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Reversal of Diastereofacial Selectivity in Hydride Reductions of *N*-*tert*-Butanesulfinyl Imines

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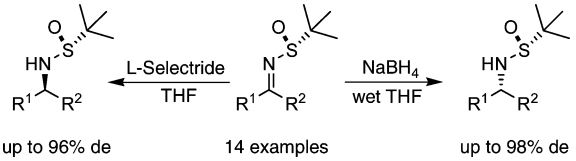

A variety of *N*-*tert*-butanesulfinyl imines were reduced with $NaBH_4$ in THF containing 2% water to provide the corresponding secondary sulfinamides in high yield and diastereoselectivity. By using the same sulfinyl imine starting materials and changing the reductant to L-Selectride, the stereoselectivity could be efficiently reversed to afford the opposite product diastereomer in high yield and selectivity.

In support of a recent medicinal chemistry SAR study, we required an efficient route to chiral secondary amines that would allow access to both product antipodes in high stereoselectivity and would be suitably flexible to work with a variety of functional groups. The reduction of *N*-sulfinyl imines, first reported by Cozzi[1] and later studied by Ellman,[2] attracted our attention in part as a result of the increasing commercial availability of both (*R*)- and (*S*)-2-methyl-2-propanesulfinamide.[3,4] Although the synthesis of amines via addition of carbon nucleophiles to various *N*-sulfinyl imines has been widely investigated[5] and exploited in the pharmaceutical industry,[6] we were surprised to find that the corresponding hydride addition reactions have not been thoroughly studied. Whereas it was clear from the work of Ellman[2] that $NaBH_4$ reduction of *tert*-butanesulfinyl imines provided high levels of diastereofacial control, it was unclear how other reducing agents would effect the stereochemical course of the reaction. Although reversals of diastereofacial selectivity had been reported for addition of carbon nucleophiles to sulfinyl imines,[7] this observation had not been clearly documented for the corresponding hydride additions.[8,9] We herein disclose our investigations into the reduction of various *N*-*tert*-butanesulfinyl imines and show that high levels of diastereofacial control can be obtained to provide

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(3) Both (*R*)- and (*S*)-2-methyl-2-propanesulfinamide are readily available from AstaTech, Inc. in kilogram quantities for $9.90/g and $6.90/g, respectively.

(4) The sulfinamide starting material may be prepared in two steps via catalytic asymmetric oxidation of *tert*-butyl disulfide. See: (a) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317. (b) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

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(7) For reversals of diastereofacial selectivity using *p*-toluenesulfinyl imines, see: (a) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621. (b) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. For reversals of diastereofacial selectivity using *tert*-butanesulfinyl imines, see: refs 6a and 6i.

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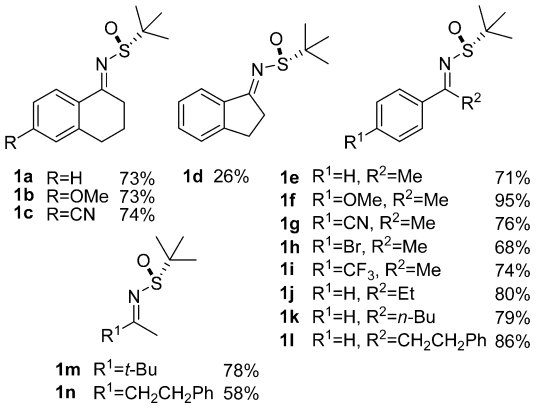
SCHEME 1[a]

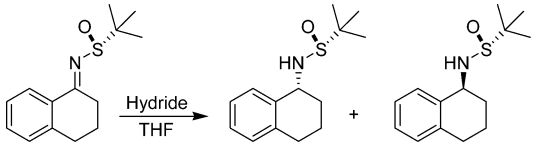


[a] Isolated yields after column chromatography.

access to either product diastereomer from a single sulfinimine enantiomer by appropriate selection of reducing agent and solvent.

Sulfinyl imines **1a**−**1n** were prepared by condensation of the appropriate ketone with 1.1 equiv of (R_S)-2-methyl-2-propanesulfinamide using $Ti(OEt)_4$ (2.0 equiv) in THF according to the procedure developed by Ellman and co-workers[2c] (Scheme 1). In all cases, the products were isolated in analytically pure form by extractive workup followed by flash chromatography. ^{1}H NMR analysis revealed that sulfinyl imines **1a**−**1n** existed solely as the (*E*)-isomers and the corresponding sulfinyl enamides were never observed. Sulfinyl imine (R_S)-**1a** was subjected to a screen of various metal hydrides in dry THF[10] (Table 1). In accordance with Ellman's findings,[2c] $NaBH_4$ proved to be optimal among the BH_4^- species examined, giving sulfinamide (R_S,*R*)-**2a**[11] in quantitative conversion and 90% diastereoselectivity.[12] Addition of 20 mol % $Ti(OEt)_4$ to the reaction mixture significantly increased the diastereoselectivity in favor of the same product stereoisomer (entry 3). Me_4NBH_4 and $NaBH_3CN$ were found to be poorly reactive, furnishing sulfinamide **2a** in 23% and 70% diastereoselectivity, respectively. Aluminum hydride reagents such as $LiAlH_4$, DIBAL-H, and Red-Al exhibited poor to modest levels of diastereoselection in favor of isomer **2a** (entries 8−10). We were gratified to find that subjection of sulfinyl imine **1a** to L-Selectride in dry THF provided the opposite product stereoisomer (R_S,*S*)-**3a** in 97% diastereoselectivity (entry 11). Addition of 20 mol % $Ti(OEt)_4$ to the reaction mixture slightly diminished the selectivity for product **3a** to 95% diastereoselectivity (entry 12).

TABLE 1. Reduction of Sulfinyl Imine (R_S)-1a Using Various Metal Hydrides



entry[a]	hydride	conversion (%)[b]	% ds (major product)[c]
1	$LiBH_4$	100	32 (**2a**)
2	$NaBH_4$	100	90 (**2a**)
3	$NaBH_4/Ti(OEt)_4$[d]	100	98 (**2a**)
4	KBH_4	100	79 (**2a**)
5	Me_4NBH_4	33	23 (**2a**)
6	$NaBH_3CN$	31	70 (**2a**)
7	BH_3·THF	100	80 (**2a**)
8	$LiAlH_4$	100	26 (**2a**)
9	DIBAL-H	97	75 (**2a**)
10	Red-Al	100	69 (**2a**)
11	L-Selectride	100	97 (**3a**)
12	L-Selectride/$Ti(OEt)_4$[d]	100	95 (**3a**)

[a] All reactions performed using 3.0 equiv of reducing agent in dry THF (−50 °C → rt). [b] Conversion based on crude ^{1}H NMR analysis. [c] Diastereoselectivity based on HPLC analysis. [d] 20 mol % Lewis acid added.

TABLE 2. Solvent Screen for Sulfinyl Imine (R_S)-1a Reduction

entry[a]	solvent	conversion (%)[b]	% ds (major product)[c]
1	toluene	100	58 (**2a**)
2	CH_2Cl_2	100	72 (**2a**)
3	CH_3CN	100	10 (**2a**)
4	THF[d]	100	97 (**2a**)
5	2-BuOH	100	82 (**2a**)
6	IPA	100	52 (**2a**)
7	EtOH	100	18 (**2a**)
8	MeOH	37	79 (**3a**)

[a] All reactions performed using $NaBH_4$ (3.0 equiv) in the appropriate solvent (−50 °C to rt). [b] Conversion based on crude ^{1}H NMR analysis after 24 h reaction period. [c] Diastereoselectivity based on HPLC analysis. [d] 2% H_2O added.

We subsequently studied the role of solvent on the reaction using substrate (R_S)-**1a** with 3.0 equiv of $NaBH_4$ as the reductant (Table 2). Toluene and CH_2Cl_2 furnished sulfinamide (R_S,*R*)-**2a** in good yield but modest selectivity (entries 1 and 2). Employing acetonitrile as the solvent led to full conversion but extremely low selectivity.

Performing the reduction in THF containing 2% water resulted in a moderate, reproducible gain in selectivity for product **2a** relative to using dry THF (cf. Table 1, entry 2).[13] Utilization of alcoholic solvents had a profound effect on the product diastereoselectivity, with 2-butanol furnishing the best result for product **2a** (82% diastereoselectivity, entry 5). Employing IPA also resulted in full conversion but with a diminished selectivity (52% diastereoselectivity). Ethanol provided diastereomer **2a** with poor selectivity (18% diastereoselectivity), and MeOH gave incomplete conversion (37%) toward the opposite stereoisomer **3a** (79% diastereoselectivity, entry 8).

To test if the reversal in diastereofacial selectivity upon using $NaBH_4$ versus L-Selectride was general, sulfinyl imines **1b**−**1n** were subjected to both reaction conditions (Table 3). In all cases, reduction with $NaBH_4$ in wet THF provided the (R_S,*R*)-diastereomer,[14] whereas utilization of L-Selectride gave

(8) Reversal of diastereofacial selectivity has been observed in the reduction of *tert*-butanesulfinyl imines bearing a hydroxyl group in the *β*-position. To explain this observation, Ellman and co-workers have proposed that coordination of catecholborane to the hydroxyl group leads to an (*E*)- to (*Z*)-imine isomerization. See refs 2a and 2b.

(9) To our knowledge only a single example of reversal in selectivity has been reported for the reduction of unfunctionalized sulfinyl imines. See: Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.

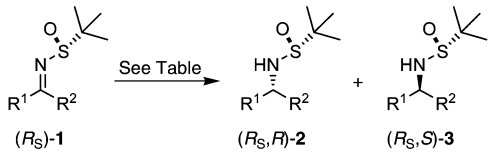
(10) The sulfinyl imine (0.2 mmol) was weighed into a reaction vessel and dissolved in 5.0 mL of dry THF. The mixture was cooled to −50 °C and treated with 3.0 equiv of the appropriate reducing agent. The resulting mixture was allowed to warm to ambient temperature over a 3 h period and subsequently subjected to a standard aqueous workup. The crude product mixtures were analyzed by ^{1}H NMR and HPLC.

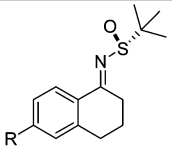
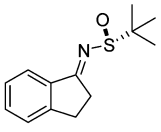
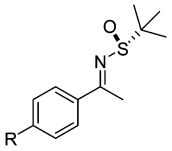
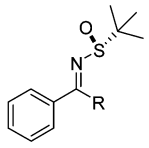
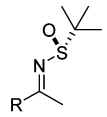
(11) The absolute configuration of product **2a** was unequivocally assigned by cleaving the sulfinamide with HCl and examining the optical rotation of the known salt.

(12) Although the product % diastereoselectivity could be ascertained by ^{1}H NMR analysis, all data reported herein is based on HPLC analysis. See Supporting Information for details.

(13) The explanation why water increases the selectivity of the reduction is unclear. Further investigation of this effect is ongoing in our laboratories.

TABLE 3. Reduction of Sulfinyl Imines 1b−1n Using $NaBH_4$ versus L-Selectride



Imine	$NaBH_4$/THF[a] Product, %de[c,d]	L-Selectride/THF[b] Product, %de[c,d]
 **1a** R=H **1b** R=OMe **1c** R=CN	**2a**, 97 **2b**, 95 **2c**, 55[e]	**3a**, 97 **3b**, 98 **3c**, 62[e]
 **1d**	**2d**, 96	**3d**, 97
 **1e** R=H **1f** R=OMe **1g** R=CN **1h** R=Br **1i** R=CF_3	**2e**, 82 **2f**, 84 **2g**, 73 **2h**, 77 **2i**, 77	**3e**, 84 **3f**, 90 **3g**, 83 **3h**, 94 **3i**, 92
 **1j** R=Et **1k** R=*n*-Bu **1l** R=CH_2CH_2Ph	**2j**, 51 **2k**, 49 **2l**, 56	**3j**, 96 **3k**, 95 **3l**, 98
 **1m** R=*t*-Bu **1n** R=CH_2CH_2Ph	**2m**, 64 **2n**, 53	**3m**, 76 **3n**, 2

[a] All reactions were carried out on a 0.2 mmol scale using 3.0 equiv of $NaBH_4$ in THF containing 2% H_2O (−50 °C to rt, 3 h). [b] All reactions carried out on a 0.2 mmol scale using 3.0 equiv of L-Selectride in dry THF (0 °C to rt, 3 h). [c] Average result obtained from two experiments unless noted otherwise. [d] Diastereoselectivity based on HPLC analysis. [e] Result obtained from a single experiment.

the corresponding (R_S,*S*)-diastereomer. In general, moderate to excellent selectivities for either product stereoisomer were observed with the major exception being sulfinyl imine **1n**. For this substrate, the steric bias between the two substituents on the imine carbon atom is not great enough to impart high levels of diastereoselection. Although the selectivity of the reductions was easily ascertained by analysis of the crude ^1H NMR spectra, we elected to verify the results by means of HPLC analysis. All reductions were carried out to full conversion, and the selectivities shown in Table 3 are unoptimized for each imine substrate.[15,16] In general, increasing the scale of the $NaBH_4$ reductions resulted in diminished selectivity, whereas no adverse effect was observed in the corresponding L-Selectride reductions (Table 4). However, we were gratified to find that many of the reduction products could be isolated by crystallization with considerable upgrade in diastereomeric purity.

TABLE 4. Gram Scale Reduction of Sulfinyl Imines 1a and 1b

imine	reduction conditions[a]	product, crude % ds[b]	isolated % ds[b]	isolated yield
1a	$NaBH_4$	75	>99[c]	84
1a	L-Selectride	96	>99[d]	90
1e	$NaBH_4$	74	94[c]	80
1e	L-Selectride	84	>99[d]	82

[a] All reactions were carried out on a 20 mmol scale using the general conditions described in Table 3. [b] Based on HPLC analysis. [c] Isolated by crystallization from hexanes. [d] Isolated by flash chromatography

TABLE 5. Cleavage of the Sulfinyl Moiety with HCl

sulfinamide[a]	yield[b,c]	sulfinamide[a]	yield[b,c]
2a	94	**3a**	98
2b	77	**3b**	96
2d	87	**3d**	93
2e	95	**3e**	98
2f	78	**3f**	92
2g	87	**3g**	90
2h	88	**3h**	93
2i	89	**3i**	81
2j	81	**3j**	91
2k	84	**3k**	86
2l	59	**3l**	84
2m	79	**3m**	83
2n	55	**3n**	84

[a] Pure sulfinamide diastereomer obtained by column chromatography. [b] Isolated yield. [c] All salts exhibited >97% chemical purity by HPLC analysis.

In our hands, treatment of the reduction products with HCl in dioxane (3.0 equiv) at room temperature cleanly provided the desired amine salts without erosion of the carbon stereochemistry. In all cases, the products were easily isolated via filtration upon addition of diethyl ether to the reaction mixture (Table 5).

To explain the origin of the reversal in diastereofacial selectivity upon changing reducing agents from $NaBH_4$ to L-Selectride, we propose that the former reactions proceed via a closed transition state wherein the sulfinyl oxygen participates in the delivery of the hydride[17] (Scheme 2). Under these circumstances (R_S-*E*)-sulfinyl imines would furnish the observed (R_S,*R*)-**2** sulfinamide products. Alternatively, poorly coordinating metal hydrides such as L-Selectride would attack the electrophilic carbon atom in a sterically controlled fashion via an open

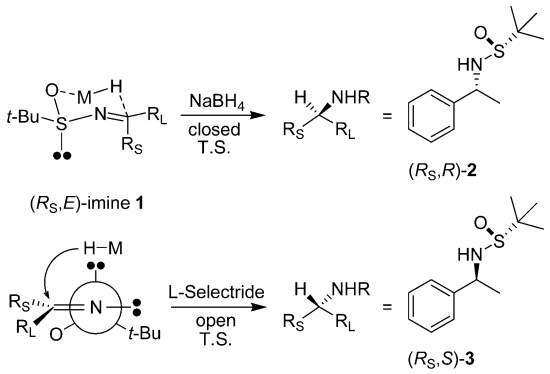
(14) The absolute configuration of the acetophenone ketimine series was established by cleaving the sulfinamide and comparing the resulting product to known samples of *sec*-phenethylamine. In addition, sulfinamide **3e** has been previously prepared by addition of MeMgBr to (R_S)-*N*-*tert*-butanesulfinyl benzaldimine and characterized by ^1H NMR. See ref 2c.

(15) The general reaction conditions shown in Table 3 were chosen for the purposes of screening. Further optimization study is ongoing in our laboratories.

(16) All reduction products shown in Table 3 were isolated by flash chromatography and fully characterized. See Supporting Information section for details.

(17) It must be noted that in the presence of protic solvents the transition state likely involves an activation of the borohydride reagent by hydrogen bonding. For a discussion see: (a) Gatling, S. C.; Jackson, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 8655. (b) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108.

SCHEME 2. Mechanistic Proposal for Origin of Stereoselectivity Reversal for Sulfinyl Imine Reduction



transition state. Hence, delivery of the hydride would occur from the same face as the sulfur lone pair to give sulfinamide products in the (R_S,*S*)-stereochemical series. This model may also explain why $NaBH_4$ reductions conducted in alcoholic solvents tend to give poorer selectivity. Under these conditions the hydrogen bonding ability of the solvent would be expected to disrupt sulfinyl oxygen mediated delivery of the hydride reagent. In the case of MeOH (Table 2, entry 8), the solvent disrupts the closed transition state to the extent that the opposite stereoisomer **3** is produced.

In conclusion, we have demonstrated that *N*-*tert*-butanesulfinyl imines can be reduced with metal hydride reagents to provide either product stereoisomer selectively in a predictable fashion. It appears that the sulfinyl oxygen atom plays a key role in the delivery of BH_4^- reagents to give products derived from a closed transition state. Reductions of sulfinyl imines using L-Selectride provide products derived from an open transition state.

Experimental Section

(R_S)-2-Methyl-*N*-((*R*)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (2a). Imine **1a** (5.00 g, 20.1 mmol) was dissolved in 98:2 THF/H_2O (50 mL) and cooled to −50 °C. To the mixture was then added $NaBH_4$ (2.28 g, 60.2 mmol), and the resulting solution was warmed to room temperature over a 3 h period. HPLC analysis of the reaction mixture showed complete consumption of imine **1a** to provide a product mixture favoring sulfinamide **2a** (75% diastereoselectivity). The solvent was then removed in vacuo, and the resulting residue was triturated with CH_2Cl_2. The solution was dried ($MgSO_4$), filtered, and concentrated to furnish a yellow oil. The crude product was dissolved in a minimum volume of hexanes at reflux and subsequently allowed to cool to ambient temperature. Product **2a** was isolated as an off-white crystalline solid (4.22 g, 84% yield) and determined to be >99% diastereoselectivity by HPLC analysis. R_f (50% EtOAc/hexanes) = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.3, 3.7 Hz, 1H), 7.23−7.17 (m, 2H), 7.10 (dd, J = 5.1, 3.7 Hz, 1H), 4.58 (dd, J = 7.7, 3.8 Hz, 1H), 3.22 (d, J = 2.5 Hz, 1H), 2.85−2.69 (m, 2H), 2.04−1.85 (m, 3H), 1.79−1.73 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.9, 129.6, 129.2, 127.5, 126.5, 55.4, 52.7, 30.5, 29.1, 22.6, 18.1; IR (neat) 3187, 1041, 1027 cm^{-1}. HRMS calcd for $C_{14}H_{21}NOS$ 252.1417 [M + H]$^+$; found 252.1429 [M + H]$^+$.

(R_S)-2-Methyl-*N*-((*S*)-1,2,3,4-tetrahydronaphthalen-1-yl)propane-2-sulfinamide (3a). Imine **1a** (5.00 g, 20.1 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. To the vessel was then added L-Selectride (60.0 mL, 1.0 M in THF, 60.0 mmol), and the resulting solution was allowed to warm to room temperature over a 3 h period. Analysis of the reaction mixture by HPLC showed complete consumption of the starting imine to give sulfinamide **3a** in 96% diastereoselectivity. The solution was then concentrated under vacuum to furnish an orange oil. The crude product was subjected to column chromatography (50% EtOAc/hexanes) to provide analytically pure product **3a** (4.54 g, 90% yield). R_f (50% EtOAc/hexanes) = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.17 (m, 2H), 7.08 (m, 1H), 4.46 (ddd, J = 10.0, 6.6, 5.9 Hz, 1H), 3.42 (d, J = 10.0 Hz, 1H), 2.85−2.69 (m, 2H), 2.35−2.28 (m, 1H), 2.10−1.88 (m, 2H), 1.8501.75 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 137.3, 129.0, 128.7, 127.1, 125.8, 56.2, 55.7, 33.0, 29.0, 22.7, 19.8; IR (neat) 3200, 1050, 1036 cm^{-1}. HRMS calcd for $C_{14}H_{21}NOS$ 252.1417 [M + H]$^+$; found 252.1423 [M + H]$^+$.

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Supporting Information Available: General methods, characterization data, NMR spectra, and analytical methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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