$ to a THF solution of **16a** at −45 °C provided an 80:20 diaster-

Scheme 4. **Asymmetric synthesis of (*R*)-sibutramine from nitrile 1**



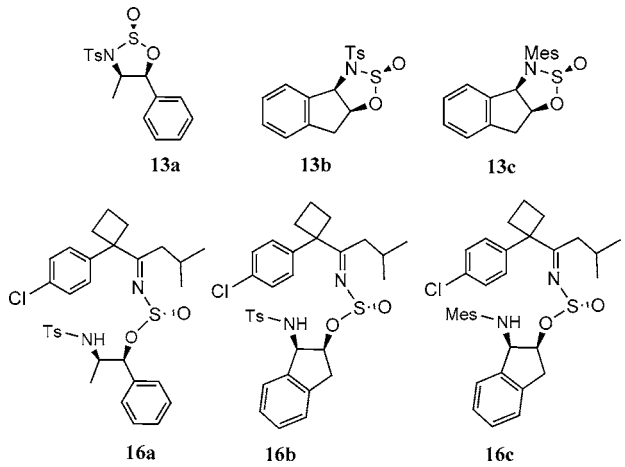


Figure 1.

Table 1. **Diastereoselective reduction of sulfinate imines 16a−c**

entry	imine **16**	reaction conditions	(*R*)/(S)[a]	% yield [b]
1	**16a**	$NaBH_4$/THF, −45 °C	80:20	97
2	**16a**	$NaBH_4$/THF/$Ti(OEt)_4$ −45 to −20 °C	82:18	93
3	**16a**	$NaBH_4$/EtOH/$Ti(OEt)_4$ −45 to −20 °C	72:28	95
4	**16a**	$NaBH_4$/MTBE/$Ti(OEt)_4$ 20 °C	83:17	78
5	**16a**	$NaBH_4$/THF/$Ti(O^iPr)_4$ −45 to −10 °C	88:12	95
6	**16a**	$NaBH_4$/THF/$Zr(OEt)_4$ −45 to −10 °C	82:18	95
7	**16a**	$NaBH_4$/THF/$ZnCl_2$ −45 to −20 °C	77:13	95
8	**16g**	$LiBH_4$/THF −78 to −30 °C	51:49	95
9	**16a**	BH_3/THF −78 to −10 °C	32:68	75[c]
10	**16a**	9-BBN/THF, 0 °C	84:16	80
11	**16a**	catechoborane/THF −45 to −20 °C	49:51	96
12	**16a**	L-Selectride/THF −78 to −20 °C	40:60	<5
13	**16a**	DIBAL-H/THF/$ZnCl_2$ −45 to 0 °C	79:21	75
14	**16b**	$NaBH_4$/THF/$Ti(O^iPr)_4$ −45 to −10 °C	84:16	90
15	**16c**	$NaBH_4$/THF/$Ti(O^iPr)_4$ −45 to −10 °C	81:19	95

[a] Ratio was determined by chiral HPLC analysis. [b] Yield is determined on HPLC based on A%. [c] Isolation yield.

eomeric ratio with 97% yield of **17a**. The stereoselectivity was determined using chiral HPLC analysis of **5** obtained after acidic hydrolysis of **17a**. We were pleased to find that use of the norephedrine-derived sulfinate ketimine not only provides reasonable selectivity with simple reducing agents such as $NaBH_4$ but also can be readily hydrolyzed to provide the desired chiral amine **5** with complete recovery of *N*-sulfonyl-norephedrine.[4b] Amine **5** can be converted to (*R*)-sibutramine using a known procedure.[2a] As reported, enantiopure oxathiazolidine **13a** can be readily regenerated by simple treatment of *N*-sulfonyl-norephedrine (**14a**) with $SOCl_2$ in the presence of pyridine in excellent yield. [4c]

Excited by this important result, our immediate attention was focused on the optimization of the stereoselective reduction using various reducing agents, additives, and solvents (Table 1).[6] When the reduction was carried out in the presence of $NaBH_4$ and $Ti(OEt)_4$ in THF, the selectivity is increased to 82:18. Surprisingly, use of $Ti(O^iPr)_4$ further increased the selectivity to 88:12, with 95% yield. Modifications of reaction conditions by changing the solvent to EtOH or MTBE and using different additives such as $Zr(OEt)_4$ or $ZnCl_2$ gave moderate selectivity or low yield. Replacement of $NaBH_4$ with $LiBH_4$ (51:49) or DIBAL-H in the presence of $ZnCl_2$ also provided poor results. Interestingly, reduction of the sulfinate imine **16a** with borane-based reducing agents such as BH_3, catecholborane, or L-selectride, provided moderate to low selectivity for the opposite diastereomer as confirmed by chiral HPLC analysis of the corresponding hydrolysis product **5**. On the other hand, sterically hindered borane reagent 9-BBN provided the desired diastereomer with good selectivity in 80% yield. When **16b** was subjected to the reduction, optimum conditions gave 84:16 selectivity (Table 1, entry 14). As anticipated, mesityl derivative **16c** gave a similar selectivity compared to **16b** (with *p*-tosyl on N), indicating that the aryl group on nitrogen has little effect on the selectivity (Table 1, entry 15). It is important to note that good to excellent yields were observed under all conditions studied (except for entry 12).

On the basis of the above results it is clear that only 76% ee of (*R*)-**5** can be obtained using an *N*-tosyl-norephedrine-based backbone **16a** (Table 1, entry 5). It occurred to us that we could rectify this shortcoming by tuning the amino alcohol backbone of the sulfinate chiral imine. Therefore, we began our investigation with preparation of various oxathiazolidines-2-oxide. The advantage of our system is that a variety of structurally diverse amino alcohols can be easily accessed using readily available amino acids. Therefore, a range of amino alcohols were prepared from inexpensive amino acids and then were conveniently converted to oxathiazolidines-2-oxides **13d**−**g** (Table 2) in good yield with excellent selectivity.[7] Treatment of imine **15** with oxathiazolidines **13d**−**g** provided corresponding sulfinate ketimine derivatives **16d**−**g**. Purification using silica gel chromatography provided analytically pure sulfinate ketimines in good yields.[8] With these diversified chiral sulfinyl ketimines in hand, we next examined the stereoselective reduction process, using the optimal conditions for **16a**. Thus, the series of sulfinate ketimines **16d**−**g** were subjected to $NaBH_4$ reduction in the presence of $Ti(O^iPr)_4$, and the results are listed in Table 2. Interestingly, switching the phenyl and methyl group of the oxathiazolidine oxide framework (**16a**

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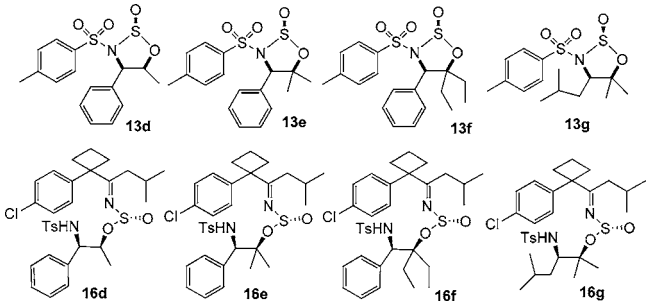
(6) See ref 2 for the determination of the stereochemistry of **5**.

(7) The Experimental Section gives the detail for the preparations of amino alcohols and oxathiazolidines. The absolute stereochemistry of **13e** was unambiguously established by single-crystal X-ray analysis.

(8) See Experimental Section for details for the preparation **16d**−**g**. Only one diastereomer was observed for chiral sulfinate ketimines based on ^1H NMR analysis.

Table 2: **Structures of oxathiazolidines (13d−g) and the results for diastereoselective reduction of their corresponding chiral sulfinate ketimines (16d−g) with $NaBH_4/Ti(O^iPr)_4$ for the synthesis of (*R*)-5**



entry	**16**	% yield for **5**	% ee for **5**
1	**16d**	95	50
2	**16e**	91	90
3	**16f**	95	76
4	**16g**	90	86

vs **16d**) provided a decreased selectivity (75:25). We were pleased to find that introducing a gem dimethyl group next to the hydroxyl functionality (**16e**) increased the selectivity from 75:25 to 95:5. Hoping to further increase the diastereoselectivity, we used gem diethyl (**16f**) derivative which provided only an 88:12 ratio of diastereomers. Replacement of the phenyl group in **16e** with isobutyl (**16g**) slightly decreased the selectivity (93:7). In conclusion, using imine **16e** in the diastereoselective reduction process, (*R*)-**5** (precursor to (*R*)-sibutramine),[2a] can be obtained in an excellent yield with 90% ee. To the reaction mixture, D-tartaric acid (D-TA) was added to form a (*R*)-**5**. D-TA salt. The salt was collected by filtration to yield the desired intermediate in >85% overall yield with >99% ee. This synthetic sequence has been consistently demonstrated in a telescoped process starting from nitrile **1** and **13e**.[9]

In summary, a practical asymmetric synthesis of (*R*)-sibutramine intermediate with excellent enantiopurity was developed by using a novel diastereoselective sulfinate ketimine reduction strategy. The sulfinate ketimine can be easily prepared by reaction of an imine nucleophile with an oxathiazolidine-2-oxide. These oxathiazolidine-2-oxides are readily reformed and recycled after treatment of recovered *N*-tosyl amino alcohol with thionyl chloride. Furthermore, it has been demonstrated that the structural backbone of these auxiliaries could be readily altered by simply varying the starting amino alcohol derivatives. Hence, these enantiopure oxathiazolidine-2-oxides can be used to tune the diastereoselective reduction process of chiral sulfinate ketimines in the production of valuable optically active amines.

Experimental Section

General. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Only anhydrous solvents were used for the reaction and were purchased from Aldrich. All reactions, unless otherwise noted, were carried out in oven-dried glassware under inert argon atmosphere. Chromatography was carried out using Silicycle 60, 230−400 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F 254 plates, and visualized using UV light and/or phosphomolybdic staining. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with a Varian Inova 300 spectrometer in $CDCl_3$ with TMS as an internal standard at room temperature. Proton and carbon spectra chemical shifts were reported using TMS and/or $CDCl_3$ as an internal standard at 0 and at 77.23 ppm, respectively. Diastereomeric ratios were determined on ^{1}H NMR spectrum analyses. Elemental analysis was performed by Quantitative Technologies, Inc. Whitehouse, NJ. Enantiomeric excess (ee) of **5** was obtained by chiral HPLC analysis on Ultron ES-OVM column, 50 mm × 4.6 mm; mobile phase, 0.01 M $KHPO_4$/MeOH (70/30); flow rate, 1.0 mL/min; wavelength, 220 nm; (*R*)-**5**, r_t = 4.6 min, (*S*)-**5**, r_t = 5.6 min).

1-[1-(4-Chloro-phenyl)cyclobutyl]-3-methyl-butan-1-one (6). To a round-bottomed flask containing a magnetic stirring bar and a distillation condenser were charged 1-(4-chloro-phenyl)cyclobutanecarbonitrile **1** (10.0 g, 95%, 49.7 mmol), toluene (30 mL), and isobutylmagnesium chloride (30 mL, 2.0 M in THF). The mixture was distilled until the internal temperature reached >105 °C and was refluxed for 3 h. The mixture was cooled to 0 °C, and HCl/MeOH (4 M prepared by dilution of concentrated aqueous HCl with MeOH) was added slowly to pH < 1. After the mixture was stirred at ambient temperature for 2 h, saturated aqueous sodium bicarbonate was added slowly to the mixture to pH ≈ 7. The aqueous phase was separated from the organic phase and extracted with EtOAc (50 mL). The combined organic phases were evaporated to dryness, and the residue was purified by flash chromatography eluting with EtOAc/hexane (3:7) to afford **6** (10.5 g) in 80% yield. ^{1}H NMR ($CDCl_3$): δ 0.66 (d, J = 8.27 Hz, 6H), 1.80−1.95 (m, 1H), 2.0−2.15 (m, 3H), 2.36−2.42 (m, 3H), 3.68−2.80 (m, 2H), 7.15−7.2 (m, 2H), 7.26−7.4 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.09, 22.46, 24.251, 30.61, 45.63, 58.86, 127.97, 128.88, 132.69, 141.75, 209.67.

(*R*)-2-Methyl-propane-2-sulfinic Acid {1-[1-(4-Chloro-phenyl)cyclobutyl]-3-methyl-butylidene}amide (7).[1] To a round-bottomed flask contained a magnetic stirring bar were charged **6** (4.9 g), THF (30 mL), (*R*)-*tert*-butanesulfinamide (2.4 g), and titanium ethoxide (44 mL, 20% ethanol solution), and the mixture was refluxed for 2 days. After cooling to ambient temperature, the mixture was poured into a brine solution (40 mL) and stirred. The mixture was filtered and the wet cake washed with EtOAc (50 mL). The organic phase was separated from the aqueous phase, washed with water (10 mL), and evaporated to dryness. The residue was purified by flash chromatography eluting with EtOAc/hexane (4:6) to afford **7** (0.4 g) in 5.8% yield. ^{1}H NMR ($CDCl_3$): δ 0.61 (d, J = 6.59, 3H), 0.80 (d, J = 6.59, 3H), 1.33 (s, 9H), 1.78−1.92 (m, 2H), 1.92−2.04 (m, 1H), 2.14−2.22 (m, 1H), 2.52−2.34 (m, 2H), 2.68−2.80 (m, 2H), 2.80−2.92 (m, 1H), 7.15−7.2 (m, 2H), 7.26−7.4 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.99,

(9) See Experimental Section for the one-pot procedure for the preparation **5** from **1** and **13e**.

22.52, 22.69, 23.00, 26.28, 32.53, 32.80, 40.97, 57.19, 57.92, 128.45, 128.73, 132.70, 142.73, 187.99. Anal. Calcd for $C_{19}H_{28}ClNOS$: C, 64.47; H, 7.97; N, 3.96; S, 9.06. Found: C, 64.54; H, 7.62, N, 3.87, S, 8.85.

***N*-Tosyl Amino Alcohol 14e.** To a 1-L three-neck round-bottom flask were added (*R*)-phenylglycine methyl ester HCl salt (25 g, 0.12 mol), $NaHCO_3$ (38 g), EtOAc (200 mL), and THF (60 mL). After the mixture was stirred at room temperature for 20 min, *p*-toluenesulfonyl chloride (22.2 g) was added, and the mixture was stirred at room temperature for 15 h. After the aqueous phase was removed, the organic phase was washed with 20% NaCl aqueous solution (40 mL) and 1.0 M HCl (20 mL) and then dried over Na_2SO_4. Evaporation of the organic solvent gave 36 g (94%) of tosylate. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.53 (s, 3H), 5.06 (d, J = 8.3 Hz, 1H), 6.00 (d, 8.2 Hz, 1H), 7.15−7.26 (m, 7H), 7.63 (dd, J = 1.8 Hz, 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 53.1, 59.5, 127.2, 127.3, 128.6, 128.9, 129.6, 135.4, 137.0, 144.4, 170.6

To the tosylate (7.2 g. 22.6 mmol) solution in THF (100 mL) under argon at 0 °C was slowly added MeMgBr (26.3 mL, 3.0 M in ether). After addition of the Grignard, the reaction mixture was warmed to ambient temperature and stirred for 4−6 h, and the reaction was monitored by TLC analysis. The reaction was quenched by 30% aqueous NH_4Ac and diluted with EtOAc (300 mL). Evaporation of the organic solvent gave a solid residue that was crystallized from MTBE/heptane to afford **14e** (6.0 g) in 83% yield and >99% ee. ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 3H), 1.33 (s, 3H), 2.28 (s, 3H), 4.16 (d, J = 8.67 Hz, 1H), 5.80 (d, J = 8.79 Hz, 1H), 6.95−7.18 (m. 7H), 7.43 (d, J = 8.18 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 26.9, 27.8, 66.3, 73.1, 127.2, 127.5, 128.1, 129.2, 137.4, 137.6, 142.9.

14f and **14g** were prepared by following the above procedure.

14f: ^{1}H NMR ($CDCl_3$): δ 0.76 (t, J = 7.33 Hz, 3H), 0.91 (t, J = 7.33 Hz, 3H), 1.02 (h. J = 7.33 Hz, 1H), 1.17 (h, J = 7.33 Hz, 1H), 1.72 (h, J = 7.33 Hz, 1H), 1.85 (h, J = 7.33 Hz, 1H), 2.27 (s, 3H), 4.29 (d, J = 8.06 Hz, 1H), 5.62 (d, J = 8.80 Hz, 1H), 6.92−7.11 (m, 7H), 7.35 (d, J = 8.43 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 7.56, 8.12, 21.54, 27.32, 28.32, 62.30, 77.80, 127.01, 127.35, 128.18, 128.37, 129.13, 137.67, 137.90, 142.64.

14g: ^{1}H NMR ($CDCl_3$): δ 0.58 (d, J = 6.00 Hz, 3H), 0.76 (d, J = 6.10 Hz, 3H), 1.13 (s, 3H), 1.16 (s, 3H), 1.16−1.36 (m, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.13−3.28 (m, 1H), 4.99 (d, J = 8.55 Hz, 1H), 7.27−7.33 (m, 2H), 7.77−7.83 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.1, 21.7, 24.0, 24.5, 25.1, 27.6, 41.2, 61. 8, 72.8, 127.3, 129.8, 138.2, 143.6

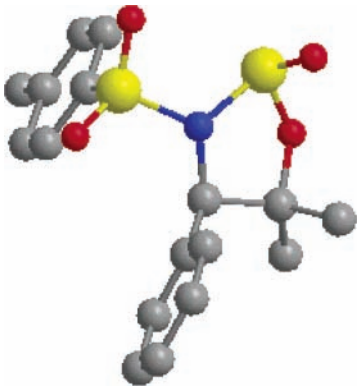
The preparation of **14a−c** was reported in the literature.

***N*-Tosyl-1,2,3-oxathiazolidine-2-oxide.** A literature method has been used for the preparation of *N*-tosyl-1,2,3-oxathiazolidine-2-oxides **13a−g** with >90% yield and 99% de.[2]

13a−c. Analytical data for compound **13a−c** were reported in the literature.[2]

13d: ^{1}H NMR ($CDCl_3$): δ 1.06 (d, J = 6.35 Hz, 3H), 2.30 (s, 3H), 4.90 (d, J = 6.53 Hz, 1H), 5.08 (p, J = 6.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 7.11−7.17 (m, 5H), 7.46 (d, 5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 17.43, 21.69, 65.26, 86.37, 127.82, 128.33, 128.54, 128.93, 129.47, 132.55, 136.03, 144.48. Anal. Calcd for $C_{16}H_{17}NO_4S_2$: C, 54.68; H, 4.88; N, 3.99. Found: C, 54.75; H, 4.76, N, 3.84.

13e: ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 3H), 1.53 (s, 3H), 2.34 (s, 3H), 4.62 (s, 1H),7.02−7.22 (m, 7H), 7.42−7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.68, 26.04, 28.93, 71.60, 98.22, 127.84, 128.37, 128.61, 129.51, 133.12, 135.60, 144.58. Anal. Calcd for $C_{17}H_{19}NO_4S_2$: C, 55.87; H, 5.24; N, 3.83; S, 17.55. Found: C, 56.02; H, 5.12; N, 3.80; S, 17.83.



13f: ^{1}H NMR ($CDCl_3$): δ 0.739 (t, J = 7.40 Hz, 3H), 0.968 (t, J = 7.42 Hz, 3H), 1.153 (h, J = 7.33 Hz, 1H), 1.588 (h, J = 7.30 Hz, 1H), 1.860 (dh, J_1 = 3.05, J_2 = 7.30 Hz, 2H), 2.310 (s, 3H), 4.806 (s, 1H), 6.98−7.22 (m, 7H), 7.40−7.46 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 7.89, 8.34, 21.69, 28.64, 29.86, 68.61, 103.51, 127.78, 128.08, 128.35, 129.11, 129.42, 133.42, 135.90, 144.36. Anal. Calcd for $C_{19}H_{23}NO_4S_2$: C, 57.99; H, 5.89; N, 3.56; S, 16.30. Found: C, 58.10; H, 5.73; N, 3.43, S, 16.28.

13g: ^{1}H NMR ($CDCl_3$): δ 0.80 (d, J = 6.59 Hz, 3H), 0.83 (d, J = 6.47, 3H), 1.30 (s, 3H), 1.59 (s, 3H), 1.44−1.70 (m, 3H), 2.46 (s, 3H), 3.60−3.66 (m, 1H), 7.36−7.42 (m, 2H), 7.81−7.87 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 22.2, 22.9, 24.6, 24.9, 28.7, 40.1, 65.0, 98.9, 127.7, 130.1, 136.5, 145.0. Anal. Calcd for $C_{15}H_{23}NO_4S_2$: C, 52.15; H, 6.71; N, 4.05; S, 18.56. Found: C, 52.10; H, 6.67; N, 3.92; S, 18.43.

Imine 16a (Scheme 4). To a 150-mL three-necked flask equipped with a magnetic stir bar, an argon inlet, a thermometer probe, and rubber septum were charged **1** (8.0 g, 41.9 mmol (96%)), toluene (70 mL), and ^{i}BuMgCl (69 mL, 0.61 mol in MTBE), and the reaction mixture was distilled until the internal temperature reached >100 °C. The reaction mixture was stirred at that temperature, and the reaction was monitored on HPLC for the disappearance of **1**. After cooling to ambient temperature, the reaction mixture was added dropwise to a solution of **13** (15.0 g, 42 mmol) in THF (100 mL) at −78 °C. After 4 h the reaction mixture was warmed 10 °C. After completion of the reaction, the reaction mixture was cooled to 0 °C, and aqueous ammonium acetate (30%, 50 mL) was added, followed by MTBE (200 mL); the mixture was then warmed to ambient temperature. The organic phase was washed with 30% $KHCO_3$ (50 mL) and 20% NaCl (50 mL) and then dried over Na_2SO_4. After

evaporation of the organic solvent, the residue was purified by flash chromatography using CH_2Cl_2/EtOAc (9.6:0.4) to furnish **16a** (3.4 g) in 95% yield. ^{1}H NMR ($CDCl_3$): δ 0.640 (d, J = 6.0 Hz, 6H), 1.043 (d, J = 6.6 Hz, 3H), 1.660 (b, 1H), 1.835−1.912 (m, 2H), 2.223−2.308 (m, 2H), 2.417 (s, 3H), 2.417−2.536 (m, 2H), 2.733−2.885 (m, 2H), 3.670−3.748 (m, 1H), 5.5.562 (d, J = 2.1 Hz, 1H), 5.905 (d, J = 9.0 Hz, 1H), 7.125−7.151 (m, 3H), 7.224−7.366 (m, 8H), 7.851 (d, J = 8.4 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ 15.19, 15.83, 21.61, 22.44, 22.56, 27.87, 32.67, 42.16, 54.27, 56.80, 77.79, 126.10, 127.28, 128.16, 128.45, 128.57, 128.87, 129.77, 133.05, 137.65, 138.24, 141.05, 143.41, 188.55. Anal. Calcd for $C_{31}H_{37}ClN_2O_4S_2$, C, 61.93; H, 6.20; N, 4.66; S, 10.67. Found: C, 61.68; H, 6.12; N, 4.47; S, 10.67.

The above method was used for the preparation of imines **16b**−**g** in 90−95% yield. The analytical data for compounds **16b**−**g** are given below.

16b: ^{1}H NMR ($CDCl_3$): δ 0.680 (t, J = 6.59 Hz, 3H), 0.949−1.150 (m, 6H), 1.700 (s, 1H), 1.857−1.951 (m, 2H), 2.180−2.358 (m, 2H), 2.432 (s, 2H), 2.430−2.544 (m, 2H), 2.720−2.920 (m, 2H), 3.660−3.770 (m, 1H), 5.574 (d, J = 2.19 Hz, 1H), 5.886 (d, J = 9.28 Hz, 1H), 7.099−7.130 (m, 2H), 7.256−7.362 (m, 8H), 7.851 (d, J = 8.30 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ 15.90, 21.75, 22.65, 22.75, 27.74, 32.18, 32.79, 39.02, 42.38, 56.80, 60.42, 76.26, 124.16, 125.24, 127.33, 127.40, 128.69, 128.96, 129.96, 133.03, 138.44, 138.89, 139.84, 143.68, 187.98.

16c: ^{1}H NMR ($CDCl_3$): δ 0.64−0.70 (m, 6H), 1.61 (m, 1H), 1.74−1.92 (m, 2H), 2.16−2.26 (m, 2H), 2.32 (s, 3H), 2.72 (s, 6H), 2.83−2.98 (m, 4H), 3.18 (dd, J_1 = 4.64 Hz, J_2 = 16.965 Hz, 1H), 3.36 (d, J = 16.84 Hz, 1H), 4.98 (dd, J_1 = 4.85 Hz, J_2 = 9.27 Hz, 1H), 5.40 (d, J = 9.03 Hz, 1H), 5.87 (m, 1H), 6.84 (d, J = 7.45 Hz, 1H), 6.99 (s, 2H), 7.10−7.15 (m, 1H), 7.18−7.23 (m, 2H), 7.31−7.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 15.89, 21.14, 22.62, 23.33, 27.63, 32.00, 32.86, 39.10, 42.41, 56.95, 60.42, 76.34, 124.13, 125.27, 127.44, 128.70, 128.94, 132.22, 132.99, 135.18, 138.96, 139.13, 140.13, 141.68, 142.44, 187.86. Anal. Calcd for $C_{33}H_{39}ClN_2O_4S_2$: C, 63.19; H, 6.27; N, 4.47; S, 10.22. Found: C, 63.17; H, 6.21; N, 4.32; S, 9.86.

16d: ^{1}H NMR ($CDCl_3$): δ 0.67−0.76 (m, 6H), 1.12 (d, J = 6.60 Hz, 3H), 1.60−1.80 (m, 1H), 1.80−1.95 (m, 2H), 2.24−2.40 (m, 2H), 2.34 (s, 3H), 2.40−2.60 (m, 2H), 2.75−2.82 (m, 2H), 2.90−3.00 (m, 1H), 4.53 (b, 1H), 5.32 (d, J = 4.00 Hz, 1H), 6.15 (d, J = 6.96 Hz, 1H), 7.00−7.20 (m, 7H), 7.30−7.40 (m, 4H), 7.45−7.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.10, 19.59, 21.26, 22.50, 27.88, 30.64, 32.67, 34.88, 42.31, 45.67, 61.24, 72.39, 127.22, 127.90, 128.00, 128.13, 128.73, 128.80, 128.91, 129.10, 129.31, 129.37, 133.26, 135.93, 137.95, 143.05, 188.78. Anal. Calcd for $C_{31}H_{37}ClN_2O_4S_2$: C, 61.93; H, 6.20; N, 4.66. Found: C, 61.93; H, 6.15; N, 4.43.

16e: ^{1}H NMR ($CDCl_3$): δ 0.586 (d, J = 6.4 Hz, 3H), 0.637 (d, J = 6.4 Hz, 3H), 1.174 (s, 3H), 1.644 (m, 1H), 1.802 (s, 3H), 1.78−1.85 (m, 2H), 2.08−2.20 9m, 2H), 2.280 (s, 3H), 2.32−2.39 (m, 1H), 2.40−2.50 (m, 1H), 2.74−2.88 (m, 2H), 4.209 (d, J = 9.52, 1H), 6.034 (d, J = 9.52, 1H), 6.94−7.14 (m, 7H), 7.22−7.26 (m, 4H), 7.36−7.42 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 15.92, 21.55, 22.0.70, 26.86, 26.98, 27.56, 32.06, 33.03, 42.59, 56.69, 66.07, 77.34, 85.43, 126.99, 127.64, 127.88, 128.43, 128.91, 129.10, 129.18, 133.04, 136.80, 137.88, 141.70, 142.73, 186.75. Anal. Calcd for $C_{32}H_{39}ClN_2O_4S_2$: C, 62.47; H, 6.39; N, 4.55; S, 10.42. Found: C, 62.47; H, 6.25; H, 4.39; S, 10.12.

16f: ^{1}H NMR ($CDCl_3$: δ 0.62−0.78 (m, 9H), 1.07 (t, J = 7.32 Hz, 3H), 1.14−1.1.28 (m 1H), 1.33−1.47 (m, 1H), 1.72 (b, 1H), 1.78−1.90 (m, 2H), 2.02−2.16 (m, 2H), 2.18−2.24 (m, 1H), 2.25 (s, 3H), 2.30−2.60 (m, 3H), 2.74−2.86 (m, 2H), 4.42 (d, J = 10. 5 Hz, 1H), 6.49 (d, J = 10. 26 Hz, 1H), 6.87−6.93 (m, 2H), 6.98−7.12 (m, 4H), 7.14−7.20 (m, 2H), 7.24 (s, 3H), 7.30−7.36 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 7.692, 8.849, 15.910, 21.518, 22.736, 25.669, 27.660, 27.923, 31.957, 33.054, 42.676, 56.814, 61.568, 92.458, 126.880, 127.337, 127.786, 128.434, 128.887, 129.021, 129.708, 133.047, 136.506, 138.210, 141.754, 142.369, 187.15. Anal. Calcd for $C_{34}H_{43}ClN_2O_4S_2$: C, 63.48; H, 6.74; N, 4.35; S, 9.97. Found: C, 63.10; H, 6.76; N, 4.04, S, 9.95.

16g: ^{1}H NMR ($CDCl_3$): δ 0.62−0.84 (m, 12H), 1.32−1.52 (m, 3H), 1.42 (s, 3H), 1.51 (s, 3H), 1.64−1.74 (m, 1H), 1.80−1.90 (m, 2H), 2.16−2.30 (m, 2H), 2.32−2.40 (m, 2H), 2.41 (s, 3H), 2.74−2.88 (m, 2H), 3.30−3.44 (m, 1H), 5.16 (d, J = 9.52 Hz, 1H), 7.24−7.34 (m, 6H), 7.73−7.78 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.9, 21.5, 21.7, 22.7, 22.8, 24.0, 24.2, 26.5, 27.4, 27.7, 32.1, 32.9, 40.4, 42.5, 56.7, 60.7, 86.9, 126.8, 128.5, 128.9, 129.6, 133.0, 139.5, 141.7, 143.1, 186.5. Anal. Calcd for $C_{30}H_{43}ClN_2O_4S_2$: C, 60.53; H, 7.28; N, 4.71; S, 10.77. Found: C, 60.16; H, 7.22; N, 4.45; S, 10.56.

Typical Procedure for Reduction of 16a to 5 Using $NaBH_4$ in the Presence of Titanium Isopropoxide. To a two-necked round-bottomed flask containing a magnetic stirring bar, a temperature probe, and an argon inlet were charged imine **16a** (0.1 g, 0.167 mmol, 1.0 equiv), THF (3 mL), and $Ti(O^iPr)_4$ (0.076 g, 2.0 equiv), and the mixture was stirred at ambient temperature for 1 h. The mixture was then cooled to −45 °C, and $NaBH_4$ (0.025 g, 4.0 equiv) was added. After stirring for 3 h, the reaction mixture was warmed slowly to −10 to −15 °C and stirred. The reaction was monitored by TLC analysis. HCl/MeOH (4.0 mL, 4 M) was added slowly to quench the reaction, and the resulting mixture was stirred at rt for 3 h. The mixture was cooled to 0 °C, and NaOH (5.0 M) was added to a pH > 10 and diluted with EtOAc (20 mL). The organic phase was washed with brine (5 mL) and evaporated to dryness. The residue was then purified by flash chromatography, eluting with EtOAc/hexane/Et_3N (80:20:0.1) to afford **14a** (50 mg, 98%) and **5** (40 mg) in 95% yield and 76% ee.

The above procedure is also used for the reduction of imines **16b**−**g**.

Typical Procedure for Reduction of Imines 16 with Other Reducing Reagents without a Lewis Acid. To a two-necked round-bottomed flask containing a magnetic stirring bar and temperature probe with an argon inlet was charged the imine (1.0 equiv). After cooling the mixture to the

reaction temperature, reducing reagent (1.5 equiv) was added dropwise with stirring, and the reaction was monitored on TLC. The reaction was then worked up by following the above procedure.

One-Pot Procedure for the Preparation of (*R*)-5·D-TA. To a 250-mL three-necked flask equipped with a magnetic stir bar, an argon inlet, a thermometer probe, and rubber septum were charged toluene (80 mL), **1** (8.0 g, 41.9 mmol), and ^{i}BuMgCl (68.5 mL, 0.61 mol in MTBE) under an argon atmosphere, and the reaction mixture was distilled until the temperature reached >100 °C. The reaction mixture was stirred at that temperature and monitored by HPLC for the disappearance of **1**. The reaction mixture was cooled to ambient temperature and added dropwise to the solution of **13e** (15.5 g, 42.4 mmol) in THF (100 mL) in a 500-mL round-bottomed flask at −45 °C. The reaction mixture was stirred for 4 h and warmed to 10 °C under stirring. The reaction was monitored by TLC analysis. The reaction mixture was cooled to 0 °C, aqueous ammonium acetate (30%, 50 mL) was added, followed by MTBE (200 mL), and the mixture was warmed to ambient temperature. The organic phase was washed with 30% $KHCO_3$ (50 mL) and 20% NaCl (50 mL) and was polish filtered. After the resulting organic phase was distilled under reduced pressure to about 50 mL (KF = 0.58%), anhydrous THF (80 mL) and Ti(O-*i*-Pr)$_4$ were added, and the mixture was stirred at ambient temperature for 1 h and cooled to −45 °C. $NaBH_4$ (6.4 g, 168 mmol) was added in one portion, and the mixture was stirred for 6 h and warmed to −10 °C, and the reaction was monitored on TLC for the disappearance of starting material. To the reaction mixture was slowly added aqueous HCl dissolved in MeOH (60 mL, 4 M), and the mixture was warmed to ambient temperature and stirred for 3 h. After the mixture was cooled to 0 °C, NaOH (5 M) was added slowly until the pH ≈ 12; the mixture was diluted with toluene (200 mL) and distilled under reduced pressure to remove the low boiling point solvents. The organic phase was allowed to separate for 20 min, and the organic phase was washed twice with aqueous NaCl (50 mL, 20%). The mixture was heated to 60−70 °C, and D-tartaric acid (6.3 g) in water (13 mL) and acetone (6 mL) were added slowly. The mixture was distilled under azeotropic conditions until the internal temperature reached >95 °C. The mixture was then cooled to ambient temperature and stirred for 1 h. The slurry formed was filtered, and the wet cake was washed with toluene (30 mL × 2) and MTBE (30 mL) and dried at 45 °C for 24 h under reduced pressure to afford 14.6 g of (*R*)-5·D-TA (86%) with 99% ee.

The mother liquor was concentrated under reduced pressure, and EtOAc (100 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL × 2), brine (30 mL), and water (20 mL). The resulting mixture was distilled, heptane was added (100 mL), and the mixture was then cooled to room temperature and stirred for 2 h. The slurry was filtered to afford **14e** (12.5 g) in 92% yield.

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