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Catalytic Asymmetric Oxidation of *tert*-Butyl Disulfide. Synthesis of *tert*-Butanesulfinamides, *tert*-Butyl Sulfoxides, and *tert*-Butanesulfinimines

Derek A. Cogan, Guangcheng Liu,† Kyungjin Kim,‡ Bradley J. Backes, and Jonathan A. Ellman*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720

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Abstract: The first example of the catalytic asymmetric oxidation of *tert*-butyl disulfide (**1**) is described. The product, *tert*-butyl *tert*-butanethiosulfinate (**2**) is obtained with 91% enantiomeric excess in yields of ≥92% on scales as large as 1 mol. The application of H_2O_2 as stoichiometric oxidant in the presence of 0.25 mol % of $VO(acac)_2$ and 0.26 mol % of a chiral Schiff base ligand, **6a**, is both convenient and cost-effective. Thiosulfinate ester **2** is chemically and optically stable and serves as an excellent precursor to chiral *tert*-butanesulfinyl compounds by the stereospecific nucleophilic displacement of *tert*-butyl thiolate. Addition of $LiNH_2$ in liquid ammonia and THF provides *tert*-butanesulfinamide (**3**; 91% yield). A single recrystallization provides enantiomerically pure **3** in 71−75% overall yield from disulfide **1**. Enantiomerically pure thiosulfinate ester **2** also reacts readily and stereospecifically with Grignard reagents, organolithiums, lithium amides, and lithium imine salts to provide enantiomerically pure chiral sulfoxides, sulfinamides, and sulfinimines in good yield.

Introduction

There have been numerous reports in which the sulfinyl group has acted as a removable source of diastereoselection in asymmetric synthesis. Sulfoxides have long been employed for a wide-range of stereoselective carbon−carbon bond-forming reactions,[1] while sulfinamides and sulfinimines[2] are increasingly being utilized as versatile chiral nitrogen intermediates for the preparation of a range of chiral amines, including α-branched amines,[3] α- and β-amino acids,[4] aziridines,[5] and amino phosphonic acids.[6] In most applications, arenesulfinyl auxiliaries, in particular *p*-toluenesulfinyl auxiliaries, have been used because practical methods for the preparation of arenesulfinyl compounds have been developed.[7] Yet, in the few comparative studies of arenesulfinyl compounds with their *tert*-butanesulfinyl counterparts, such as in additions of lithiated sulfoxides to α,β-unsaturated esters[8] or methyl iodide,[9] and reactions of sulfin-

† Present address: NTH 2122, GlaxoWellcome Inc., P.O. Box 13398, Research Triangle Park, NC 27709-3398.

‡ Present address: Roche Research Center, 340 Kingsland St., Nutley, NJ 07110.

(1) (a) Solladié, G. *Synthesis* **1981**, 185−196. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (c) Patai, S. *The Chemistry of Sulphinic Acids, Esters and their Derivatives*; John Wiley & Sons: Chichester, England, 1990. (d) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1983; Vol. 4, p 227.

(2) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Reddy, G. V.; Zhou, P. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1997**, *120&121*, 291−303.

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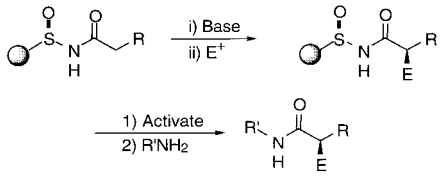
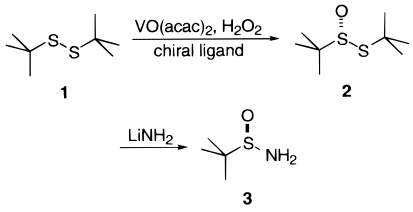
Scheme 1



imines with sulfur ylides,[5b] the *tert*-butanesulfinyl auxiliary provided higher levels of diastereoselectivity. To best elaborate upon the role of the *tert*-butanesulfinyl moiety as an auxiliary, methods for the preparation of enantiomerically pure *tert*-butanesulfinyl compounds, including sulfinamides, sulfinimines, and sulfoxides, must be developed.

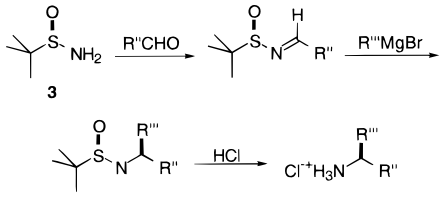
Our interest in the synthesis of *tert*-butanesulfinyl compounds arose during explorations of diastereoselective alkylations of *N*-acylsulfinamide enolates (Scheme 1). The goal has been the development of a support-bound sulfinamide linker that serves both as a chiral auxiliary and an activatable linkage functionality for nucleophile-mediated release of products from solid supports.[10] In initial solution studies, the *N*-acyl derivatives of the more sterically hindered *tert*-butanesulfinamide provided levels of diastereoselection superior to that of the *N*-acyl derivatives of arenesulfinamides.[11] Unfortunately, the chiral precursor, *tert*-butanesulfinamide (**3**) had never been isolated.[12] As a result, there was no information regarding the chemical or configurational stability of enantiomerically pure **3**.

In a preliminary account,[3a] we described a method for preparing enantiomerically enriched *tert*-butyl *tert*-butanethiosulfinate (**2**) in the first example of an asymmetric catalytic oxidation upon a disulfide (eq 1). Reaction of $LiNH_2$ with **2**



(1)

provided the sulfinamide **3** in high yield with absolute stereospecificity. In addition, another application of chiral *tert*-butanesulfinyl compounds was described in the general stereoselective synthesis of α-branched amines from **3** (eq 2). In this



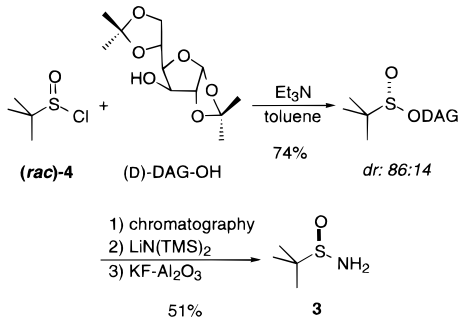
(2)

procedure, the sulfinamide **3** is readily condensed with aldehydes to provide sulfinimines in high yield. Additions of Grignard reagents to the sulfinimines proceed with high levels of diastereoselection and with no competitive addition at sulfur. In contrast, arenesulfinamides must be N-silylated in order to condense with most aldehydes,[13] and unstabilized Grignard reagents have been reported to attack at sulfur for the related *p*-toluenesulfinimines.[3b] Thus, in addition to differences in diastereoselection, there are distinct differences in chemical reactivities between *tert*-butanesulfinyl compounds and their arenesulfinyl counterparts.

The application of thiosulfinate ester **2** as a chiral *tert*-butanesulfinyl intermediate was instrumental in developing the first practical route to multigram quantities of enantiopure sulfinamide **3**. In this article, we describe the series of experiments that led us to recognize *tert*-butanethiosulfinate, **2**, as a precursor for a range of enantiomerically pure *tert*-butanesulfinyl compounds. We further define optimized reaction parameters for the highly catalytic asymmetric oxidation of *tert*-butyl disulfide (**1**) to provide access to large quantities of **2**. Finally, we describe the scope and limitations of nucleophilic additions to **2**, efficiently affording enantiomerically pure *tert*-butanesulfinyl compounds, including sulfinamides, sulfinimines, and sulfoxides in high yield.

Results

Initial Efforts. At the time we began our efforts, Alcudia and co-workers had described the most practical method for the preparation of enatiomerically pure *tert*-butyl sulfoxides and *tert*-butanesulfinimines by the addition of nucleophiles to diastereomerically pure diacetone-D-glucose (DAG) *tert*-butanesulfinate esters.[14] Therefore, this technology was applied to the synthesis of the sulfinamide **3** by addition of lithium bis(trimethylsilyl)amide to (D)-DAG-(R_S)-*tert*-butanesulfinate esters (eq 3). After treatment with $KF-Al_2O_3$, the enantiomerically



(3)

pure *tert*-butanesulfinamide was isolated in modest yield as a stable, white crystalline solid. Significantly, no racemization

(5) (a) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243−3245. (b) Ruano, J. L. G.; Fernández, I.; Catalina, M. d.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407−3414. (c) Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525−7528. (d) Davis, F. A.; Reddy, G. V.; Liang, C.-H. *Tetrahedron Lett.* **1997**, *38*, 5139−5142.

(6) (a) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991−3994. (b) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532−7533. (c) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, J. *J. Chem. Soc., Chem. Commun.* **1996**, 1503−1504.

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(10) For examples of enolate alkylation and derivatizable cleavage from solid support, see: (a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172. (b) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055−3056.

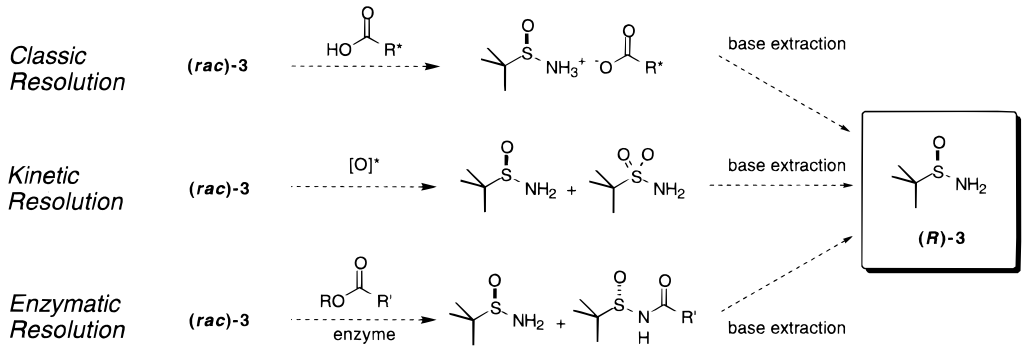
(11) Backes, B. J.; Ellman, J. A. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1997; ORGN 066.

(12) In one case, **3** has been prepared in situ and directly consumed: Bleeker, I. P.; Engberts, J. B. F. N. *J. Org. Chem.* **1981**, *46*, 1012−1014.

(13) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563.

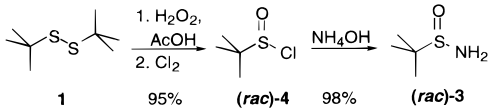
(14) (a) Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789−6796. (b) Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719−5722.

Chart 1. Methods for the Resolution of *tert*-Butanesulfinamide **3**



or decomposition of the crystalline sulfinamide has been observed over at least 18 months.[15] Although **3** could be prepared by this procedure, it was readily apparent that the DAG approach was not practical for the efficient production of large quantities of sulfinamide. In particular, this method requires a chromatographic separation of a diastereomerically enriched mixture of high-molecular-weight DAG-sulfinates. Other diastereomeric sulfinyl intermediates have been described, but these routes also require chromatographic separations and employ expensive and high-molecular-weight chiral auxiliaries.[16]

Methods for the resolution of racemic sulfinamide **3**, which can be accessed in high yield on large scale from extremely inexpensive reagents, were next investigated (Chart 1). Treatment of disulfide **1** with H_2O_2 followed by Cl_2, according to the procedure of Prinzbach, provides *tert*-butanesulfinyl chloride, (*rac*)-**4**.[17] Treatment of (*rac*)-**4** with concentrated ammonium hydroxide provided racemic *tert*-butanesulfinamide ((*rac*)-**3**) in 93% overall yield (eq 4). Unfortunately, attempts to resolve

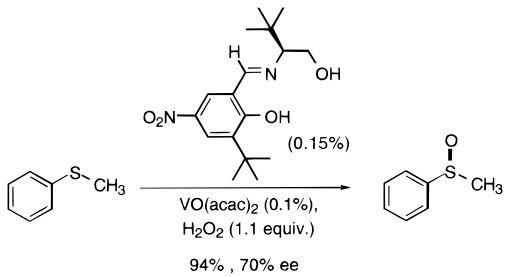


(4)

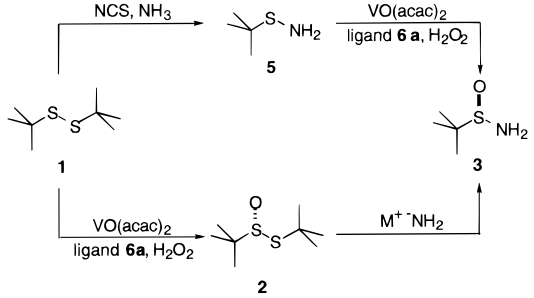
(*rac*)-**3** with inexpensive chiral acids, including camphorsulfonic, tartaric, mandelic and malic acids, were unsuccessful. Kinetic resolution procedures were explored, such as oxidation of racemic sulfinamide as precedented by related resolutions of sulfoxides,[18] but were quickly dismissed, since at least half of the material would necessarily be discarded. In the same way, enzymatic resolution by acylation of the sulfinamide was also briefly explored but abandoned.

Catalytic Methods. Catalytic asymmetric oxidation at sulfur would be more attractive than the aforementioned routes but only if high selectivities and catalytic efficiencies could be achieved with inexpensive and nontoxic stoichiometric oxidants. Such a catalyst system had recently been reported for the oxidation of thioethers by Bolm and Bienewald.[19] Employing Schiff base−vanadium complexes, oxidations proceeded in up to 85% enantiomeric excess (ee), with catalyst loadings as low as 0.01% and with hydrogen peroxide as a clean and inexpensive stoichiometric oxidant (Scheme 2). Preparation of the Schiff

Scheme 2



Scheme 3



base ligands is straightforward,[20] enabling numerous derivatives to be evaluated.

A number of sulfur-containing oxidation substrates that would provide sulfinamide **3** could be envisioned. An obvious choice is *tert*-butanesulfenamide (**5**), prepared in one step from the very inexpensive *tert*-butyl disulfide (**1**) (Scheme 3). An equally practical route is the direct oxidation of **1** to *tert*-butyl *tert*-butanethiosulfinate (**2**) (Scheme 3), followed by nucleophilic amide addition, known to occur with inversion.[21] Notably, *tert*-butanethiosulfinate esters are optically and chemically stable[22] in contrast to other thiosulfinate derivatives.[23]

For the pilot oxidations of disulfide **1** and sulfenamide **5**, ligand **6a** (eq 5, Table 1), formed by the condensation of 3,5-di-*tert*-butylsalicylaldehyde with (*S*)-*tert*-leucinol, was used. The

(15) Other sulfinamides are less optically stable: Booms, R. E.; Cram, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 5438−5446

(16) (a) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977−5985. (b) Rebiére, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991−5999.

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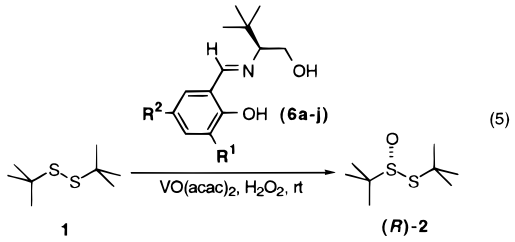
(20) (a) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385−4398. (b) Hayashi, M.; Tanaka, K.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *6*, 1833−1836. (c) Hayashi, M.; Kaneda, H.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2511−2516. (d) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839−1844.

(21) (a) Sagramora, L.; Koch, P.; Garbesi, A.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1967**, 985−986. (b) Mikolajczyk, M.; Drabowicz, J. *J. Chem. Soc., Chem. Commun.* **1976**, 220−221. (c) Kishi, M.; Ishihara, S.; Komeno, T. *Tetrahedron* **1974**, *30*, 2135−2142.

(22) (a) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 6, 3921−3929. (b) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929−3944.

(23) Takata, T.; Endo, T. In *The Chemistry of Sulfinic Acids, Esters and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons: Chichester, England, 1990; pp 527−575.

Table 1. Effect of Varying the Salicylaldehyde Portion of Ligands **6** on the Oxidation of Disulfide **1** (eq 5)[a]



(5)

	ligand **6**		conv, %[b]	ee, %[c]
	R^1	R^2		
6a	*t*-Bu	*t*-Bu	94	82
6b	*t*-Bu	NO_2	18	45
6c	*t*-Bu	OMe	85	79
6d	*t*-Bu	H	88	83
6e	H	H	50	46
6f	OMe	H	17	<10[d]
6g	NO_2	Br	15	<10[d]
6h	Br	Br	10	25
6i	Cl	Cl	12	<10[d]
6j	Br	Me	23	50
6k	2-hydroxy-1-naphthaldimine		60	42

[a] All reactions were performed at 23 °C at 0.8 M in CH_2Cl_2 with 2% $VO(acac)_2$ and 3% ligand. [b] Conversions determined by GC analysis with tridecane as an internal standard. [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Impurities limited accuracy of ee determination.

first oxidations (2-mmol scale) were performed with 4 mol % of $VO(acac)_2$ and 6 mol % of **6a** with CH_2Cl_2 as solvent (0.5 M in substrate). Oxidation of **5** proceeded with only 4% ee. Preliminary oxidation studies employing alternative catalyst systems were equally disappointing. In contrast, the vanadium catalyst system afforded thiosulfinate ester (*R*)-**2** with 82% ee.[24] Clearly, oxidation of *tert*-butyl disulfide, followed by amide displacement, was the more promising approach.

Even without optimization, this oxidation of **1** marks the highest optical purity for the asymmetric oxidation of a disulfide. Previous reports have described stoichiometric oxidations with chiral peracids,[21a,25] a chiral oxaziridine,[26] or modified Sharpless conditions.[27] Thiosulfinate esters other than **2** have been obtained with a high degree of stereospecificity by acid treatment of enantiomerically enriched sulfinamides in the presence of thiols.[28]

Optimization of Disulfide Oxidation. We chose to first improve the catalytic efficiency of the oxidation of disulfide **1**. When the oxidation of **1** was performed under the same reaction conditions, but with a reduction in the amount of $VO(acac)_2$ from 4 to 1 mol %, thiosulfinate ester **2** was produced in only 38% conversion with a 71% ee. However, by increasing the concentration of disulfide from 0.5 to 1.5 M, the oxidation proceeded with 89% conversion and 81% ee. The disulfide concentration can be further increased to 2 M without a deleterious effect on yield or enantioselection, but higher concentrations reduced the solubility of the catalyst.

(24) The absolute sense of stereochemistry was assigned by addition of MeMgBr, known to proceed with inversion (vide infra), to deliver (*S*)-*tert*-butyl methyl sulfoxide.

(25) (a) Savage, W. E.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1965**, 417−418. (b) Kice, J. L.; Large, G. B. *Tetrahedron Lett.* **1965**, 3537−3541.

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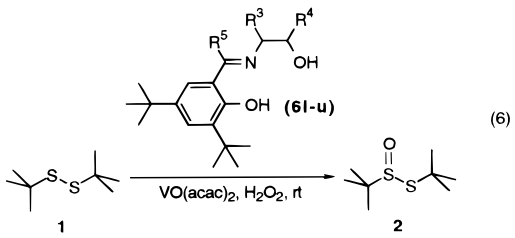
(28) Drabowicz, J.; Mikolajczyk, M. *Tetrahedron Lett.* **1985**, *26*, 5703−5706.

Table 2. Effect of Varying the Amino Alcohol Portion of Ligands **6** for the Oxidation of Disulfide **1**[a]



(6)

	ligand **6**			conv, %[b]	ee, %[c] (config)
	R^3 (config)	R^4 (config)	R^5		
6a	*t*-Bu (*S*)	H	H	94	82 (*R*)
6l	*i*-Pr (*S*)	H	H	65	60 (*R*)
6m	Ph (*R*)	H	H	47	25 (*S*)
6n	Bn (*S*)	H	H	69	53 (*R*)
6o	Ph (*S*)	Ph (*R*)	H	60	44 (*S*)
6p	H	Me (*S*)	H	40	19 (*R*)
6q	Me (*R*)	Ph (*S*)	H	85	41 (*R*)
6r	(1*S*,2*R*)-1-amino-2-indanol		H	81	58 (*S*)
6s	*i*-Pr (*S*)	H	Me	16	53 (*R*)
6t	*t*-Bu (*S*)	H	Me	10	19 (*R*)
6u	Me (*S*)	H	Me	16	41 (*R*)

[a] All reactions were performed at 23 °C at 0.8 M in CH_2Cl_2 with 2% $VO(acac)_2$ and 3% ligand. [b] Conversions determined by ^1H NMR. [c] Enantiomeric excess determined by chiral HPLC analysis.

At 0.8−1.5 M in disulfide, investigations toward ligand optimization were initiated. The Schiff base ligands, **6a**−**r**, were easily prepared by condensation of salicylaldehydes with amino alcohols. Previous work with these ligands has indicated a necessity for sterically bulky substituents ortho to the phenol, but electronic effects about the salicylaldehyde portion vary widely among different transformations and substrates.[19,20] Therefore, it would be prudent to screen a number of different ligands.

The ligands **6a**−**j** were chosen to probe the effects of substituents at R^2 (eq 5, Table 1). A linear relationship of electron donation from the R^2 substituent with either enantioselection or conversion is not evident, although the electron-withdrawing nitro substituent (**6b**) is clearly undesirable. Not surprisingly, there appears to be no steric effect at R^2 (**6a**,**d**). The remainder of Table 1 describes data for ligands derived from various commercially available salicylaldehydes. Substitution at R^1 is critical, with the large *tert*-butyl substituent being essential for high conversions and enantioselections.

Various amino alcohols were next condensed with 3,5-di-*tert*-butyl salicylaldehyde and its ketone derivative to examine steric effects at R^3 and R^4 (eq 6, Table 2). None of these ligands performed better than **6a**. Interestingly, substantial steric demand at R^3 or R^4 had a favorable influence upon both enantioselection and conversion. Ketimine ligands have provided improved selectivities in the Ti-catalyzed reactions of diketene with aldehydes.[29] However, for the oxidation of disulfide **1**, poorer selectivities were observed with ketimine ligands **6s**−**u**. On the basis of the results from the ligand-screening efforts, ligand **6a** was chosen for further optimization of oxidation conditions due to superior enantioselection, high conversions, and the availability of its amino alcohol and aldehyde precursors.

Solvent effects were also found to be important. Data summarized in Table 3 clearly indicate that oxidations performed in chlorinated solvents proceeded with the highest enantiose-

(29) Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 341−342.

Table 3. Effect of Solvent on ee for the Oxidation of Disulfide **1**[a]

solvent	ee, %[b]	solvent	ee, %[b]
CH_2Cl_2	82	$(CH_2Cl)_2$	81
$CHCl_3$	88	CCl_4	nr[c]
MeCN	44	$CH_3C_6H_5$	70
$MeNO_2$	62	*t*-BuOH	11
$C_6H_3Cl_3$	74	$CF_3C_6H_5$	nr[c]
EtOAc	29	*i*-PrOAc	13

[a] All reactions were performed at room temperature with 2% $VO(acac)_2$ and 3% ligand **6a**. [b] Enantiomeric excess determined by chiral HPLC analysis. [c] The catalyst system was not soluble in these solvents.

Table 4. Effect of Temperature on ee and Yield for the Oxidation of Disulfide **1**[a]

$VO(acac)_2$, %	temp, °C	yield, %	ee, %
4.0	32	46	77[b]
4.0	23	89	81[b]
1.0	20	98	91
0.25	20	93	91
0.25	15	93	91
0.25	10	85	91
0.10	15	57	91

[a] Except where noted, experiments were performed at 1.5 M in $CHCl_3$ with 0.5 mol of **1**, with 1:1.1 $VO(acac)_2$/ligand **6a**. [b] Experiments were performed at 1.0 M in CH_2Cl_2 with 2 mmol of **1**.

lectivities. The most favorable results are observed with chloroform as solvent, resulting in thiosulfinate ester **2** with a substantially better ee than for oxidations performed in CH_2Cl_2.

In addition to solvent effects, temperature, stir rate, and even the size and shape of the reaction flask had significant impacts upon the yield and enantioselection of the oxidation of **1**. The effects of temperature and catalyst loadings are summarized in Table 4. The oxidation proceeds smoothly in a very narrow, but convenient temperature range without substantial loss in yield when as little as 0.25% $VO(acac)_2$ and 0.26% ligand **6a** is employed.

Oxidations of thioethers by $VO(acac)_2$ and ligands **6a**,**b** are most effective when rapidly stirred.[19] However, the oxidation of disulfide **1** does not proceed under these conditions. Instead, stirring must be performed sufficiently slowly that the aqueous−organic interface is not broken. The surface area at the interface is also important.[30] With common and inexpensive glassware, the oxidation of disulfide **1** can be reproducibly performed on a 1-mol scale with only 0.25% catalyst and 460 mL of $CHCl_3$, providing thiosulfinate ester **2** with 91% ee in 92% conversion and isolated in 88% yield.

Mechanistic Considerations. There are a number of similarities between the oxidation of thioethers described by Bolm and Bienewald and the oxidation of disulfide **1**.[19] As was the case for thioether oxidations, $VO(acac)_2$ alone does not catalyze the oxidation of **1**. Use of 2 equiv of $VO(acac)_2$ with respect to ligand **6a** had no effect on either the rate of oxidation or the enantioselection. The apparent ligand acceleration eliminates the impact of vanadium species not complexed with the chiral ligand and precludes the need for excess ligand.[31]

The use of 2 equiv of ligand with respect to $VO(acac)_2$ also had no impact on either the oxidation rate or the enantioselection. This suggests that, at a 1:1 ligand/V ratio, the formation of a **6a**−VO complex is favored, and that excess ligand does not result in the formation of higher-order **6a**−VO complexes. In agreement with this conclusion, oxidations performed with ligands of varying enantiopurity exhibited a linear dependence of product ee with ligand ee. Therefore, aggregation of diastereomeric **6a**−VO complexes either does not occur or does not have an effect on enantioselectivity. A nonlinear dependence of product ee upon catalyst ee in unrelated systems has been attributed to formation diastereomeric aggregates with different reactivities.[32] The same linear dependence on catalyst ee was observed in the **6**−VO-catalyzed oxidations of thioethers.[19]

The addition of hydroperoxides to V(IV) or V(V) species commonly results in the formation of vanadium peroxide complexes [L−$VO(O_2)$].[33] Such complexes have been widely studied both as oxidants for synthesis[34] and as bioinorganic mechanistic models.[33,35] There are a number of L−$VO(O_2)$ complexes with ligands similiar to **6a** (Schiff base, O−N−O donors).[35a,36] In one case, Butler and co-workers reported that peroxide oxidation of a VO−Schiff base complex to the peroxy−vanadium complex could be monitored by a blue shift in the UV−visible spectrum. Treatment of a **6a**−VO solution in $CHCl_3$ with H_2O_2 resulted in a similar blue shift in the UV−visible spectrum, from a local maximum at 302 nm to λ_{max} at 264 nm. Infrared data taken in $CHCl_3$ showed no shift in the V═O stretch of $VO(acac)_2$ (929 cm^{-1}) upon addition of **6a**. Addition of disulfide **1** and H_2O_2 to the **6a**−VO complex resulted in a very minor shift in the V═O stretch (931 cm^{-1}).

Although these data are consistent with the production of a vanadium peroxide complex, other active oxidants are still conceivable. One possible mechanism is via the oxaziridine of Schiff base **6a**. Page and co-workers have formed oxaziridines by the oxidation of imines with H_2O_2, that have in turn oxidized thioethers.[37] However, **6a** and H_2O_2 do not oxidize **1** or thioethers, and the imine stretching frequency in the IR spectrum of **6a** is not affected by $VO(acac)_2$ and H_2O_2, making this route seem unlikely.

Nucleophilic Additions to *tert*-Butyl *tert*-Butanethiosulfinate (2). Our interest in thiosulfinate **2** was primarily as a chiral *tert*-butanesulfinyl intermediate to which $LiNH_2$ could be added to afford sulfinamide **3**. In the same way, carbanions, N-substituted metal amides, and metal imine salts could be used to displace the thiolate of **2** to deliver sulfoxides, sulfinamides, and sulfinimines directly. Such nucleophilic displacements typically proceed with inversion at the sulfinyl sulfur.[21]

Although it has not been unequivocally demonstrated, nucleophilic displacements are believed to proceed via an addition−elimination mechanism similar to additions to carboxylic acid derivatives (Scheme 4).[38] Both incoming and departing ligands of the proposed sulfurane intermediates are believed to reside in the apical positions so that an overall inversion is observed. In this scheme, Berry psuedorotation[39] of the purported sulfurane intermediate would account for deterioration

(30) See the Experimental Section for details.

(31) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

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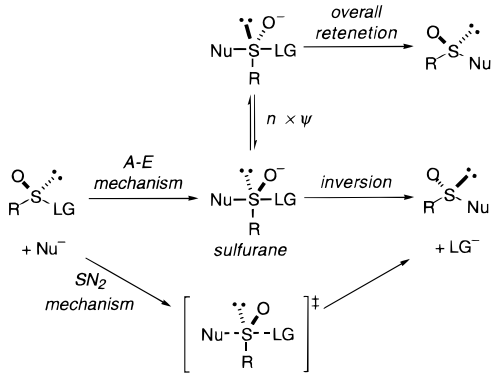
(36) (a) Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* **1986**, *108*, 3711−3718. (b) Nakajima, K.; Kojima, M.; Toriumi, K.; Saito, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 760−767. (c) Schmidt, H.; Baskirpoor, M.; Rehder, S. *J. Chem. Soc., Dalton Trans.* **1996**, 3865−3870.

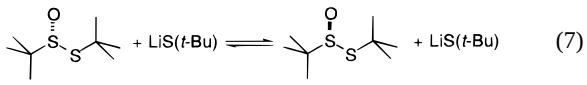
(37) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *SYNLETT* **1995**, 773−775.

Scheme 4



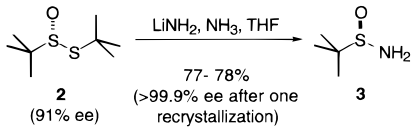
of stereospecificity observed under some conditions. Alternatively, an SN_2-like mechanism is also consistent with the stereochemical outcome of these displacements.

When **2** was treated with commercially available metal amides ($LiNH_2$, $NaNH_2$) in a number of solvents (tetrahydrofuran (THF), dioxane, dimethoxyethane (DME), diethyl ether) at −78 °C, there was no appreciable addition after several hours. Warming the reaction mixture to ambient temperature over 12 h provided only small quantities of nearly racemic sulfinamide **3**. Addition of $(Et)_2NMgBr$ to a thiosulfinate ester had also been reported to proceed with some loss of optical activity.[21b] Racemization may have occurred through the proposed sulfurane intermediate by psuedorotation or by an alternative mechanism. Interestingly, $LiNH_2$ provided more highly enantiomerically enriched product (8−12% ee) than the less soluble $NaNH_2$ (0% ee).[40] The ee of the recovered thiosulfinate was also nearly racemic. It appeared likely that, at low amide salt concentrations, the *tert*-butanethiolate byproduct could competitively racemize the thiosulfinate ester (eq 7).



(7)

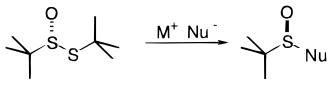
Indeed, treatment of **2** with 25 mol % of lithium thiolate resulted in nearly complete racemization at 0 °C over the course of 90 min. In contrast, the racemization process is very slow at −78 °C. If nucleophilic displacement of thiolate proceeds quickly at low temperatures, highly stereospecific additions may be achieved. To boost the solubility of the metal amides at lower temperatures, the use of additives such as crown ethers, and more polar solvents such as TMEDA, was investigated without success. However, when performed in ammonia with THF as cosolvent, the reaction of $LiNH_2$ with thiosulfinate ester **2** occurred almost instantaneously (eq 8). The amide addition



(8)

upon **2** (91% ee) has been performed numerous times on 0.5 mol or larger scale in high yield and without racemization (91% yield, 91% ee). In each case, a single recrystallization provided enantiopure (minor isomer not detected by chiral HPLC) **3** in good yield (77−78%).

Table 5. Addition of Nucleophiles to Thiosulfinate Ester **2**



nucleophile	product (config)[a]	yield, %	racemization, %
LiNHBn	**7a** (*R*)	89	<0.1[b,f]
Li(*c*-NC_5H_{10})	**7b** (*R*)	98	<0.1[d,f]
LiNHPh	**7c** (*R*)	91	1.0[b]
LiN=C(Me)Ph	**8** (*R*)	92	<0.1[b,f]
LiHMDS		0	
MeMgBr	**9a** (*S*)	91	<0.1[c,f]
EtMgBr	**9b** (*S*)	82	<0.1[c,f]
i-PrMgBr	**9c** (*S*)	55	*e*
vinyl-MgBr	**9d** (*S*)	81	<0.1[b,f]
MeLi	**9a** (*S*)	88	<0.1[c,f]
PhLi	**9e** (*R*)	98	<0.1[c,f]
$LiCH_2CO_2Et$		0	

[a] Stereochemical assignments are consistent with known compounds (**9a**, **9b**, **9e**) or are correlated with known compounds (vide infra). [b] Enantiomeric excess determined by chiral HPLC analysis. [c] Enantiomeric excess determined by chiral GC analysis. [d] Enantiomeric excess determined by HPLC analysis of **9e** obtained after **7b** was treated with PhLi. [e] All methods for determining optical purity, including chiral HPLC and GC, and NMR with various chiral shift reagents failed. [f] There was no racemization evident at the level of detection of the analytical methods employed.

Recrystallization readily affords **3** of >99% ee. However, for additions upon thiosulfinate ester **2** where the *tert*-butanesulfinyl product is not crystalline, it is advantageous to employ enantiomerically pure **2**. Careful crystallization of thiosulfinate ester **2** twice from hexanes provides (*R*)-**2** with >99% ee and 52% recovery.

Addition of lithium amides in THF at −78 °C provided the sulfinamides, **7a**,**b** (Table 5), with high levels of stereospecificity and presumably the product of inversion at sulfur. In contrast to the addition of $LiNH_2$ into thiosulfinate ester **2**, THF is an effective solvent for the synthesis of **7a**,**b** due to the higher solubility of the N-substituted amide salts. Although the addition of lithium anilide to **2** proceeded with poor conversion at −78 °C and with substantial racemization at higher temperatures, addition in ammonia and THF proceeded smoothly to afford sulfinamide **7c** in high yield. The lithium imine salt prepared by addition of methyllithium to benzonitrile also provided the sulfinimine, **8**, stereospecifically in high yield as only one isomer. In contrast, lithium bis(trimethylsilyl)amide did not react with thiosulfinate ester **2**. None of these sulfinamide derivatives prepared by nucleophilic additions to **2** have been prepared by other means. Moreover, these additions are the first examples of reaction of a thiosulfinate ester with the lithium salts of ammonia, primary amines, and imines.

Carbon nucleophiles also react with thiosulfinate esters to provide sulfoxides. The first account of the attempted addition of MeMgI into **2** did not succeed.[21b] A later attempt with

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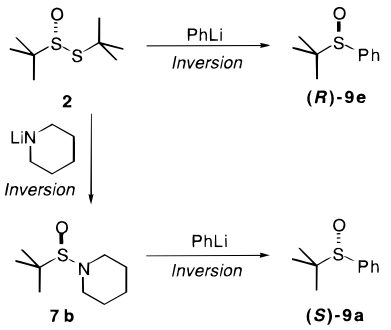
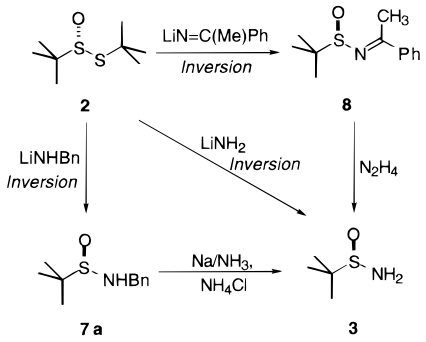
(39) Holmes, R. *Acc. Chem. Res.* **1979**, *12*, 257−265.

(40) A cation effect may also be responsible. Addition of LiHMDS in DAG sulfinate esters is stereospecific, but NaHMDS proceeds with considerable racemization. Kim, K.; Backes, B. J.; Ellman, J. A., unpublished results.

Scheme 5



Scheme 6



p-tolyl-MgBr did proceed in high yield.[27] In our hands, the addition of Grignard reagents provided the corresponding known sulfoxides **9a**,**b** and **9d** without racemization (Table 5). The hindered Grignard reagent *i*-PrMgCl reacts with **2** in lower yield, but the product sulfoxide's ee could not be determined. Alkyl and aryllithiums also react with **2** with absolute stereospecificity (MeLi, **9a**; PhLi, **9e**). Unfortunately, the less nucleophilic lithium enolate of ethyl acetate did not react with thiosulfinate ester **2**.

Stereochemical Correlations. The addition of MeMgBr to **2** affords the known (*S*)-*tert*-butyl methyl sulfoxide (**9a**)[41] indicating that **2** is the *R* isomer. The addition of lithium piperidide to (*R*)-**2** is expected to deliver **7d** with an *R* configuration at sulfur (Scheme 5). Indeed, the reaction of sulfinamide **7b** with PhLi delivered the expected (*S*)-**9e**, the product of two inversions at sulfur. The product of the addition of PhLi to **2** provided (*R*)-**9e** as expected for only one inversion.

The configuration of sulfinamide **3** was assigned *R* since **3** obtained from thiosulfinate **2** and from the known (D)-DAG-(R_S)-*tert*-butanesulfinate ester was identical. Reduction of sulfinamide **7a** also provides **3** as the *R* isomer (Scheme 6). Similarly, hydrazinolysis of sulfinimine **8** provided **3** with the expected *R* configuration at sulfur. Therefore, the additions of amide salts also react with thiosulfinate ester **2** with inversion.

Conclusion

The development of the novel yet practical asymmetric oxidation of **1** has been instrumental in our synthesis of **3**, which serves as a versatile chiral nitrogen synthon. On 1 mol of **1**, oxidation with H_2O_2 as stoichiometric oxidant and only 0.25 mol % $VO(acac)_2$ and 0.26 mol % of a chiral Schiff base ligand provides **2** in 91% ee and ≥92% yield. Thiosulfinate ester **2** is also chemically and optically stable, showing no signs of racemization or decomposition over an extended period of time (>8 months). Strong nucleophiles react stereospecifically with thiosulfinate ester **2** in high yield. Addition of $LiNH_2$ in liquid ammonia and THF provides **3** (91% yield). A single recrystallization provides enantiomerically pure product in 71−75% overall yield from disulfide **1**. Thiosulfinate ester **2** also reacts readily with Grignard reagents, organolithiums, other lithium amides, and metal imine salts to give chiral sulfoxides, sulfinamides, and sulfinimines in good yield and high levels of stereospecificity. This expedient route to enantiomerically pure *tert*-butanesulfinyl compounds should have significant utility in asymmetric synthesis.

Experimental Section

General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. All solvents were distilled under nitrogen from the following drying agents immediately before use: THF, diethyl ether, and DME were distilled from sodium/benzophenone ketyl; dichloromethane and chloroform were distilled from calcium hydride; toluene was distilled from sodium. Chromatography was carried out using Merck 60 230−400-mesh silica gel. IR spectra of liquids were recorded as thin films on NaCl plates and IR spectra of solids were recorded as KBr pellets. Chemical shifts in NMR spectra are expressed in ppm. All NMR spectra were obtained at room temperature in $CDCl_3$ with TMS as an internal standard.

The general procedures for the preparation of racemic **3**, and ligands **6a**−**r** have been previously described.[3a] The preparation of 3-*tert*-butyl-5-nitrosalicylaldehyde and spectral data for all the Schiff base ligands are included in the Supporting Information. The ligand precursors 3-*tert*-butyl-5-methoxysalicylaldehyde,[42] 3-*tert*-butylsalicylaldehyde,[43] and (2-hydroxy-3,5-di-*tert*-butyl)phenylmethyl ketone[29] were prepared as previously described.

(*R*)-(+)-*tert*-Butyl *tert*-Butanethiosulfinate (2). 1-Mol Scale. Into a 100 × 190 mm crystallizing dish containing a 2.5-in. Teflon-coated magnetic stir bar[44] was added 663 mg (2.50 mmol) of $VO(acac)_2$ and 868 mg (2.60 mmol) of ligand **6a** followed by 475 mL of $CHCl_3$. The resulting blue-green solution was stirred for ∼10 min before 178 g (1.00 mol) of *tert*-butyl disulfide was added. The dish was immersed in a water bath, and the stir rate set for the fastest rate that would not break the phase interface. At this time, 130 mL (1.15 mol) of cold 30% aqueous hydrogen peroxide was added in a slow steady stream. The cooling bath temperature was maintained at 15−20 °C. The color of the organic phase became dark brown, and the aqueous phase became yellow. After 40 h, the color of the organic phase faded to yellow and the aqueous phase became orange. Brine (75 mL) was added, and the layers were shaken and then separated. The aqueous layer was extracted once with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated. NMR analysis of the crude material indicated a 92% conversion. Kugelrohr distillation at 30 °C (5 μTorr) removed unreacted disulfide. Kugelrohr distillation at 37 °C (5 μTorr) subsequently delivered 189 g (88%) of **2** as a clear colorless oil that crystallized upon standing at room temperature. The ee was determined to be 91% by chiral HPLC analysis (Diacel Chiralpak AS column, 97:3 hexanes/2-propanol; 1 mL/min, 258 nm; (*S*)-**2**, r_t = 6.5 min; (*R*)-**2**, r_t = 7.9 min). Crystallization of **2** (91.0 g of 91% ee) twice from hexanes (95 mL, 70 mL) at −20 °C delivered 47.6 g (52%) of (*R*)-**2** as white crystals (99.8% ee). The absolute configuration of the major enantiomer was determined to be *R* by addition of MeMgBr to enantiomerically pure **2**, providing the (*S*)-*tert*-butyl methyl sulfoxide with inversion of the stereochemistry:[41] $[\alpha]^{23}_D$ +150° (*c* 0.55, CH_2Cl_2); mp 30−32 °C; IR 1046, 3190 cm^{-1}; ^1H NMR (400 MHz) δ 1.38 (s, 9H), 1.56 (s,

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(44) To attain the optimal interface surface area, the crystallizing dish described here was effective. For 0.5-mol-scale oxidations of disulfide **1**, a simple 500-mL Erlenmeyer flask provided the best interface area. Stirring was always performed with a magnetic stir bar; overhead mechanical stirrers break the organic−aqueous interface.

9H); ^{13}C NMR (101 MHz) δ 24.1, 32.2, 48.5, 59.3. Anal. Calcd for $C_8H_{18}OS_2$: C, 49.44; H, 9.33. Found: C, 49.26; H, 9.29.

(*R*)-(+)-*tert*-Butanesulfinamide (3). Method 1: From Bis(trimethylsilyl)-*tert*-Butanesulfinamide. To a solution of (D)-DAG-(R_S)-*tert*-butanesulfinate ester (510 mg, 1.4 mmol) in 10 mL of THF at −78 °C was added 2.8 mL of 1 M LHMDS in THF. The mixture was allowed to warm to room temperature while stirring overnight. To the solution at 0 °C was added 2 g of wet KF−Al_2O_3[45] in one portion. After being shaken vigorously for 1 h, the mixture was filtered and concentrated in vacuo. Chromatography (3% Et_3N in EtOAc) furnished 87 mg (51%) of **1** as a white crystalline solid.

Method 2: From (*R*)-2. A 5-L three-necked round-bottomed flask equipped with a mechanical stirrer, an ammonia condenser, and a nitrogen inlet was charged with 500 mL of liquid ammonia. A few crystals of $Fe(NO_3)_3$ were added, and lithium wire (8.1 g, 1.16 mol) were slowly added in ∼500-mg portions, each portion being added as the blue color disappeared. A −78 °C bath was periodically raised to the bottom of the flask to abate refluxing. When all the lithium wire was added, resulting in a gray suspension, the flask was submerged into the −78 °C bath. After 30 min, a solution of **2** (90.2 g, 0.465 mol) with 91% ee in 175 mL of THF was slowly added over the course of 1 h. Once the addition was complete, the mixture was stirred an additional 15 min before 74.5 g (1.40 mol) of NH_4Cl was added slowly and carefully. The cold bath was removed, and stirring continued until the mixture reached ambient temperature. The remaining volatile material was removed under aspirator pressure. To the remaining residue was added 50 mL of water with swirling. To the resulting mixture was added 500 mL of EtOAc. After vigorous stirring, the organic layer was decanted away. The EtOAc was washed with 25 mL of brine. This process was repeated three more times, and the washed organic layers were combined and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue recrystallized once from hexanes to provide 43.4 g (77%; 75% overall from *tert*-butyl disulfide) of enantiomerically pure (*R*)-**3** (HPLC, Diacel Chiralpak AS column, 90:10 hexanes/ethanol; 1.2 mL/min, 222 nm; (*R*)-**3**, r_t = 6.6 min; (*S*)-**3**, r_t = 9.4 min): $[\alpha]^{23}_D$ +4.9° (*c* 1.0, $CHCl_3$); mp 101−102 °C; IR 1032, 1364, 1474 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.18 (s, 9H), 3.82 (br s, 2H); ^{13}C NMR (101 MHz) δ 22.1, 55.3. Anal. Calcd for $C_4H_{11}NOS$: C, 39.64; H, 9.15; N, 11.56. Found: C, 39.74; H, 9.14; N, 11.24.

(*R*)-(−)-*N*-Benzyl *tert*-Butanesulfinamide (7a). To a 50-mL round-bottomed flask was added 0.48 g (4.48 mmol) of benzylamine. Next was added 7.5 mL of THF, and the flask was placed into a −78 °C bath. While the solution was vigorously stirred, 1.50 mL (3.73 mmol) of 2.5 M butyllithium in hexanes was added slowly. The mixture was stirred at −78 °C for 30 min before 150 mg (0.77 mmol) of **2** in 1.5 mL of THF was added. The mixture was then gradually warmed to room temperature and stirred overnight. Saturated NaCl was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic portions were dried over Na_2SO_4 and concentrated. Chromatography (50:50 EtOAc/hexanes) provided 144 mg of **7a** as fluffy white crystals. Analysis by chiral HPLC indicated that there was no racemization (HPLC, Diacel Chiralcel OD column, 90:10 hexanes/2-propanol, 1 mL/min, 260 nm; (*S*)-**7a**, r_t = 6.0 min; (*R*)-**7a**, r_t = 9.6 min). Recrystallization from hexanes furnished enantiomerically pure product (minor enantiomer not detected): $[\alpha]^{23}_D$ −35.9° (*c* 1.0, $CHCl_3$); mp 71−72 °C; IR 1076, 1365, 1459, 2963 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.25, (s, 9), 3.47 (br m, 1), 4.26 (dd, *J* = 8.0, 13.7 Hz, 1H), 4.37, (dd, *J* = 4.7, 13.7, 1H), 7.27−7.35 (m, 5); ^{13}C NMR (101 MHz) δ 22.6, 49.3, 55.8, 127.5, 128.0, 128.5, 138.4. Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.32; H, 8.11; N, 6.60.

Reduction of 7a. A 2-L three-necked round-bottomed flask in a −40 °C bath was equipped with a mechanical stirrer, an ammonia condenser, and a nitrogen inlet. The flask was charged with 400 mL of ammonia and then 13.2 g of NH_4Cl (246 mmol) and 25.0 g (119 mmol) of **7a** (91% ee) in 200 mL of THF. Lithium pieces (2.06 g total, 296 mmol) were slowly added to the mixture in 500-mg portions. After 30 min, another 13 g of NH_4Cl was then very carefully added, and the mixture was slowly warmed to room temperature with evaporation of ammonia. The remaining material was diluted with 200 mL of CH_2Cl_2 and then filtered through a Celite pad. The resulting solution was dried (Na_2SO_4) and concentrated to provide unpurified (*R*)-**3** of 91% ee. Recrystallization from hexanes provide 10.7 g (82%) of (*R*)-**3** of >99% ee (minor enantiomer not detected).

(*R*)-(−)-1-*tert*-Butanesulfinylpiperidine (7b). To a solution of 0.508 mL (5.13 mmol) of piperidine in 12 mL of THF at −78 °C was added 2.05 mL of BuLi (2.40 M, 5.13 mmol). Stirring was continued for 45 min. To the resulting slurry was slowly added 398 mg of **2** (>99% ee; minor enantiomer not detected) in 2 mL of THF. The reaction vessel was maintained at −78 °C for 1 h, whereupon excess saturated aqueous NH_4Cl was added and the mixture warmed to room temperature. The mixture was concentrated under a gentle stream of N_2, and the resulting residue was dissolved in 15 mL of CH_2Cl_2 and 3 mL of brine. The layers were shaken and separated, and the aqueous layer was extracted twice with 3 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (gradient elution; 5−10% acetone in CH_2Cl_2) afforded 380 mg (98%) of **7b** as a clear oil, whose ee was determined to be >99% (minor isomer not detected) after treatment with PhLi: $[\alpha]^{23}_D$ −6.7° (*c* 1.0, acetone); IR 1080, 1359, 1453 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.10 (s, 9H), 1.48−1.55 (m, 6H), 2.90−2.95 (m, 2H), 3.05−3.10 (m, 2H); ^{13}C (101 MHz) δ 23.0, 24.3, 26.1, 47.8, 58.1. Anal. Calcd for $C_9H_{19}NOS$: C, 57.10; H, 10.12; N, 7.40. Found: C, 57.02; H, 10.06; N, 7.50.

Addition of PhLi to 7b. A solution of 110 mg (0.580 mmol) of **7b** in 1 mL of THF was chilled to −78 °C and added dropwise to phenyllithium (1.8 M in cyclohexanes/ether; 0.645 mL, 1.16 mmol) in 3 mL at −50 °C. The mixture was stirred for 1 h at −50 °C before 2 mL of saturated aqueous NH_4Cl was added and then the THF was removed under a gentle stream of N_2. Chiral HPLC analysis indicated that sulfoxide isolated from this procedure was the *S* enantiomer with >99% ee (minor enantiomer not detected).

(*R*)-(−)-*N*-Phenyl *tert*-Butanesulfinamide (7c). To 10 mL of ammonia at −78 °C was added a crystal of $Fe(NO_3)_3$ followed by 86 mg (3.0 mmol) of lithium metal. The resulting blue solution was stirred with slow warming to ∼−40 °C until the blue color was replaced by a gray precipitate. The resulting $LiNH_2$ mixture was chilled to −78 °C, and aniline (1.17 mL, 12.8 mmol) was added slowly. After stirring for 1 h at −78 °C, a solution of 800 mg (4.12 mmol) of **2** (90.2% ee) in 2 mL of THF was added very slowly to the pink lithium anilide solution. This mixture was stirred for 2 h at −78 °C, at which time excess NH_4Cl crystals were carefully added. The volatile material was removed by slowly warming the solution while under a steady but gentle flow of N_2. The resulting residue was filtered with 75 mL of CH_2Cl_2, and the filtrate was concentrated. Chromatography of the red solution (gradient elution; 3−10% acetone in CH_2Cl_2) afforded 730 mg of **7c** as white crystals with an 89.2% ee (HPLC, Diacel Chiralcel OD column, 90:10 hexanes/2-propanol, 1 mL/min, 254 nm; (*R*)-**7c**, r_t = 5.4 min; (*S*)-**7c**, r_t = 7.7 min). Recrystallization from EtOAc/hexanes furnished the enantiomerically pure product (minor enantiomer not detected): $[\alpha]^{23}_D$ −181° (*c* 1.0, $CHCl_3$); IR 1044, 1061, 1498, 1600 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.32 (s, 9H), 5.65 (s, 1H), 6.96−7.03 (m, 3H), 7.12−5.25 (m, 2H); ^{13}C (101 MHz) δ 22.4, 56.4, 118.2, 122.7, 129.3, 142.0. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found: C, 61.01; H, 7.60; N, 7.00.

(*R*)-(−)-*N*-(1-Phenylethylidene)-*tert*-butanesulfinamide (8). To 566 μL (5.55 mmol) of benzonitrile in 12 mL of THF at 0 °C was added 3.80 mL (5.33 mmol) of 1.4 M ethereal MeLi solution. The mixture was stirred for 45 min and was then cooled to −78 °C. After addition of 431 mg (2.22 mmol) of (*R*)-**2** (>99% ee; minor isomer not detected) in 2 mL of THF, the mixture was stirred at −78 °C for 1 h. Brine was added to quench the reaction followed by EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (20:80 EtOAc/hexanes) provided 456 mg (92%) of enantiopure (minor isomer not detected) **8** (HPLC, Diacel Chiralpak OD column, 90:10 hexanes/2-propanol, 1.0 mL/min, 250 nm; (*R*)-**8**, r_t = 6.1 min; (*S*)-**8**, r_t = 7.6 min): $[\alpha]^{23}_D$ −0.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.32 (s, 9H), 2.77 (s, 3H), 7.26−7.89 (m, 5H); ^{13}C NMR (125 MHz) δ 22.5, 24.2, 57.4, 127.2, 128.4, 131.6, 138.7, 176.4. Anal.

(45) Bergbreiter, D. E.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601−1603.

Calcd for $C_{12}H_{17}NSO$: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.66; H, 7.47; N, 6.32

Hydrazinolysis of 8. A solution of 237 mg (1.06 mmol) of enantiopure **8** and 0.26 mL (5.3 mmol) of hydrazine in 1 mL of THF was warmed to 50 °C for 20 min. The mixture was concentrated, and the resulting biphasic mixture was dissolved in 8 mL of CH_2Cl_2 and then washed once with water. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (1:1 hexanes/EtOAc to elute hydrazones, then gradient elution; 1−5% MeOH in EtOAc) delivered 85 mg (66%) of (*R*)-**3** (>99% ee; minor enantiomer not detected).

General Procedure for the Addition of Grignard Reagents to 2. In a round-bottomed flask under a nitrogen atmosphere, **2** (1 equiv) was dissolved in THF, resulting in a 0.2 M solution. The flask was placed into a −78 °C cold bath, and a solution of Grignard reagent (2.5 equiv) was added slowly with stirring. The resulting mixture was stirred for 4 h. Once complete as judged by TLC, a minimum of saturated NH_4Cl in water was carefully added. The cold bath was removed, and the mixture was transferred to a separatory funnel and EtOAc (about twice the volume of THF) was added. The layers were shaken and separated, and the aqueous layer was washed twice with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Column chromatography delivered the desired sulfoxides.

(*S*)-(+)-*tert*-Butyl methyl sulfoxide (9a) was prepared by the general procedure from 100 mg (0.52 mmol) of (*R*)-**2** (>99% ee) and 0.43 mL of MeMgBr (3.0 M in Et_2O; 1.29 mmol) in 300 μL of THF. Chromatography (gradient elution; 1−2% MeOH in EtOAc) provided 56 mg (91%) of **9a** (>99% ee; capillary GC: Astec Chiraldex G-BP column, 20 psi He, 90−180 °C at 2 °C/min; (*R*)-**9a**, r_t = 11.7 min; (*S*)-**9a**, r_t = 12.3 min) as a colorless oil, whose spectroscopic data corresponded to those found in the literature:[16a] $[\alpha]^{23}_D$ +7.6° (*c* 1.0, $CHCl_3$) (lit.[16a] $[\alpha]^{23}_D$ +7.8° (*c* 1, $CHCl_3$)); IR 1044 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (s, 9H), 2.34 (s, 3H); ^{13}C NMR (101 MHz) δ 22.4, 31.5, 52.5.

(*S*)-(−)-*tert*-Butyl ethyl sulfoxide (9b) was prepared by the general procedure from 100 mg (0.52 mmol) of (*R*)-**2** (>99% ee) and 0.43 mL of EtMgBr (3.0 M in Et_2O) in 300 μL of THF. Chromatography (gradient elution; 1−2% MeOH in EtOAc) provided 57 mg (82%) of **9b** (>99% ee; capillary GC: Astec Chiraldex G-BP column, 20 psi He, 50−180 °C at 0.4 °C/min; (*S*)-**9b**, r_t = 87.2 min; (*R*)-**9b**, r_t = 89.4 min) whose spectroscopic data corresponded to those found in the literature:[46] $[\alpha]^{23}_D$ −85.9° (*c* 1.0, $CHCl_3$); IR 1046 cm^{-1}; ^1H NMR (400 MHz) δ 1.20 (s, 9H), 1.35 (t, *J* = 7.44, 3 H), 2.36−2.52 (m, 2H); ^{13}C NMR (101 MHz) δ 8.4, 22.8, 39.0, 52.7.

(*S*)-(−)-*tert*-Butyl 2-propyl sulfoxide (9c) was prepared by the general procedure from 97 mg (0.50 mmol) of (*R*)-**2** (>99% ee) and 0.75 mL of *i*-PrMgCl (2.0 M in THF) in 2 mL of THF. Chromatography provided 40 mg of **9c** (55%), whose spectroscopic data corresponded to that found in the literature:[45] $[\alpha]^{23}_D$ −62.8° (*c* 1.0, $CHCl_3$); IR 1043, 1368, 1464, 2964 cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (d, *J* = 6.9, 3H), 1.13 (s, 9H), 1.19 (d, *J* = 7.1, 3H), 2.77 (dq, *J* = 6.9, 7.1, 1 H); ^{13}C NMR (101 MHz) δ 15.0, 20.2, 23.1, 44.2, 53.80. Calcd for $C_7H_{16}OS$: C, 56.71; H, 10.88. Found: C, 56.56; H, 10.97.

(*S*)-(+)-*tert*-Butyl vinyl sulfoxide (9d) was prepared by the general procedure from 400 mg (2.06 mmol) of (*R*)-**2** (90.2% ee) and 5.2 mL of vinyl-MgBr (1.0 M in THF) in 5 mL of THF. Chromatography (gradient elution; 5−10% acetone in CH_2Cl_2) provided 219 mg of **9d** (81%) as a clear colorless oil, and with an 90.2% ee (HPLC, Diacel Chiralpak AS column, 90:10 hexanes/2-propanol, 1.2 mL/min, 254 nm; retention times: (*R*)-**9d**, 7.5 min; (*S*)-**9d**, 10.1 min): $[\alpha]^{23}_D$ −321° (*c* 1.0, acetone) (lit.[16b] (*R*)-**9d**: $[\alpha]^{23}_D$ +283° (*c* 1, acetone); IR 1056, 1367, 1458 cm^{-1}; ^1H NMR (400 MHz) δ 1.15 (s, 9H), 5.94 (d, *J* = 10.0, 1H), 6.00 (d, *J* = 16.6, 1H), 6.49 (dd, *J* = 10.0, 16.6, 1H); ^{13}C (101 MHz) δ 22.7, 54.5, 123.6, 136.4. Anal. Calcd for $C_9H_{19}NOS$: C, 54.50; H, 9.15. Found: C, 54.26; H, 9.29.

(*R*)-(+)-*tert*-Butyl Phenyl Sulfoxide (9e). Thiosulfinate **2** (98.5% ee; 345 mg, 1.77 mmol) was dissolved in 9 mL of THF, and the solution placed into a −78 °C cold bath. To the mixture was added 2.67 mL of phenyllithium (2.0 M in cyclohexane/Et_2O; 5.34 mmol). The mixture became dark brown. The reaction was judged complete by TLC within 30 min, and the cold bath removed. Saturated NH_4Cl (1 mL) was added while the mixture was still cold. The mixture was stirred until it reached room temperature. After addition of 1 mL of water and 18 mL of EtOAc, the layers were shaken and separated. The aqueous layer was extracted twice with EtOAc (20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (50:50 hexanes/EtOAc) provided 314 mg of **9e** (98%) as a white crystalline solid with 98.5% ee (Chiral HPLC: Chiralpak AS column, 90:10 hexanes/ethanol, 1.0 mL/min, 256 nm; (*S*)-**9e**, r_t = 7.5 min, (*R*)-**9e**, r_t = 9.5 min). Recrystallization from hexanes furnished the enantiomerically pure product (minor enantiomer not detected): $[\alpha]^{23}_D$ +181° (*c* 1.0, $CHCl_3$) (lit.[16b] (*S*)-**9e**: $[\alpha]^{23}_D$ −175° (*c* 1, $CHCl_3$)); IR cm^{-1} 1034, 1365, 1401, 1443; ^1H NMR (400 MHz) δ 1.14 (s, 9H), 7.44−7.49 (m, 3H), 7.53−7.58 (m, 2H); ^{13}C NMR (101 MHz) 22.7, 55.7, 126.2, 128.3, 131.0, 139.9.

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Supporting Information Available: Experimental details for the synthesis of 3-*tert*-butyl-5-nitrosalicylaldehyde, as well as 400-MHz ^1H and 101-MHz ^{13}C NMR spectral data for ligands **6a**−**u** (4 pages print). See any current masthead page for ordering information and Web access instructions.

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