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Asymmetric Synthesis of *syn*- and *anti*-1,3-Amino Alcohols

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The addition of nucleophiles to *N*-sulfinyl imines is used extensively for the asymmetric synthesis of a broad range of amine-containing compounds.[1] In contrast, despite the importance of metalloenamines as enolate equivalents,[2] the chemistry of metalloenamines derived from *N*-sulfinyl imines has not previously been reported. Herein we describe the highly diastereoselective addition of a metalated *tert*-butanesulfinyl imine to aldehydes (Figure 1). We further describe the highly diastereoselective reduction of the *β*-hydroxy-*N*-sulfinyl ketimine products to obtain *N*-sulfinyl derivatives of either *syn*- or *anti*-1,3-amino alcohols, which are present in many molecules of pharmaceutical and biological interest.[3] To our knowledge this is the first method to be reported for the stereoselective synthesis of both the *syn*- and *anti*-1,3-amino alcohols from a common synthetic intermediate.[4]

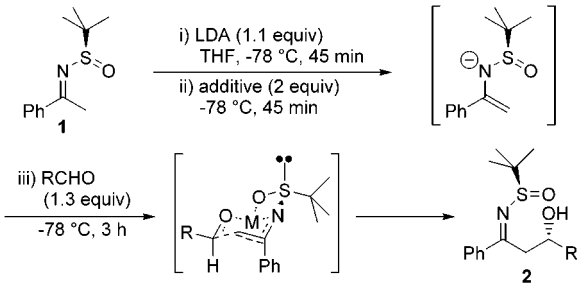

Figure 1. Addition of metalated *N*-sulfinyl imine **1** to aldehydes (M = MgBr or ZnBr).

We first examined the metalation of *tert*-butanesulfinyl ketimine **1** followed by addition to propionaldehyde (Table 1). Deprotonation of **1** with LDA in THF followed by reaction with propionaldehyde afforded *β*-hydroxy sulfinyl imine **2a** in 80% yield and with 86:14 dr (entry 1). Changing the solvent to toluene or diethyl ether resulted in lower diastereoselectivities. However, the addition of metal salts resulted in a dramatic increase in diastereoselectivity. Specifically, addition of $MgBr_2$ and $ZnBr_2$ afforded **2a** with ratios of 96:4 and 93:7, respectively, with the addition of $MgBr_2$ providing the highest yield (entry 2). Using the optimal conditions, the metalloenamine of **1** was next added to an α-branched aldehyde (entry 4), a *β*-branched aldehyde (entry 5), and an α,α-dibranched aldehyde (entry 6). The addition reactions proceeded with high diastereoselectivity for each aldehyde substrate (96:4 to 98:2), and diastereomerically pure **2b**−**d** were obtained in high yields after chromatography. Notably, addition of the metalloenamine of **1** to benzaldehyde proceeded with highest stereoselectivity when $ZnBr_2$ (entry 8) rather than $MgBr_2$ (entry 7) was added. The sense of induction for the addition to aldehydes was confirmed by X-ray crystallography of product **2e** from addition to benzaldehyde and can be predicted by the mnemonic in Figure 1.

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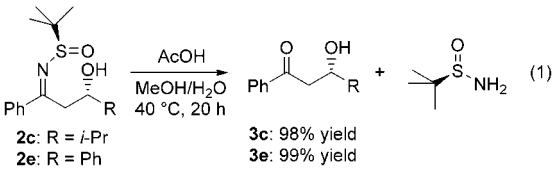
Table 1. Preparation of *β*-Hydroxy-*N*-sulfinyl Imines **2**

entry	R	additive	product	dr[a]	yield (%)[b]
1	Et	−	**2a**	86:14	80
2	Et	$MgBr_2$	**2a**	96:4	84
3	Et	$ZnBr_2$	**2a**	93:7	62
4	*i*-Bu	$MgBr_2$	**2b**	96:4	75
5	*i*-Pr	$MgBr_2$	**2c**	98:2	88
6	*t*-Bu	$MgBr_2$	**2d**	98:2	64
7	Ph	$MgBr_2$	**2e**	76:2	66
8	Ph	$ZnBr_2$	**2e**	92:8	79

[a] Diastereomeric ratios. [b] Isolated yields of diastereomerically pure material.

Hydrolysis of the addition product **2c** with acetic acid in MeOH/H_2O afforded *β*-hydroxy ketone **3c** in quantitative yield with 1−2% racemization (eq 1). The absolute configuration of **3c** was determined by comparison of the optical rotation to the literature value, confirming that the sense of induction is the same for additions to both aliphatic and aromatic aldehydes. *tert*-Butanesulfinamide was also isolated in 99% yield and without racemization (>99% ee). Hydrolysis of **2e** similarly proceeded in quantitative yield with <2% racemization.



The reduction of *β*-hydroxy-*N*-sulfinyl imines **2** was next examined. A number of reducing agents were first screened for the reduction of **2c** (Table 2). The *N*-sulfinyl 1,3-amino alcohol ***syn*-4c** was obtained with the highest selectivity (96:4 *syn*/*anti*) by reduction with catecholborane at −10 °C, with the diastereomerically pure material isolated in 84% yield after chromatography. Alternatively, reduction of **2c** with $LiBHEt_3$ at −78 °C provided the *anti* product **4c** in 83% yield. Reduction of **2c** with LiBH(*s*-Bu)$_3$ provided the same yield and selectivity observed for $LiBHEt_3$. The generality of the optimal reducing conditions was demonstrated by reducing *β*-hydroxy *N*-sulfinyl imines **2a**−**e** (Table 3). For all substrates, very high diastereoselectivities and good yields were observed for reductions with both catecholborane and $LiBHEt_3$.[5]

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. 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.[6] The opposite diastereoselectivity for the

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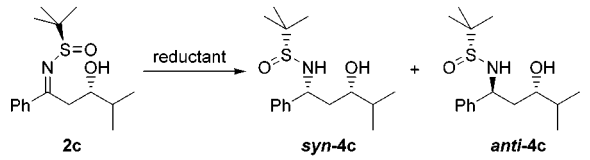
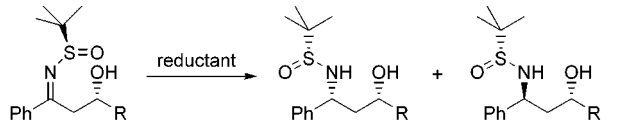
Table 2. Reduction of β-Hydroxy-*N*-sulfinyl Imine **2c** with Various Reducing Agents



reductant	solvent	major isomer	dr[a]	yield (%)[b]
$NaBH_4$	THF	***anti*-4c**	66:34	45
$NaCNBH_3$	THF/AcOH	***syn*-4c**	83:17	78
catecholborane	THF	***syn*-4c**	96:4	88
$LiBHEt_3$	THF	***anti*-4c**	>99:1	83
$LiBH(s\text{-}Bu)_3$	THF	***anti*-4c**	>99:1	83

[a] Diastereomeric ratios. [b] Isolated yields of diastereomerically pure material.

Table 3. Highly Diastereoselective Reduction of β-Hydroxy-*N*-sulfinyl Imines **2**



R	reductant	major isomer	dr[a]	yield (%)[b]
Et	catecholborane[c]	***syn*-4a**	95:5	94
	$LiBHEt_3$[d]	***anti*-4a**	>99:1	69
i-Bu	catecholborane[c]	***syn*-4b**	96:4	84
	$LiBHEt_3$[d]	***anti*-4b**	>99:1	85
i-Pr	catecholborane[c]	***syn*-4c**	96:4	88
	$LiBHEt_3$[d]	***anti*-4c**	>99:1	83
t-Bu	catecholborane[c]	***syn*-4d**	96:4	89
	$LiBHEt_3$[d]	***anti*-4d**	>99:1	91
Ph	catecholborane[c]	***syn*-4e**	96:4	84
	$LiBHEt_3$[d]	***anti*-4e**	>99:1	73

[a] Diastereomeric ratios. [b] Isolated yields of diastereomerically pure material. [c] Reaction was performed with 5 equiv of catecholborane in THF at −10 °C for 20 h. [d] Reaction was performed with 2.5 equiv of $LiBHEt_3$ in THF at −78 °C for 3 h.

reduction with catecholborane versus $LiBHEt_3$ can be rationalized by considering the geometry of the *N*-sulfinyl imine during the reduction step (Figure 2). The *E*-geometry of β-hydroxy *N*-sulfinyl

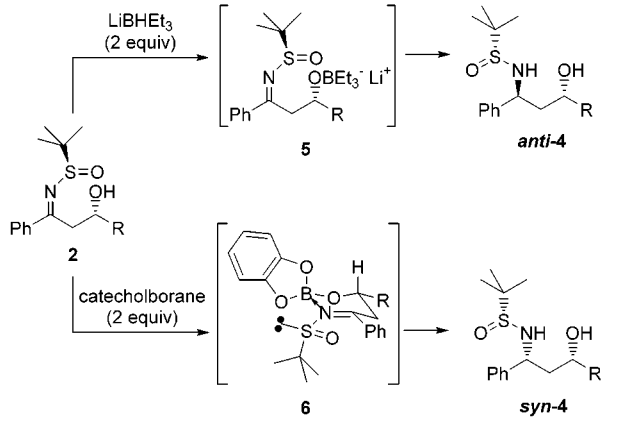


Figure 2. Stereoselective reduction of *N*-sulfinyl imines **2**.

imine **2** is based upon the X-ray crystal structure of **2e**. 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 **6** analogous to the stereoselective reduction of β-hydroxy ketones reported by Evans and Hoveyda.[7] Isomerization from the *E*- to the *Z*-imine would presumably result in the observed reversal in the stereoselectivity of the catecholborane reduction.

In conclusion, the first application of metalloenamines derived from *N*-sulfinyl imines is reported for the highly diastereoselective addition to aldehydes. The reduction of the resulting β-hydroxy sulfinyl imines **2** with catecholborane and $LiBHEt_3$ provides *syn*- and *anti*-1,3-amino alcohols, respectively, with very high diastereomeric ratios. The addition chemistry of metalloenamines derived from *N*-sulfinyl α-substituted ketimines, aliphatic ketimines, and aldimines is currently under investigation, as is the addition of carbon-based nucleophiles to β-hydroxy imines **2**.

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Supporting Information Available: Synthetic procedures, characterization, and stereochemical determination of new compounds (PDF). An X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The relative configuration of **4** was determined by NMR studies on cyclic carbamates derived from ***syn*-** and ***anti*-4c**,**e** and X-ray crystallography of ***syn*-4e**. See Supporting Information.

(6) 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).

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