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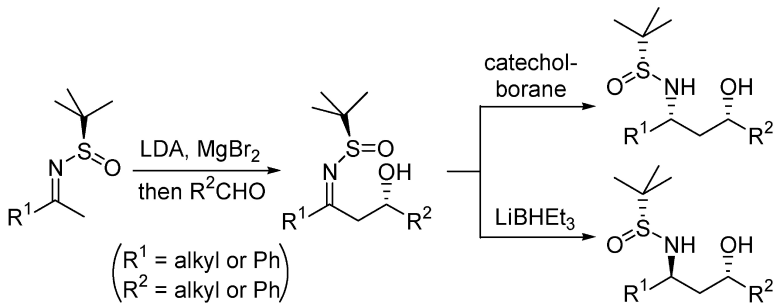

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Development and Application of a New General Method for the Asymmetric Synthesis of *syn*- and *anti*-1,3-Amino Alcohols

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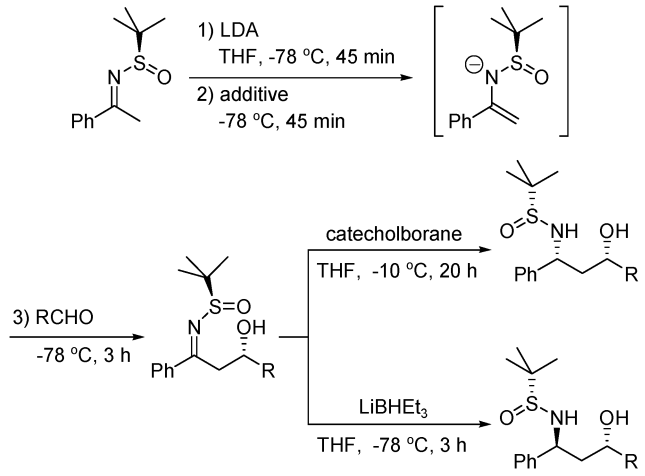
Abstract: A general method is described for asymmetric synthesis of both *syn*- and *anti*-1,3-amino alcohols. The first application of metalloenamines derived from *N*-sulfinyl imines is reported for the highly diastereoselective addition to aldehydes. The reduction of the product β-hydroxy *N*-sulfinyl imines **2** with catecholborane and $LiBHEt_3$ provides *syn*- and *anti*-1,3-amino alcohols with very high diastereomeric ratios. This method was found to be effective for a variety of substrates incorporating either aromatic or various aliphatic substituents. The convergent and efficient asymmetric syntheses of the two natural products, (−)-8-epihalosaline and (−)-halosaline, were also accomplished.

Introduction

1,3-Amino alcohols are found in many natural products[1] and potent drugs,[2] including a number of nucleoside antibiotics[1a−d] and the HIV protease inhibitors, ritonavir and lopinavir.[2a−d] They have also been used as ligands for asymmetric catalysts and as synthetic intermediates.[3] However, despite the importance of 1,3-amino alcohols, there are relatively few methods for their stereoselective synthesis.[4]

Recently, we published a preliminary communication on a new, straightforward method for the asymmetric synthesis of both *syn*- and *anti*-1,3-amino alcohols.[5] The metalloenamine derived from the *tert*-butanesulfinyl imine of acetophenone was added to a range of aldehydes with high diastereoselectivities. Stereoselective methods were then identified for the reduction of the β-hydroxy *N*-sulfinyl imine products to provide both the *syn*- and *anti*-1,3-amino alcohols with high diastereoselectivities and yields (Scheme 1). This sequence represents the first efficient and general approach to access both the *syn*- and *anti*-stereoisomers from a common precursor.

Scheme 1



In the preliminary communication, the *N*-sulfinyl imine of acetophenone was the only substrate to be reported. Herein, we report greatly expanded substrate scope, with *tert*-butanesulfinyl imines derived from structurally diverse methyl ketones serving as suitable substrates. For the large majority of *N*-sulfinyl imine and aldehyde coupling partners, good yields and high diaste-

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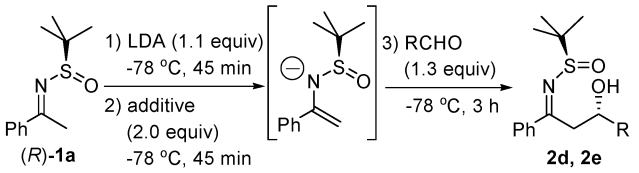
10.1021/ja0363462 CCC: $25.00

Table 1. Optimization of the Addition of an *N*-Sulfinyl Metalloenamine to Aldehydes



entry	R	product	solvent	additive	dr[a]	yield (%)[b]
1	Et	**2d**	THF	−	86:14	80
2	Et	**2d**	Et_2O	−	81:19	nd
3	Et	**2d**	toluene	−	73:23	nd
4	Et	**2d**	THF	$MgBr_2$	96:4	84
5	Et	**2d**	THF	$ZnBr_2$	93:7	62
6	Ph	**2e**	THF	−	73:27	64
7	Ph	**2e**	THF	$MgBr_2$	76:24	56
8	Ph	**2e**	THF	$ZnBr_2$	92:8	79

[a] Diastereomeric ratio. [b] Isolated yield of diastereomerically pure material.

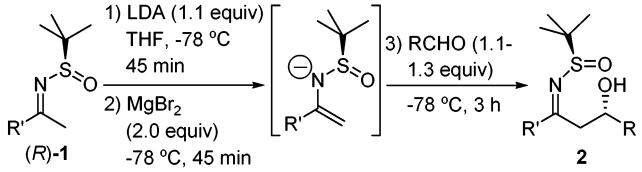
reoselectivities are observed for both the metalloenamine addition step and the reduction steps to provide both the *syn*- and *anti*-1,3-amino alcohol products. Experiments are also described that contribute to an understanding of the high diastereoselectivity observed in both steps. Finally, the utility of the method is demonstrated by the convergent and efficient asymmetric syntheses of (−)-halosaline (***anti*-10**) and (−)-8-epihalosaline (***syn*-10**).

Results and Discussion

A. Asymmetric Additions of *N*-Sulfinyl Metalloenamines to Aldehydes. The addition of nucleophiles to *N*-sulfinyl imines has become an important and extensively used method for the asymmetric synthesis of a wide range of amine-containing compounds.[6,7] In contrast, the chemistry of metalloenamines[8] derived from sulfinyl imines has not been explored. We envisioned that the addition of *N*-sulfinyl metalloenamines to different electrophiles could provide access to diverse *N*-sulfinyl imine products, which could then serve as versatile intermediates in the asymmetric synthesis of amines. The addition of *N*-sulfinyl metalloenamines to aldehydes would be particularly useful because the β-hydroxy *N*-sulfinyl imine products could serve as convenient intermediates to the important class of 1,3-amino alcohols.

A.1. Optimization Studies for the Addition of *N*-Sulfinyl Metalloenamines to Aldehydes (Table 1). In the initial studies, the (*R*)-*tert*-butanesulfinyl imine of acetophenone, **1a**, was chosen because deprotonation would only occur on the α-methyl group. Treatment of **1a** with LDA at −78 °C in THF, followed by reaction of the resulting metalloenamine with propionaldehyde afforded the desired β-hydroxy sulfinyl imine **2d** in 80% yield and 86:14 dr (entry 1). A similar reaction with benzaldehyde afforded the corresponding product **2e** in 64% yield and 73:27 dr (entry 6).

Table 2. Addition of *N*-Sulfinyl Metalloenamines to Aldehydes



entry	substrate	R	product	dr[a]	yield (%)[b]
1	**1a** (R′ = Ph)	*t*-Bu	**2a**	98:2	64
2	**1a**	*i*-Pr	**2b**	98:2	88
3	**1a**	*i*-Bu	**2c**	96:4	75
4	**1a**	Et	**2d**	96:4	84
5[c]	**1a**	Ph	**2e**	92:8	79
6	**1b** (R′ = *t*-Bu)	*t*-Bu	**2f**	99:1	92
7	**1b**	*i*-Pr	**2g**	99:1	80
8	**1b**	Et	**2h**	98:2	84
9[d]	**1b**	Ph	**2i**	90:10	76
10	**1c** (R′ = *i*-Pr)	*t*-Bu	**2j**	99:1	85
11	**1c**	*i*-Pr	**2k**	97:3	81
12	**1c**	Et	**2l**	91:9	73
13[d]	**1c**	Ph	**2m**	77:23	75
14	**1d** (R′ = Et)	*t*-Bu	**2n**	98:2	70
15	**1d**	*i*-Pr	**2o**	92:8	65
16	**1d**	Et	**2p**	80:20	51
17[d]	**1d**	Ph	**2q**	60:40	50

[a] Diastereomeric ratio. [b] Isolated yield of diastereomerically pure material. [c] $ZnBr_2$ was used as an additive instead of $MgBr_2$. [d] Reaction with aldehyde was carried out for 1 h instead of 3 h.

The reaction conditions for the metalloenamine addition were optimized to improve the diastereomeric ratios. First, solvent effects were examined. When toluene and ether were used instead of THF, lower diastereoselectivities were observed (entries 2, 3). However, addition of metal salts resulted in a dramatic increase in diastereoselectivity. For the reaction with propionaldehyde, the addition of 2.0 equiv of $MgBr_2$ (entry 4) and $ZnBr_2$ (entry 5) afforded **2d** with 96:4 and 93:7 ratios, respectively, with the addition of $MgBr_2$ providing the highest yield. In this reaction, the use of 2 equiv of $MgBr_2$ was found to give a higher diastereoselectivity than 1.0 or 0.5 equivalents (92:8 and 88:12, respectively). Notably, addition of the metalloenamine of **1** to benzaldehyde proceeded with highest stereoselectivity when $ZnBr_2$ (entry 8) rather than when $MgBr_2$ (entry 7) was added.

A.2. Reaction Scope for the Addition of *N*-Sulfinyl Metalloenamines to Aldehydes (Table 2). With these promising results, the addition of the metalloenamine derived from **1a** to a variety of aldehydes was investigated. With $MgBr_2$, the addition to the α,α-dibranched aldehyde, pivaldehyde (entry 1), the β-branched aldehyde, isovaleraldehyde (entry 2), and the α-branched aldehyde, isobutyraldehyde (entry 3), each exhibited excellent diastereoselectivities and afforded the desired products **2a**, **2b**, and **2c** in good yields. In all the cases, the reaction with no additive resulted in poorer diastereoselectivity (77:23, 97:3 and 84:16 dr, respectively).

The additions of metalloenamines derived from aliphatic *N*-sulfinyl imines were next investigated to greatly expand the scope of the reaction. The reactions of **1b**, in which deproto-

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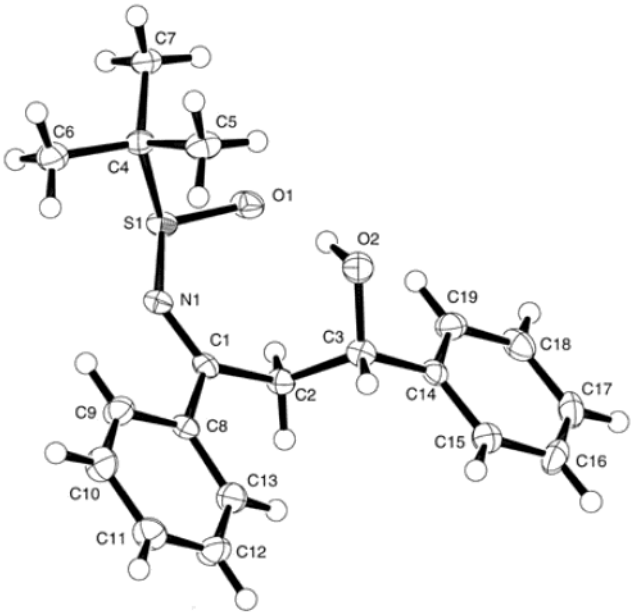


Figure 1. Structure of **2e**.

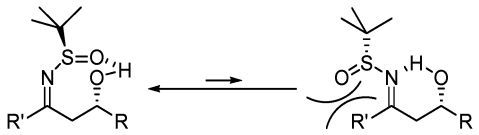
nation can only occur at the α-methyl group, with aliphatic aldehydes proceeded with excellent diastereoselectivities and afforded the desired β-hydroxy sulfinyl imines in high yields (> 98:2 dr, >80% yield) (entries 6−8). *N*-Sulfinyl imines **1c** and **1d** have two possible deprotonation sites potentially resulting in the formation of two metalloenamine regioisomers. However, products resulting from deprotonation at the more hindered site were not observed (entries 10−12, 14−16). The diastereoselectivities for the metalloenamine addition reaction of **1c** and **1d** with aliphatic aldehydes exceeded 90:10 in most cases, and the major diastereomers were isolated in good yields.

When benzaldehyde was used as an electrophile in the additions of metalloenamines derived from aliphatic *N*-sulfinyl imines, diastereoselectivities were not as high as those for the reactions with aliphatic aldehydes (entries 9, 13, 17). Upon reexamining the effects of additives for the reaction of **1c**, $MgBr_2$ provided higher stereoselectivity (77:23) than $ZnBr_2$ or in the case where no additive was used (72:28 and 68:32 dr, respectively). Therefore, the reactions of the other *N*-sulfinyl imines were carried out with $MgBr_2$. Using these conditions the reaction of **1b** with benzaldehyde proceeded with 90:10 dr (entry 9), but the reaction of **1d** proceeded with only 60:40 dr (entry 17).

A.3. Structures of β-Hydroxy *N*-Sulfinyl Imines. The crystal structure of β-hydroxy sulfinyl imine **2e** is shown in Figure 1. The *N*-sulfinyl imine group adopts an approximate synperiplanar structure as observed for most crystal structures of *N*-sulfinyl imines[9] and as predicted in theoretical studies,[10] although the dihedral angle between the C═N bond and the S═O bond is 30°, which is larger than usual. The short S−N bond (1.66 Å) also indicates a strong interaction between the sulfinyl group and the C═N group, such as $n_N-\sigma^*_{S-O}$ interactions.[10] The distance between the oxygen atom of the hydroxyl group and that of the sulfinyl group is 2.75 Å and indicates a hydrogen-bond interaction between the alcohol hydrogen and the oxygen atom of the sulfinyl group.

Although *N*-sulfinyl imines exhibit a rapid equilibrium between *E* and *Z* isomers,[11] the barrier to isomerization is sufficiently high that the individual isomers can readily be observed by NMR at room temperature.[7f] For most of the β-hydroxy *N*-sulfinyl imines (**2a**−**m**) only one out of the two possible geometric isomers was present as determined by ^{1}H NMR, while for those *N*-sulfinyl imines that have ethyl substitution on the C═N bond (**2n**−**q**), only a small amount of the minor geometric isomer (<10% compared to the major isomer) was present. NOESY experiments for β-hydroxy *N*-sulfinyl imines **2e** and **2q** suggested that the sulfinyl groups are proximal to the β-hydroxyl groups in the major isomer present in solution. While the occurrence of this isomer can be argued on purely steric grounds for imines **2a**−**m**, steric interactions cannot explain the preponderance of this isomer for imines **2n**−**q**. For these and the other imines the isomer preference is likely enforced by a hydrogen-bonding interaction between the sulfinyl oxygen and the hydrogen of the hydroxyl group as is observed in the crystal structure for **2e** (Scheme 2).

Scheme 2



A.4. A Stereochemical Model for the Aldol-Type Reaction. Although the source of diastereocontrol is unclear, the stereochemistry of the products can be explained with a stereochemical model (Figure 2). First, the use of smaller and more covalently bonded metals generally resulted in higher diastereoselectivities. Therefore, the reaction may occur via a closed transition state. There is no direct information about structures of metalated sulfinyl imines or sulfinamides, but a M−O bond may be expected to be formed in the ground state, as seen in lithium sulfoxides.[12] If we assume that the M−N interaction arises during the reaction, the stereoselectivity observed can be explained by using a Zimmerman−Traxler-type transition-state model.[13]

The reaction may proceed via **A** instead of **B**, because the large *tert*-butyl group can hinder the attack of an aldehyde. Given the preference of **A** over **B**, the stereoselectivity of the reaction is consistent with a simple Zimmerman−Traxler-type transition state, favoring **C** over **D**, in which a 1,3-diaxial interaction arises. If the reaction proceeds via **B**, the opposite stereoselectivity may be observed according to the Zimmerman−Traxler-type transition-state model. That is, the steric repulsion between the *tert*-butyl group and the approaching aldehydes may play a very important role in the diastereo-

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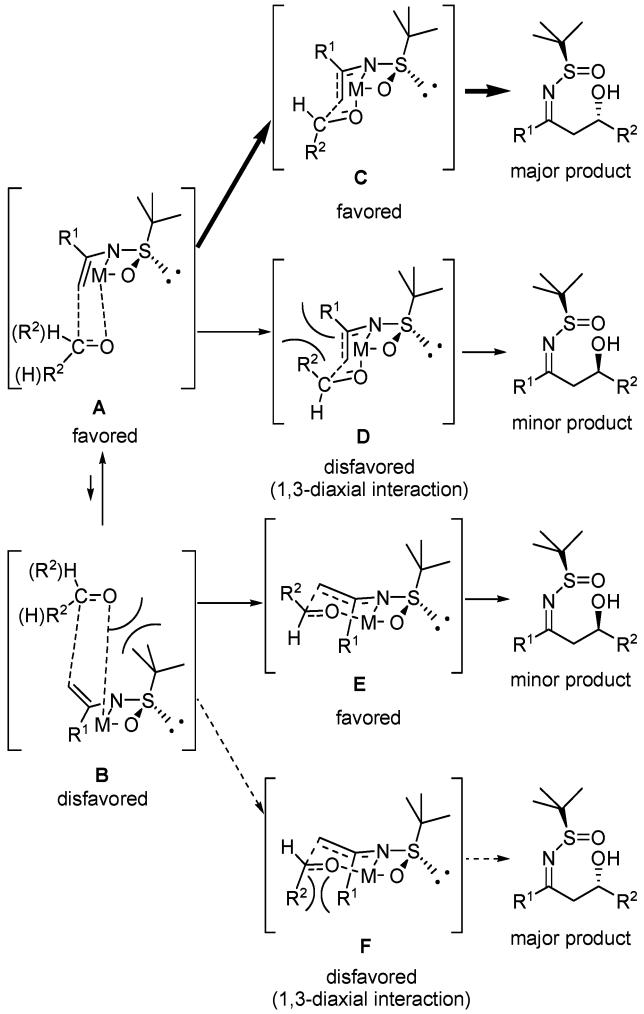
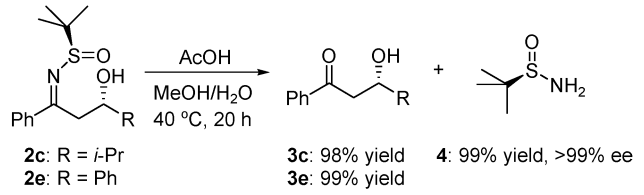


Figure 2. Stereoselective addition of *N*-sulfinyl metalloenamines to aldehydes.

Scheme 3



selection. A similar transition-state model was indicated by Narasaka for the aldol-type reaction of chiral stannous azaenolates.[14]

B. Hydrolysis of *β*-Hydroxy Sulfinyl Imines (Scheme 3). The hydrolysis of the *β*-hydroxy-*N*-sulfinyl imines was next investigated. Aqueous HCl hydrolyzed **2e** completely in 20 h, but the α,*β*-unsaturated ketone was formed as a byproduct. When the reaction with aqueous AcOH was carried out at room temperature, imine starting material was still observed at 20 h. However, upon heating to 40 °C, complete hydrolysis was achieved, and *β*-hydroxy ketone **3e** was isolated in quantitative yield with <2% racemization. Hydrolysis of **2c** similarly proceeded to afford **3c** in quantitative yield with <2% racemization. The absolute configurations for **3c** and **3e** were

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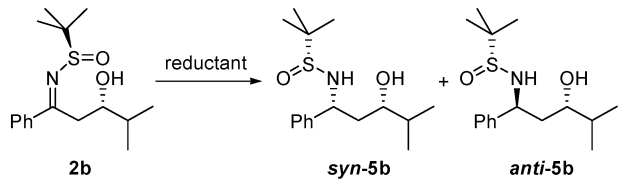
Scheme 4



determined by comparison of the optical rotations to the literature values,[15] confirming that the sense of induction is the same for additions to both aliphatic and aromatic aldehydes. (*R*)-*tert*-Butanesulfinamide **4** was also recovered in the hydrolysis of **3c**, and the chiral auxiliary was isolated in 99% yield and without racemization (>99% ee).

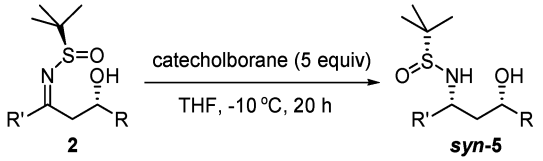
C. Diastereoselective Reductions of *β*-Hydroxy Sulfinyl Imines. C.1. Optimization Studies. The reduction of *β*-hydroxy-*N*-sulfinyl imines **2** was next examined. Several strategies have been reported to convert *β*-hydroxy imines to either *syn*- or *anti*-1,3-amino alcohols by choosing an appropriate protecting group on the nitrogen atom or geometry of the imines.[16] However, general methods have not been reported for the stereoselective reduction of a single *β*-hydroxy imine to either the *syn*- or *anti*-1,3-amino alcohol through the use of different reagents and reaction conditions. In contrast, the stereoselective reduction of *β*-hydroxy ketones to either the *syn*- or *anti*-1,3-diol can be accomplished through appropriate choice of the reducing agent.[17] Therefore, our goal for this reduction step was to identify general conditions to selectively access both the *syn*- and *anti*-1,3-amino alcohols.

The reduction of **2b** with a number of reducing agents was initially investigated (Scheme 4). The reaction with $NaBH_4$ was slightly *anti*-selective (∼2:1), and *N*-sulfinyl 1,3-amino alcohol ***anti*-5b** was isolated in 45% yield after chromatography. While $NaBH(OAc)_3$ is well documented to stereoselectively reduce *β*-hydroxy ketones to deliver *anti*-1,3-diols,[17] the $NaBH(OAc)_3$ reduction of **2b** under various conditions afforded only trace amounts of the desired product with low selectivity (<2:1 *anti*/*syn*). Interestingly, the reduction of **2b** with $NaCNBH_3$ in THF/AcOH proceeded with 83:17 *syn* selectivity, and ***syn*-5b** was isolated in 78% yield. Among the reducing agents we examined, catecholborane reduced **2b** to afford ***syn*-5b** with the highest *syn* selectivity and the diastereomerically pure material was isolated in 84% yield. On the other hand, complete *anti* selectivity was observed for the reduction of **2b** with $LiBHEt_3$ at −78 °C and provided the pure *anti* product **5b** in 83% isolated yield. Reduction of **2b** with $LiBH(s\text{-}Bu)_3$ provided a result similar to that observed for $LiBHEt_3$ (83% yield, >99:1 *anti*/*syn*).

C.2. *syn*-Selective Reduction with Catecholborane (Table 3). The reduction of a variety of *β*-hydroxy-*N*-sulfinyl imines **2** with catecholborane was investigated to determine the generality of this reaction. The reductions of aromatic *N*-sulfinyl imines **2a**−**e** generally proceeded with 95:5 to 96:4 dr, and the corresponding *N*-sulfinyl 1,3-amino alcohols ***syn*-5a**−**e** were isolated in higher than 84% yields (entries 1−5). When aliphatic

(15) Loh, T.-P.; Li, X.-R. *Tetrahedron* **1999**, *55*, 10789−10802.
(16) (a) Narasaka, K.; Ukaji, Y. **1984**, 147−150. (b) Narasaka, K.; Yamazaki, S.; Ukaji, Y. **1984**, 2065−2068. (c) Williams, D. R.; Osterhout, M. H. *J. Am. Chem. Soc.* **1992**, *114*, 8750−8751. (d) Haddad, M.; Dorbais, J.; Larcheveque, M. *Tetrahedron Lett.* **1997**, *38*, 5981−5984.
(17) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

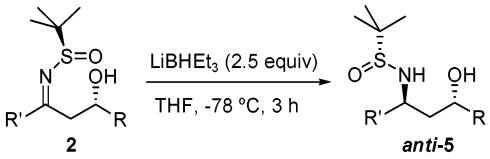
Table 3. *syn*-Selective Reduction of β-Hydroxy Sulfinyl Imines with Catecholborane



entry	substrate	R′	R	product	dr[a]	yield (%)[b]
1	**2a**	Ph	*t*-Bu	***syn*-5a**	96:4	89
2	**2b**	Ph	*i*-Pr	***syn*-5b**	96:4	88
3	**2c**	Ph	*i*-Bu	***syn*-5c**	96:4	84
4	**2d**	Ph	Et	***syn*-5d**	95:5	94
5	**2e**	Ph	Ph	***syn*-5e**	96:4	84
6	**2f**	*t*-Bu	*t*-Bu	***syn*-5f**	95:5	79
7	**2g**	*t*-Bu	*i*-Pr	***syn*-5g**	96:4	91
8	**2h**	*t*-Bu	Et	***syn*-5h**	95:5	81
9	**2i**	*t*-Bu	Ph	***syn*-5i**	98:2	77
10	**2j**	*i*-Pr	*t*-Bu	***syn*-5j**	95:5	93
11	**2k**	*i*-Pr	*i*-Pr	***syn*-5k**	96:4	82
12	**2l**	*i*-Pr	Et	***syn*-5l**	95:5	82
13	**2m**	*i*-Pr	Ph	***syn*-5m**	90:10	81
14	**2n**	Et	*t*-Bu	***syn*-5n**	92:8	82
15	**2o**	Et	*i*-Pr	***syn*-5o**	97:3	91
16	**2p**	Et	Et	***syn*-5p**	94:6	76
17	**2q**	Et	Ph	***syn*-5q**	76:24	69

[a] Diastereomeric ratio. [b] Isolated yield of diastereomerically pure material.

Table 4. *anti*-Selective Reduction of β-Hydroxy Sulfinyl Imines with $LiBHEt_3$



entry	substrate	R′	R	product	dr[a]	yield (%)[b]
1	**2a**	Ph	*t*-Bu	***anti*-5a**	>99:1	91
2	**2b**	Ph	*i*-Pr	***anti*-5b**	>99:1	83
3	**2c**	Ph	*i*-Bu	***anti*-5c**	>99:1	85
4	**2d**	Ph	Et	***anti*-5d**	>99:1	69
5	**2e**	Ph	Ph	***anti*-5e**	>99:1	73
6	**2f**	*t*-Bu	*t*-Bu	***anti*-5f**	>99:1	83
7	**2g**	*t*-Bu	*i*-Pr	***anti*-5g**	>99:1	96
8	**2h**	*t*-Bu	Et	***anti*-5h**	>99:1	96
9	**2i**	*t*-Bu	Ph	***anti*-5i**	>99:1	95
10	**2j**	*i*-Pr	*t*-Bu	***anti*-5j**	99:1	96
11	**2k**	*i*-Pr	*i*-Pr	***anti*-5k**	99:1	94
12	**2l**	*i*-Pr	Et	***anti*-5l**	98:2	94
13	**2m**	*i*-Pr	Ph	***anti*-5m**	92:8	85
14	**2n**	Et	*t*-Bu	***anti*-5n**	97:3	90
15	**2o**	Et	*i*-Pr	***anti*-5o**	95:5	94
16	**2p**	Et	Et	***anti*-5p**	93:7	78
17	**2q**	Et	Ph	***anti*-5q**	88:12	80

[a] Diastereomeric ratio. [b] Isolated yield of diastereomerically pure material.

imines were subjected to the same reaction conditions, excellent diastereoselectivities were achieved for almost all of the reactions, and pure *syn*-1,3-amino alcohol products were isolated in good yields (>76%). Only for the reduction of **2q** (R′ = ethyl and R = phenyl) was poor selectivity observed (entry 17).

C.3. *anti*-Selective Reduction with $LiBHEt_3$ (Table 4). The generality of the reaction with $LiBHEt_3$ was also examined with various β-hydroxy-*N*-sulfinyl imines **2**. The reduction of aromatic sulfinyl imines **2a**−**e** was first examined (entries 1−5). All five substrates afforded the *anti*-1,3-amino alcohols ***anti*-5a**−**e** exclusively, and the diastereomerically pure products were isolated in good yields. The reduction of the aliphatic imines

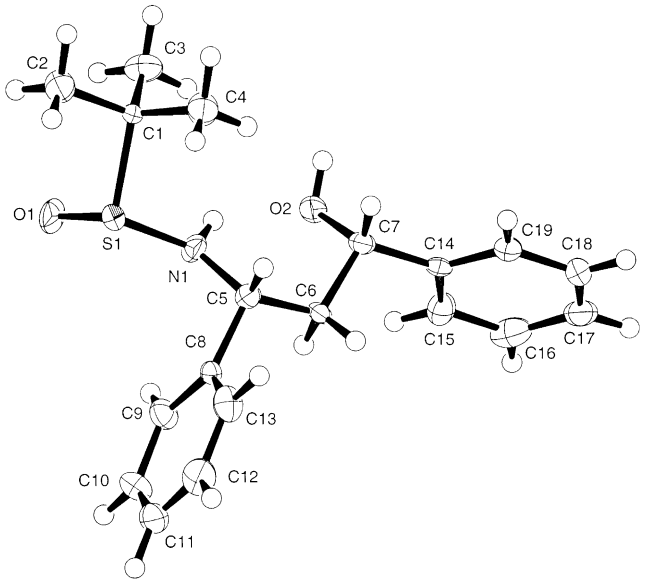


Figure 3. Structure of ***syn*-5e**.

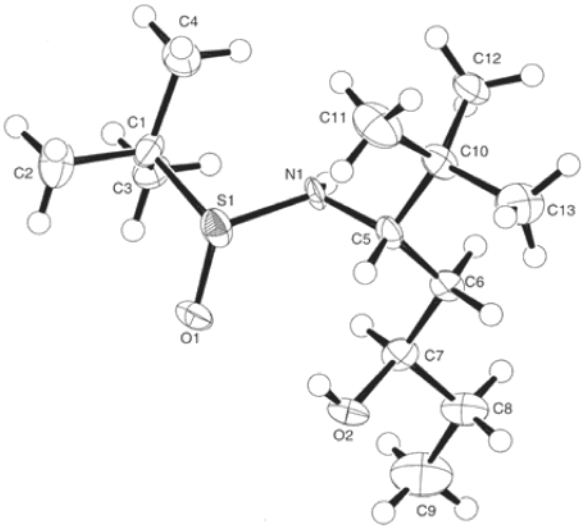


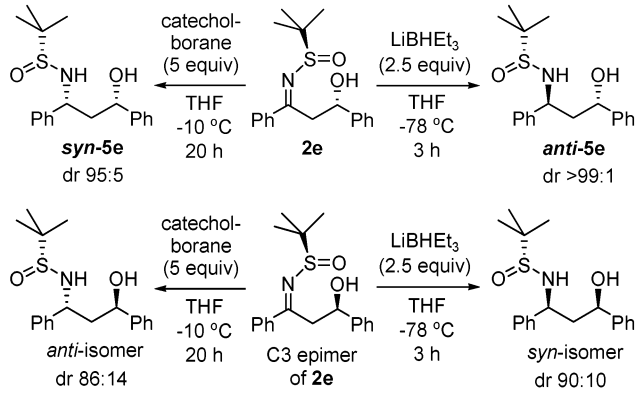
Figure 4. Strucuture of ***anti*-5h**.

was next investigated.[18] Reductions of substrates **2f** to **2i** (R = *tert*-butyl) also proceeded with >99:1 diastereoselectivity, and the pure *anti*-isomers were isolated in >83% yields (entries 6−9). β-Hydroxy-*N*-sulfinyl imines **2j**−**q** were also reduced to afford *anti*-1,3-amino alcohol derivatives with good to high selectivity (>88:12 to 99:1 dr), and in all cases the pure *anti*-isomers were isolated in good yields (entry 10−17).

C.4. Determination of the Sense of Induction for the Preparation of *N*-Sulfinyl-1,3-amino Alcohols. The crystal structures of *N*-sulfinyl-1,3-amino alcohols ***syn*-5e** and ***anti*-5h** were obtained (Figures 3, 4). In the structure of ***syn*-5e**, the nitrogen and the oxygen of the hydroxyl group are separated by a short distance (2.74 Å), and the amine hydrogen is located at a reasonable position for an intramolecular hydrogen bond with the oxygen atom. On the other hand, the crystal structure of ***anti*-5h** shows that the oxygen of the hydroxy group is in close contact with the oxygen of the sulfinyl group (2.78 Å) and the alcohol hydrogen is located at the position for an

(18) Reduction of **2n** with $LiBH(s\text{-}Bu)_3$ resulted in a slight decrease in diastereoselectivity (95:5 *anti*/*syn*).

Scheme 5



intramolecular hydrogen bond with the sulfinyl group. Although the solution-state conformations for ***syn*-5** and ***anti*-5** could certainly be different from the observed solid-state structures, the distinct conformations and hydrogen-bonding patterns observed for ***syn*-5e** and ***anti*-5h** could explain the consistent elution order and very large chromatographic separations that are consistently observed for the *syn*- and *anti*-isomers (the separability factors[19] of the two diastereomers by HPLC range from 1.78 to 6.65 and are averaged at 3.18).

Furthermore, these crystal structures established the sense of induction for the catecholborane and $LiBHEt_3$ reductions to give ***syn*-** and ***anti*-5e** and **5h**, respectively. The relative stereochemistry of *N*-sulfinyl-1,3-amino alcohols, ***syn*-** and ***anti*-5b** and **5e** were also determined by NMR analysis of the corresponding cyclic carbamates, which were prepared by the two-step sequence of sulfinyl group cleavage followed by reaction with phosgene.[20]

C.5. Stereochemical Models for the Diastereoselective Reductions. To understand the origin of the reduction stereoselectivities, the reduction of the C-3 epimer of **2e** was investigated. Reduction with catecholborane provided the *anti*-1,3-amino alcohol product with 86:14 diastereoselectivity, while reduction with $LiBHEt_3$ provided the *syn*-1,3-amino alcohol with 90:10 diastereoselectivity (Scheme 5). Clearly, the selectivity of the reduction is primarily controlled by the stereochemistry of the *N*-sulfinyl group rather than by the stereochemistry of the alcohol.[21] The opposite diastereoselectivity for the reduction with catecholborane versus $LiBHEt_3$ can be rationalized by considering the geometry of the *N*-sulfinyl imine during the reduction step (Figure 5). The *E*-geometry of β-hydroxy *N*-sulfinyl imine **2** is based upon the X-ray crystal structure of **2e** and NMR analysis of **2e** and **2q** (see Section A.3). The addition of $LiBHEt_3$ is unlikely to change the *N*-sulfinyl imine geometry. In contrast, addition of catecholborane may provide the stable six-membered ring intermediate **H** in analogy to the stereoselective reduction of β-hydroxy ketones reported by Evans and Hoveyda.[22] Boron chelation clearly plays a significant role in the reduction because less than 10% reduction was observed upon reaction of the *N*-sulfinyl imine derived from

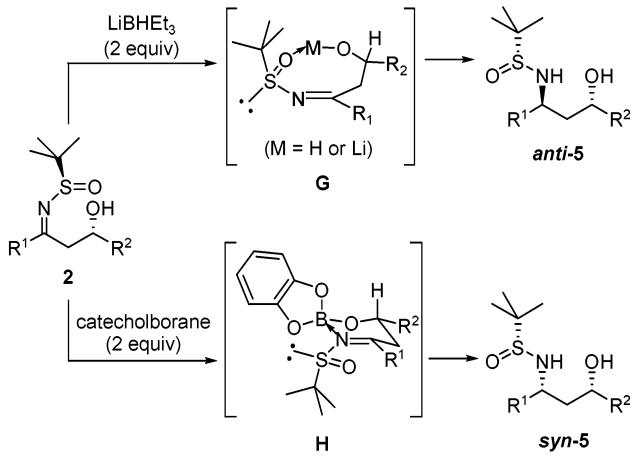
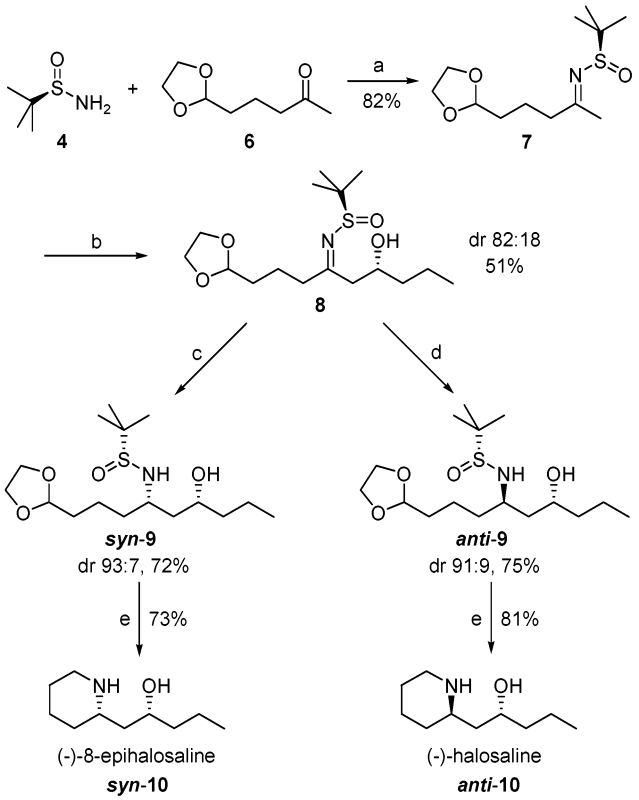


Figure 5. Stereoselective reduction of *N*-sulfinyl imines **2**.

Scheme 6. Total Synthesis of (−)-Halosaline and (−)-8-Epihalosaline[a]



[a] Reaction Conditions: (a) $Ti(OEt)_4$, THF, 75 °C, 15 h; (b) i) LDA, THF, − 78 °C, 45 min; ii) $MgBr_2$, − 78 °C, 45 min; iii) butyraldehyde, THF, − 78 °C, 20 min; (c) catecholborane, THF, − 48 °C, 3 h; (d) $LiBHEt_3$, THF, − 78 °C, 3 h; (e) H_2 gas (1 atm), PtO_2 (10 mol %), TFA/EtOH/H_2O (1:5:5), rt, 15 h.

acetophenone with catecholborane under the standard conditions. Isomerization from the *E*- to the *Z*-imine would presumably result in the observed reversal in the stereoselectivity for the catecholborane reduction.

D. Total Synthesis of (−)-Halosaline and (−)-8-Epihalosaline (Scheme 6). More than 10 2-(2-hydroxyalkyl)piperidine alkaloid natural products have been isolated (Figure 6). The natural products differ in the structure and length of the R^2 substituents, the substitution on nitrogen, and the occurrence of all four possible stereoisomers. To demonstrate the versatility of the reported 1,3-amino alcohol synthesis methods we sought

(19) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520−2527.
(20) See Supporting Information of ref 8.
(21) Reduction of the *N*-sulfinyl imine derived from acetophenone with $LiBHEt_3$ proceeds with 96: 4 dr and with the same relative stereochemistry as observed for the reductions of **2** with $LiBHEt_3$. In contrast, reduction with catecholborane proceeds in very poor yield (<10%) and with poor selectivity (<2:1).
(22) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5, 5190−5192.

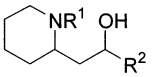


Figure 6. 2-(2-Hydroxyalkyl)piperidine alkaloids.

to carry out the asymmetric syntheses of two members of this family, (−)-halosaline (***anti*-10**)[23] and (−)-8-epihalosaline (***syn*-10**).[24] A convergent route to these two natural products was specifically designed such that it also could be employed to prepare any other member of this family of natural products.

First, protected ketone **6** was prepared according to the procedure of Grigg and co-workers[25] in two steps from the inexpensive starting materials, ethyl acetoacetate and 2-(2-bromoethyl)-1,3-dioxolane. Condensation of (*R*)-*tert*-butanesulfinamide with ketone **6** then provided *N*-sulfinyl imine **7** in 82% yield. Formation of the metalloenamine of **7** followed by addition of butyraldehyde under standard conditions provided *β*-hydroxy *N*-sulfinyl imine **8** with 82:18 dr. Column chromatography delivered the pure major isomer in 51% yield. The catecholborane reduction of **8** at the standard temperature of −10 °C resulted in significant product decomposition due to the lability of the acetal under the reaction conditions. Fortunately, when the catecholborane reduction was performed at −48 °C the reaction proceeded to completion within 3 h and with 93:7 dr. After column chromatography, diastereomerically pure ***syn*-9** was isolated in 72% yield. The reaction of **8** with $LiBHEt_3$ was performed at −78 °C for 3 h and proceeded with high diastereoselectivity (91:9) to provide diastereomerically pure ***anti*-9** in 75% yield after column chromatography. We envisioned that the acidic conditions necessary to remove the sulfinyl group and cleave the acetal present in ***syn*-9** or ***anti*-9** could also be appropriate for cyclization to the imine and its reduction, thereby enabling the final product to be obtained in a single step. Indeed, hydrogenation of ***syn*-9** and ***anti*-9** with PtO_2 in the presence of TFA was performed cleanly, and (−)-8-epihalosaline (***syn*-10**) and (−)-halosaline (***anti*-10**) were isolated after column chromatography in 73 and 81% yield, respectively.

(23) (a) Michel, K.-H.; Sandberg, F.; Haglid, F.; Norin, T. *Acta Pharm. Suec.* **1967**, *4*, 97−116. (b) Michel, K.-H.; Sandberg, F.; Haglid, F.; Norin, T.; Chan, R. P. K.; Craig, J. C. *Acta Chem. Scand.* **1969**, *23*, 3479−3481.
(24) Mill, S.; Hootele, C. *J. Nat. Prod.* **2000**, *63*, 762−764.
(25) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929−6952.

Conclusions

A general method is described for asymmetric synthesis of both *syn*- and *anti*-1,3 amino alcohols. The first application of metalloenamines derived from *N*-sulfinyl imines is reported for the highly diastereoselective addition to aldehydes. The reduction of the product *β*-hydroxy *N*-sulfinyl imines **2** with catecholborane and $LiBHEt_3$ provides *syn*- and *anti*-1,3-amino alcohols with very high diastereomeric ratios. This method was found to be effective for a variety of substrates incorporating either aromatic or various aliphatic substituents. Finally, the convergent and efficient asymmetric syntheses of the two natural products, (−)-8-epihalosaline and (−)-halosaline, were accomplished.

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Supporting Information Available: Experimental details, including synthetic procedures and characterization, and X-ray crystallographic data of ***anti*-5h** (PDF/CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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