JOC The Journal of Organic Chemistry

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Diastereoselective Hydroxymethylation of Cyclic *N-tert*-Butanesulfinylketimines Using Methoxymethanol as Formaldehyde Source

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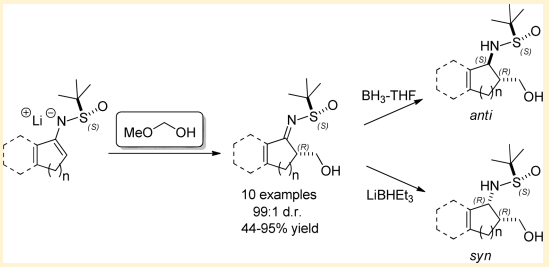
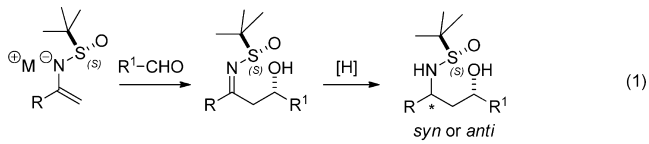
Supporting Information

ABSTRACT: Hydroxymethylation of cyclic *tert*-butanesulfinylketimine-derived lithium enamides with methoxymethanol proceeds with excellent diastereoselectivity (99:1 dr). Methoxymethanol is a stable and easy-to-handle source of anhydrous monomeric formaldehyde in the reaction with lithium enamides. Cyclic α-hydroxymethyl ketimines undergo highly diastereoselective reduction to *syn*- or *anti*-1,3-amino alcohols.

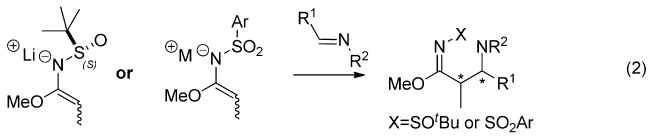


The chiral 1,3-amino alcohol structural motif is widely employed in medicinal and organic chemistry. Thus, a number of marketed drugs such as the analgesic tramadol, the antihistamine terfenadine, the antidepressant venlafaxine, and the HIV protease inhibitors ritonavir and lopinavir contain the 1,3-amino alcohol fragment. Moreover, chiral 1,3-amino alcohols have been used in the design of second generation HIV-1 entry inhibitors,[1] in the development of drugs for treatment of Alzheimer's disease[2] and in the preparation of monoamine reuptake inhibitors.[3] There are also a number of reports on application of chiral, nonracemic 1,3-amino alcohols in stereoselective synthesis.[4,5]

Among various methods for the synthesis of enantioenriched 1,3-amino alcohols, a diastereoselective reduction of the parent β-hydroxyketimines possessing *N-tert*-butylsulfinyl chiral auxiliary (Ellman's auxiliary)[6] is particularly useful as it provides access to both *syn*- and *anti*-1,3-amino alcohols simply by choosing the proper reducing agent (eq 1).[7,8] Furthermore,



(1)



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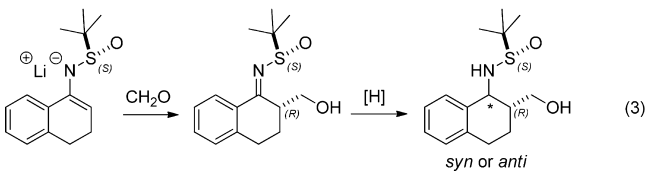

(3)

Ellman's chiral auxiliary also controls the formation of the β-stereogenic center in the addition of *N*-sulfinylketimine-derived metalloenamines to aldehydes.[7] Therefore, the *N-tert*-butylsulfinyl chiral auxiliary has been widely employed for diastereoselective synthesis of 1,3-amino alcohols having a 1,3 relationship between the chiral centers (eq 1).[7,9] Surprisingly, there are no literature precedents for the formation of a stereogenic center in the α-position relative to the ketimine moiety in the reaction of *N*-sulfinylketimine-derived metalloenamines with aldehydes. However, it is worth noting that chirality α to the structurally related imidate moiety has been created in a Mannich-type reaction of chiral *N-tert*-butanesulfinyl imidates[10] or *N*-sulfonylimidates[11] with aldimines (eq 2).

Herein we report a highly diastereoselective aldol-type reaction of (hetero)arene-fused cyclic five- and six-membered *N*-sulfinylketimines with methoxymethanol (MM) as the formaldehyde source (eq 3). At the outset of our investigation we screened various conditions for the hydroxymethylation of ketimine (*E*)-(S_S)-**1a**.[12] Treatment of (*E*)-(S_S)-**1a** with LDA, followed by transmetalation with $ZnBr_2$[7] afforded intermediate zinc enamide (S_S)-**2** (M = ZnBr), which reacted with an excess of anhydrous CH_2O (5 equiv) and produced α-hydroxymethyl ketimine (*E*)-(S_S,*R*)-**3a** in almost quantitative yield and with excellent diastereoselectivity (99:1 dr; entry 1, Table 1).[13] Notably, diastereomerically pure ketimine (*E*)-(S_S,*R*)-**3a** (99:1 dr) could also be obtained from the lithium enamide (S_S)-**2** (M = Li) and CH_2O without the addition of $ZnBr_2$ (entries 2, 3). Although both LDA and LiHMDS were equally efficient as bases, a commercially available LiHMDS solution was employed to avoid the preparation of fresh LDA for each experiment (entries 3–8).

Received: March 3, 2014
Published: March 25, 2014

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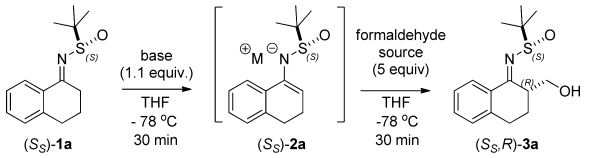
dx.doi.org/10.1021/jo500506u | *J. Org. Chem.* 2014, 79, 3715–3724

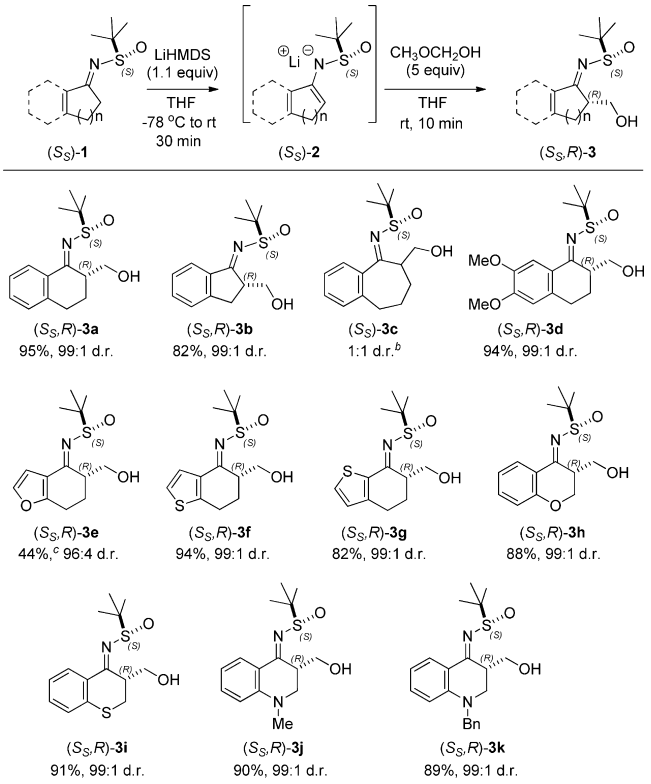
Table 1. Survey of Hydroxymethylation Conditions



no.	base	formaldehyde source[a]	yield[b] (%)	dr
1	LDA, $ZnBr_2$ (2 equiv)	CH_2O[c]	99	99:1
2	LDA	CH_2O[c]	99	99:1
3	LiHMDS	CH_2O[c]	99	99:1
4	LiHMDS	paraform[d]	<1	–
5	LiHMDS	trioxane[d]	<1	–
6	LiHMDS	$MeOCH_2OH$[d]	99 (95)[e]	99:1
7	LiHMDS	$MeOCH_2OH$[d] (3 equiv)	86[e]	99:1
8	LiHMDS	$MeOCH_2OH$[d] (1 equiv)	41[e]	77:23
9	CH_3OCH_2OLi	$MeOCH_2OH$[d] (4 equiv)	99	99:1

[a]5 equiv of formaldehyde source were used. [b]Determined by HPLC–MS assay. [c]0.1 M solution in THF. [d]Reaction was warmed to room temperature prior to the quench with aqueous saturated NH_4Cl. [e]Yield of >95% pure imine (*E*)-(S_S,*R*)-**3a** (3.6 mmol scale).

Scheme 1. Substrate Scope for Hydroxymethylation[a]



[a]Yield of >95% pure products (S_S,*R*)-**3a–k**. Ratio of diastereomers was determined for the crude reaction mixture by HPLC–MS assay. [b]Product was not isolated. [c]89% yield based on recovered (*E*)-(S_S)-**1e**.

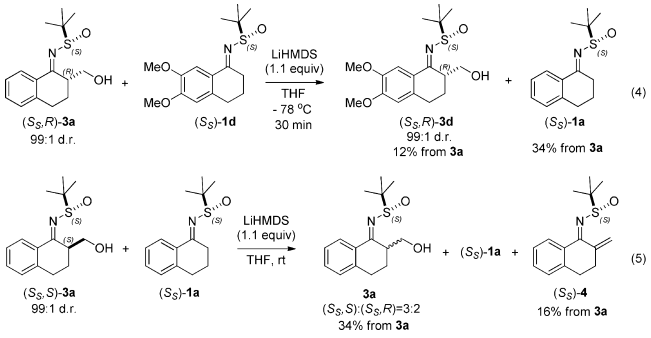
With a suitable lithium base in hand, a search for an alternative formaldehyde source was performed because of the difficulties in preparation and handling of anhydrous gaseous CH_2O. Thus, a 0.1 M solution of anhydrous monomeric CH_2O in THF[14] is unstable, and the aldehyde polymerizes upon handling. Therefore, the THF solution must be prepared shortly prior to use and titrated to establish an exact concentration of formaldehyde.[15] Among various formaldehyde precursors examined, paraform and trioxane were not suitable for the hydroxymethylation reaction (entries 4,5, Table 1). However, we found that MM, a stable and easy-to-handle hemiacetal of formaldehyde, is a convenient source of monomeric CH_2O in the reaction with metalloenamine (S_S)-**2a**.[16] Presumably, MM generates monomeric CH_2O species and methanol under equilibrium conditions. A 5-fold excess of MM was necessary to achieve high yields in the hydroxymethylation reaction. The use of smaller amounts of MM (1 or 3 equiv) resulted in reduced yields and lower diastereoselectivity (entries 7, 8). The efficiency of MM in the hydroxymethylation reaction indicates that lithium *N*-*tert*-butylsulfinyl enamide (S_S)-**2a** is less basic than the alkoxides derived from alcohol species present in the reaction mixture. This was confirmed by a control experiment where $LiOCH_2OCH_3$ was employed as a base instead of LiHMDS in the hydroxymethylation of ketimine (S_S)-**1a** with MM (entry 9, Table 1). α-Hydroxymethyl ketimine (S_S,*R*)-**3a** was formed with diastereoselectivity and chemical yields comparable to those obtained with LiHMDS as a base (entry 9 vs entry 6). To the best of our knowledge, this is the first example of the use of MM as a source of formaldehyde in reactions with organometallic species.[17]

With the best conditions for hydroxymethylation in hand, the scope of ketimines was surveyed (Scheme 1). Remarkable hydroxymethylation diastereoselectivity (99:1 dr) was observed for most of the ketimines (S_S)-**1** (Scheme 1). Among all of the ketimines tested, only the benzosuberone derivative (S_S)-**1c** provided a 1:1 mixture of diastereomers (S_S)-**3c**. The presence of a heteroatom in the aliphatic moiety of ketimines (S_S)-**1h–k** does not influence the diastereoselectivity of the reaction with MM. Ketimine (S_S)-**3e** was among the least reactive substrates in a series, and prolonged reaction times resulted in the concomitant formation of bis-hydroxymethylation product. Therefore, the hydroxymethylation of (S_S)-**3e** was stopped at partial conversion, and the unreacted starting **3e** was recovered.

The relative configuration of the asymmetric center created in the hydroxymethylation reaction was established to be *R* by X-ray crystallographic analysis of ketimines (*E*)-(S_S,*R*)-**3a,f**.[18] Consequently, the *R* absolute configuration of the stereogenic α-carbon was assigned to all of the hydroxymethylation products (*E*)-(S_S,*R*)-**3**. In the crystal lattices of sulfinylimines (*E*)-(S_S,*R*)-**3a,f** a hydrogen-bonding interaction between sulfinyl oxygen and the hydroxyl proton can be observed. This intramolecular hydrogen bond presumably provides an additional stabilization of (*E*)-(S_S,*R*)-**3a,f** in the crystalline form and points toward higher thermodynamic stability of the favored (*E*)-(S_S,*R*)-**3** diastereomers compared to their (*E*)-(S_S,*S*)-**3** counterparts. Ab initio DFT calculations using the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++g(d,p) basis sets confirmed that ketimine (*E*)-(S_S,*R*)-**3a** is 1.3 kcal/mol more stable than its C2-epimer (*E*)-(S_S,*S*)-**3a**.[18] The higher thermodynamic stability of the favored (*E*)-(S_S,*R*)-**3** diastereomers suggests their formation under equilibrium conditions. This would involve the forward aldol reaction between metalloenamine (S_S)-**2** and formaldehyde and the corresponding reverse reaction, the retro-aldol fragmentation of anionic (S_S,*R*)-**3**. In a control experiment, a 1:1 mixture of (S_S,*R*)-**3a** and imine (S_S)-**1d** was treated with LiHMDS (1.1 equiv) in THF, and after 30 min at −78 °C, the formation of a new aldol

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715–3724

product (S_S,R)-**3d** was observed (ca. 12%) together with ketimine (S_S)-**1a** (34%, see eq 4). Notably, both the newly



formed ketimine (S_S,R)-**3d** and the unreacted starting (S_S,R)-**3a** were diastereomerically almost pure (99:1 dr), and both possessed the R absolute configuration at the stereogenic α-carbon.

Next, the retro-aldol fragmentation of diastereomerically pure C2-epimeric ketimine (S_S,S)-**3a**[19] (the thermodynamically less stable epimer) in the presence of equimolar amounts of (S_S)-**1a** and LiHMDS was examined (eq 5). Only 34% of ketimine (S_S,S)-**3a** remained in the reaction mixture after 30 min at room temperature, and 16% of the unsaturated ketimine (S_S,S)-**4** was also observed together with several unidentified decomposition products. Importantly, the diastereomeric ratio of (S_S,S)-**3a** decreased from 99:1 to 3:2, and the ratio did not change after an additional hour (eq 5). The latter experiment indicates that retro-aldol fragmentation could influence the diastereoselectivity of hydroxymethylation by conversion of the less stable diastereomer (S_S,S)-**3a** into the more stable (S_S,R)-**3a** during the reaction. On the other hand, the diastereomeric purity of hydroxymethylation product (S_S,R)-**3a** was equally high (99:1) both at low (ca. 10%) and high (>90%) conversions of (S_S)-**1a** (Table 1). This observation renders unlikely the involvement of retro-aldol side-process in the hydroxymethylation reaction. Furthermore, the effective amount of formaldehyde in the control experiments (eqs 4 and 5) was less than 0.5 equiv with respect to ketimine species. In contrast, a 5-fold excess of MM was employed in the hydroxymethylation reaction (Scheme 1). The excess of MM should slow down the retro-aldol process by shifting the equilibrium toward the forward hydroxymethylation process. Indeed, the more stable (S_S,R)-**3a** diastereomer was not obtained from the less stable (S_S,S)-**3a** upon treatment with LiHMDS (1.1 equiv), followed by addition of excess of MM (5 equiv). The collected data strongly points against thermodynamic control in the hydroxymethylation reaction and suggests that the observed high diastereoselectivity is determined kinetically at the stage of C−C bond formation.

The observed R absolute configuration of the newly created α-stereogenic center in ketimines (S_S,R)-**3** is consistent with diastereoselective addition of lithium enamide (S_S)-**2a** to formaldehyde from the less sterically hindered *Re*-face of (S_S)-**2a** (Figure 1). In the transition state (TS) for the hydroxymethylation (**TS-1**), the nitrogen-bonded lithium cation presumably coordinates to sulfinyl oxygen and forms a 4-membered chelate.[7,20] As a result, the bulky *t*-Bu group hinders approach of the aldehyde from the *Si*-face of the enamide (S_S)-**2a**. Alternatively, involvement of a closed six-center chairlike TS is also plausible where the lithium cation is

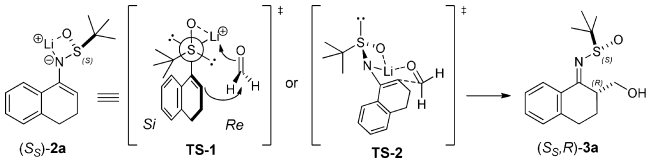
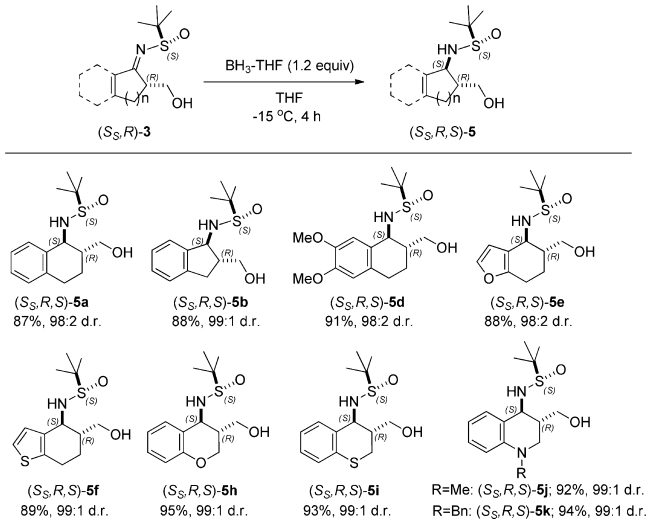


Figure 1. Transition state for the hydroxymethylation reaction.

coordinated both with sulfinyl oxygen and formaldehyde oxygen (**TS-2**).

With highly diastereoselective hydroxymethylation approach in hand, reduction of the ketimine was addressed. The reduction of α-hydroxymethyl-ketimines (S_S,R)-**3** with BH_3-THF proceeded with excellent diastereoselectivity (>98:2) and high yields for all substrates (Scheme 2). Diastereomeric purity

Scheme 2. *anti*-Diastereoselective Reduction of Ketimines (S_S,R)-3 with BH_3-THF[a]



[a]Yield of >95% pure products (S_S,R,S)-**5a**−**k**. Ratio of diastereomers was determined for the crude reaction mixture by HPLC−MS assay.

of the reduction products **5** could be further improved by simple recrystallization. The relative configuration of the newly created stereogenic center in sulfinamides (S_S,R,S)-**5a**,**f**,**h** was determined to be *S* by X-ray crystallographic analysis.[18] Consequently, reduction with BH_3-THF provided *anti*-1,3-amino alcohols (S_S,R,S)-**5a**,**f**,**h**. On the basis of structural analogy, the *anti* configuration was assigned for all of the reduction products (S_S,R,S)-**5** (Scheme 2).

The observed sense of asymmetric induction in the reduction of ketimines (S_S,R)-**3** with BH_3-THF implies a cyclic reduction TS and chelation-controlled delivery of hydride from *Re*-face of the sulfinylketimine to afford *anti*-products (S_S,R,S)-**5** (Figure 2, **TS-3**).[7,21] Accordingly, sulfinyl oxygen forms an "ate" complex with BH_3-THF, and thus controls the diastereoselectivity of the reduction (**TS-3**). However, the β-hydroxymethyl moiety can also direct the delivery of hydride from the *Re*-face of the sulfinylketimine by forming an "ate" complex with borane.

To understand the origins of the stereoselectivity, reduction of the ketimine (S_S,S)-**3a**,[19] a C2-epimer of (S_S,R)-**3a**, was investigated (Figure 2). *syn*-Amino alcohol (S_S,S,S)-**6a** was obtained with 84:16 dr from (S_S,S)-**3a** and BH_3-THF under standard conditions, and the *S* configuration of the newly

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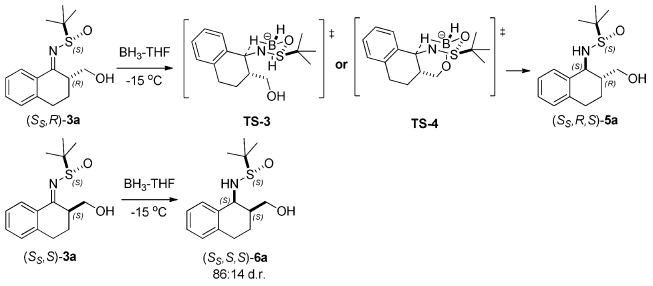
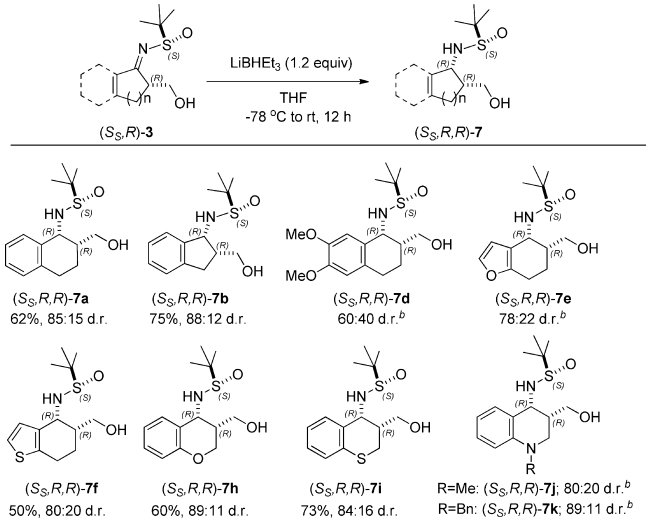


Figure 2. Transition states for diastereoselective reduction of ketimines **3**.

created asymmetric carbon was established using X-ray crystallographic analysis.[18] The formation of the *S* stereogenic center in the reduction of both (S_S,*R*)-**3a** and its C2-epimer (S_S,*S*)-**3a** confirms that the selectivity of the reduction is primarily controlled by the stereochemistry of the *N*-sulfinyl group rather than by the hydroxymethyl moiety. Nevertheless, a synergistic directing effect of both the sulfinyl oxygen and hydroxymethyl moiety also is conceivable (**TS-4**, Figure 2).

We envisioned that the diastereomeric *syn*-1,3-amino alcohols could be obtained from the parent α-hydroxymethyl ketimines (S_S,*R*)-**3** by using a reducing agent that cannot coordinate to sulfinyl oxygen and, hence, would not form the cyclic TS for the reduction. Indeed, the use of $LiBHEt_3$[7b] afforded reduction products (S_S,*R*,*R*)-**7** with the opposite sense of asymmetric induction, although diastereoselectivity was moderate (Scheme 3).

Scheme 3. *syn*-Diastereoselective Reduction of Ketimines (S_S,*R*)-3 with $LiBHEt_3$[a]



[a]Yield of >95% pure major diastereomer. Ratio of diastereomers was determined by HPLC−MS assay. [b]Product was not isolated.

In summary, we have demonstrated that hydroxymethylation of cyclic (S_S)-*tert*-butylsulfinylketimine-derived lithium enamides with methoxymethanol as a source of anhydrous monomeric CH_2O affords (S_S,*R*)-α-hydroxymethyl ketimines with excellent diastereoselectivity (99:1 dr).[22] Subsequent diastereoselective reduction of the ketimine from the *Re*-face with BH_3-THF provided (S_S,*R*,*R*)-*N*-sulfinyl-1,3-amino alcohols. The diastereomeric (S_S,*R*,*S*)-1,3-amino alcohols were also obtained by using $LiBHEt_3$ as the reducing agent. The *tert*-butylsulfinyl chiral auxiliary controls the diastereoselectivity of both the hydroxymethylation reaction and the subsequent reduction of ketimines.

EXPERIMENTAL SECTION

General Information. All reagents were obtained commercially and used as received. THF, Et_2O, and toluene were purified by distillation from sodium benzophenone ketyl. Methanol was purified by distillation from magnesium methoxide. All reactions were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS or to a residual solvent peak as an internal reference. HRMS spectra were acquired on an electrospray ionization mass spectrometer with a TOF analyzer, using the following parameters: positive ionization mode, drying gas 10 mL/min and 325 °C, fragmentor ionization 100 V. The ratio of diastereomers was established by HPLC−MS assay. Accordingly, peaks of diastereomers were identified on the basis of a mass trace (TIC) of the chromatogram, whereas dr was determined by integration of the corresponding peaks in the UV trace.

General Procedure for Synthesis of Ketimines 1a−k. Following the procedure reported in the literature,[12] heating of appropriate ketones with (S_S)-*tert*-butanesulfinamide and $Ti(OEt)_4$ at 66 °C for 12 h afforded sulfinylimines **1a−k**.

*(S_S)-2-Methyl-propane-2-sulfinic acid [3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S)-**1a**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to EtOAc afforded product as a brown amorphous solid (989 mg, 66% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.48; IR (film, cm^{-1}) 1608 (C═N), 1578 (C═N); ^1H NMR (600 MHz, THF-d_8, ppm) δ 8.1 (1H, dd, J = 8.0, 1.2 Hz), 7.35 (1H, td, J = 7.4, 1.4 Hz), 7.23−7.18 (2H, m), 3.31 (1H, ddd, J = 17.6, 10.0, 4.7 Hz), 3.08 (1H, ddd, J = 17.6, 7.4, 4.3 Hz), 2.90−2.82 (2H, m), 2.01−1.88 (2H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (150.9 MHz, THF-d_8, ppm) δ 176.3, 143.1, 134.4, 132.4, 129.7, 127.6, 127.2, 57.6, 32.7, 30.3, 23.7, 22.9; HRMS-ESI (m/z) calcd for $C_{14}H_{19}NOS$ $[M + H]^+$ 250.1260, found 250.1267; optical rotation $[\alpha]^{20}_D$ 27.0 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid indan-(1E)-ylideneamide ((S_S)-**1b**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 1% MeOH/CH_2Cl_2 to 15% MeOH/CH_2Cl_2 afforded the product as a brown amorphous solid (237 mg, 24% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.46; IR (film, cm^{-1}) 1617 (C═N), 1598 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.77−7.71 (1H, m), 7.50−7.46 (1H, dd, J = 7.6, 1.2 Hz), 7.43−7.40 (1H, m), 7.34−7.26 (1H, m), 3.50−3.41 (1H, m), 3.13−3.08 (2H, m), 3.07−2.98 (1H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 183.4, 151.6, 140.6, 133.8, 127.8, 126.7, 124.1, 57.5, 32.3, 29.9, 22.9; HRMS-ESI (m/z) calcd for $C_{13}H_{17}NOS$ $[M + H]^+$ 236.1104, found 236.1101; optical rotation $[\alpha]^{20}_D$ 177.3 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [6,7,8,9-tetrahydro-benzocyclohepten-(5E)-ylidene]-amide ((S_S)-**1c**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to 50% EtOAc/Hex afforded the product as a yellow amorphous solid (890 mg, 89% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.59; IR (film, cm^{-1}) 1605 (C═N), 1584 (C═N), 1565 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.52 (1H, dd, J = 7.6, 1.2 Hz), 7.30 (1H, ddd, J = 7.3, 7.3, 1.4 Hz), 7.21 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.18−7.13 (1H, m), 3.40−3.29 (1H, m), 2.97−2.81 (3H, m), 1.90−1.75 (4H, m), 1.26 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 184.5, 141.6, 141.0, 130.9, 130.3, 128.9, 127.1, 57.4, 34.8, 33.5, 26.9, 25.6, 22.9; HRMS-ESI (m/z) calcd for $C_{15}H_{21}NOS$ $[M + H]^+$ 264.1417, found 264.1423; optical rotation $[\alpha]^{20}_D$ 38.0 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [6,7-dimethoxy-3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S)-**1d**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to EtOAc afforded the product as a beige amorphous solid (225 mg, 36% yield): analytical TLC on

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715−3724

silica gel, 1:1 diethylether/CH_2Cl_2, R_f = 0.44; IR (film, cm^{-1}) 1612 (C═N), 1595 (C═N), 1590 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.63 (1H, s), 6.70 (1H, s), 3.82 (3H, s), 3.76 (3H, s), 3.22 (1H, ddd, J = 17.6, 9.3, 4.9 Hz), 3.00 (1H, ddd, J = 17.6, 7.3, 4.4 Hz), 2.85−2.72 (2H, m), 2.01−1.83 (2H, m), 1.26 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 174.8, 153.1, 148.2, 136.4, 125.7, 110.6, 108.7, 56.1, 55.0, 54.9, 31.2, 28.9, 23.0, 21.8; HRMS-ESI (m/z) calcd for $C_{16}H_{23}NO_3S$ $[M + H]^+$ 310.1471, found 310.1473; optical rotation $[\alpha]^{20}_D$ 3.0 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [6,7-dihydro-5H-benzofuran-(4E)-ylidene]-amide ((S_S)-**1e**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to EtOAc afforded the product as a brown oil (297 mg, 62% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.6; IR (film, cm^{-1}) 1606 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.40 (1H, d, J = 1.9 Hz), 6.61 (1H, d, J = 1.9 Hz), 3.12 (1H, ddd, J = 17.1, 9.1, 5.0 Hz), 2.93 (1H, ddd, J = 17.1, 7.1, 4.7 Hz), 2.81−2.75 (2H, m), 2.09−1.94 (2H, m), 1.20 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 171.8, 162.8, 143.5, 121.7, 107.6, 57.0, 30.7, 23.8, 23.7, 22.7; HRMS-ESI (m/z) calcd for $C_{12}H_{17}NO_2S$ $[M + H]^+$ 240.1053, found 240.1049; optical rotation $[\alpha]^{20}_D$ 203.6 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [6,7-dihydro-5H-benzo[b]-thiophen-(4E)-ylidene]-amide ((S_S)-**1f**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to 80% EtOAc/Hex afforded the product as a yellow amorphous solid (663 mg, 70% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.41; IR (film, cm^{-1}) 1575 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.37 (1H, d, J = 5.2 Hz), 7.16 (1H, d, J = 5.3 Hz), 3.20 (1H, ddd, J = 17.2, 9.4, 4.8 Hz), 3.01 (1H, ddd, J = 17.3, 7.2, 4.4 Hz), 2.96−2.90 (2H, m), 2.12−1.96 (2H, m), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 172.5, 150.7, 137.4, 125.8, 123.5, 57.2, 31.0, 25.6, 25.0, 22.8; HRMS-ESI (m/z) calcd for $C_{12}H_{17}NOS_2$ $[M + H]^+$ 256.0824, found 256.0827; optical rotation $[\alpha]^{20}_D$ 122.2 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [5,6-dihydro-4H-benzo[b]-thiophen-(7E)-ylidene]-amide ((S_S)-**1g**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded the product as a yellow amorphous solid (46 mg, 55% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.19; IR (film, cm^{-1}) 1585 (C═N); ^1H NMR (400 MHz, $CDCl_3$ ppm) δ 7.43 (1H, d, J = 5.1 Hz), 6.89 (1H, d, J = 5.1 Hz), 3.19 (1H, ddd, J = 17.1, 9.1, 4.8 Hz), 2.99 (1H, ddd, J = 17.2, 7.4, 4.5 Hz), 2.84−2.72 (2H, m), 2.13−1.96 (2H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 172.8, 148.7, 137.0, 131.9, 128.3, 57.2, 31.2, 25.8, 23.9, 22.4; HRMS-ESI (m/z) calcd for $C_{12}H_{17}NOS_2$ $[M + H]^+$ 256.0824, found 256.0829; optical rotation $[\alpha]^{20}_D$ 16.7 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid chroman-(4E)-ylideneamide ((S_S)-**1h**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to 70% EtOAc/Hex afforded the product as a red oil (605 mg, 70% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.41; IR (film, cm^{-1}) 1613 (C═N), 1591 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.95 (1H, dd, J = 8.0, 1.8 Hz), 7.35 (1H, ddd, J = 8.8, 7.2, 1.7 Hz), 6.94 (1H, ddd, J = 8.2, 7.2, 1.2 Hz), 6.88 (1H, dd, J = 8.3, 1.1 Hz), 4.38−4.23 (2H, m), 3.48 (1H, ddd, J = 17.6, 9.2, 4.7 Hz), 3.32 (1H, ddd, J = 17.6, 7.0, 4.1 Hz), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 168.7, 159.2, 133.5, 126.4, 121.3, 120.7, 117.7, 65.4, 57.2, 30.2, 21.9; HRMS-ESI (m/z) calcd for $C_{13}H_{17}NO_2S$ $[M + H]^+$ 252.1053, found 252.1044; optical rotation $[\alpha]^{20}_D$ 99.5 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid thiochroman-(4E)-ylideneamide ((S_S)-**1i**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to 50% EtOAc/Hex afforded the product as a yellow amorphous solid (423 mg, 79% yield): analytical TLC on silica gel, 1:3 EtOAc/Hex, R_f = 0.40; IR (film, cm^{-1}) 1591 (C═N), 1566 (C═N), 1551 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 8.13 (1H, dd, J = 8.1, 1.5 Hz), 7.28 (1H, ddd, J = 8.3, 7.1, 1.5 Hz), 7.23−7.19 (1H, m), 7.11 (1H, ddd, J = 8.1, 7.1, 1.4 Hz), 3.66−3.59 (1H, m), 3.49 (1H, ddd, J = 17.2, 6.6, 5.1 Hz), 3.16−3.05 (2H, m), 1.28 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 172.7, 140.2, 132.7, 132.2, 129.5, 128.8, 125.6, 58.3, 32.9, 26.6, 23.0; HRMS-ESI (m/z) calcd for $C_{13}H_{17}NOS_2$ $[M + H]^+$ 268.0824, found 268.0829; optical rotation $[\alpha]^{20}_D$ 132.8 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [1-methyl-2,3-dihydro-1H-quinolin-(4E)-ylidene]-amide ((S_S)-**1j**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to EtOAc afforded the product as a yellow oil (346 mg, 60% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.25; IR (film, cm^{-1}) 1612 (C═N), 1570 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.06 (1H, dd, J = 8.0, 1.3 Hz), 7.36−7.31 (1H, m), 6.75−6.67 (2H, m), 3.44−3.35 (1H, m), 3.34−3.25 (2H, m), 3.17 (1H, ddd, J = 16.0, 8.2, 4.2 Hz), 2.95 (3H, s), 1.30 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 173.1, 150.9, 134.1, 127.9, 120.2, 117.4, 113.2, 57.5, 50.4, 39.5, 31.4, 22.7; HRMS-ESI (m/z) calcd for $C_{14}H_{20}N_2OS$ $[M + H]^+$ 265.1369, found 265.1394; optical rotation $[\alpha]^{20}_D$ 212.6 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [1-benzyl-2,3-dihydro-1H-quinolin-(4E)-ylidene]-amide ((S_S)-**1k**).* Purification of the crude product by column chromatography on silica gel using gradient elution from 40% EtOAc/Hex to 50% EtOAc/Hex afforded the product as a yellow amorphous solid (315 mg, 57% yield): analytical TLC on silica gel, 1:3 EtOAc/Hex, R_f = 0.44; IR (film, cm^{-1}) 1611 (C═N), 1569 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.08 (1H, dd, J = 8.0, 1.7 Hz), 7.36−7.31 (2H, m), 7.30−7.20 (4H, m), 6.74−6.64 (2H, m), 4.53 (2H, s), 3.51−3.36 (3H, m), 3.27−3.17 (1H, m), 1.32 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, pmm) δ 173.0, 149.8, 137.5, 134.2, 128.9, 128.1, 127.5, 126.9, 120.0, 117.2, 113.4, 57.5, 55.4, 48.5, 31.1, 22.7; HRMS-ESI (m/z) calcd for $C_{20}H_{24}N_2OS$ $[M + H]^+$ 341.1682, found 341.1707; optical rotation $[\alpha]^{20}_D$ 184.4 (c 1, CH_2Cl_2).

Experimental Procedure for Preparation of Methoxymethanol Solution in THF. To a suspension of paraformaldehyde (660 mg, 22 mmol, 1.1 equiv) in anhydrous THF (8 mL) in a glass pressure tube under an argon atmosphere was added anhydrous methanol (0.81 mL, 20 mmol, 1.0 equiv). The pressure tube was sealed, and the suspension was heated at 100 °C for 1 h, whereupon clear solution formed. After cooling the volume was adjusted to 10 mL by addition of anhydrous THF in a volumetric flask. The resulting 2 M solution of methoxymethanol in THF can be stored in a closed vessel for 2 weeks.

General Procedure for Synthesis of Imino Alcohols (S_S,*R*)-3a−k. LiHMDS (1.0 M solution in THF; 1.1 equiv) was added dropwise to a solution of appropriate imine (S_S)-**1** (1.0 equiv) in anhydrous THF (10 mL/mmol of imine **1**) under an argon atmosphere at −78 °C. After stirring for 10 min at −78 °C, the reaction was warmed to room temperature within 20 min, whereupon a solution of methoxymethanol in anhydrous THF (2 M solution; 5 equiv) was added. The resulting solution was stirred at room temperature under argon atmosphere for approximately 10 min, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase 1:1 hexanes/EtOAc). Immediately upon full conversion of the starting imine (S_S)-**1** saturated aqueous NH_4Cl solution (10 mL/mmol of imine (S_S)-**1**) was added (prolonged reaction time results in the formation of bis-hydroxymethyl side-products). Layers were separated, and aqueous layer was extracted with EtOAc (2 × 10 mL/mmol of imine (S_S)-**1**). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). The residue was purified by column chromatography on silica gel.

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-2-hydroxymethyl-3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S,R)-**3a**).* Following the General Procedure, imine (S_S)-**1a** (1.0 g, 4.0 mmol) was converted into hydroxymethyl sulfinamide (S_S,*R*)-**3a**. Purification of crude product by column chromatography using gradient elution from 30% EtOAc/hexanes to EtOAc afforded **3a** as a beige solid (1.05 g, 95% yield): analytical TLC on silica gel, 1:1 EtOAc/hexanes, R_f = 0.44. Pure material was obtained by recrystallization from hexanes/Et_2O 1:1; mp 116−118 °C; IR (film, cm^{-1}) 3359 (OH), 1610 (C═N), 1582 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 8.06 (1H, dd, J

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715−3724

= 8.0, 1.1 Hz), 7.36 (1H, td, J = 7.5, 1.4 Hz), 7.20 (2H, dd, J = 15.9, 7.9 Hz), 4.25 (1H, dd, J = 6.9, 4.1 Hz), 3.87−3.81 (1H, m), 3.80−3.75 (1H, m), 3.64−3.60 (1H, m), 3.06 (1H, ddd, J = 18.0, 13.3, 5.3 Hz), 2.74 (1H, ddd, J = 17.5, 5.4, 1.7 Hz), 2.23−2.16 (1H, m), 2.06 (1H, ddd, J = 13.4, 5.5, 4.1 Hz), 1.31 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 177.6, 141.8, 133.5, 132.5, 130.1, 128.4, 127.1, 62.1, 58.5, 43.9, 25.1, 25.0, 23.2; optical rotation $[\alpha]^{20}_D$ −83.2 (c 1, CH_2Cl_2). Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.59; H, 7.59; N, 4.92.

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-2-hydroxymethyl-indan-(1E)-ylidene]-amide ((S_S,R)-**3b**).* A modified General Procedure was employed for conversion of imine (S_S)-**1b** (94 mg, 0.4 mmol) into (S_S,R)-**3b**. Thus, after addition of LiHMDS, the reaction was warmed to −20 °C, whereupon 3 equiv of metoxymethanol was added. Purification of the crude product by column chromatography on silica gel using gradient elution from 50% EtOAc/Hex to EtOAc afforded (S_S,R)-**3b** as a beige amorphous solid (87 mg, 82% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.25; IR (film, cm^{-1}) 3385 (OH), 1617 (C═N), 1594 (C═N); NMR (400 MHz, THF-d_8, ppm) δ 7.73−7.64 (1H, m), 7.50−7.43 (1H, m), 7.42−7.37 (1H, m), 7.33−7.25 (1H, m), 4.41−4.35 (1H, m), 3.76−3.64 (2H, m), 3.55−3.46 (1H, m), 3.15 (1H, dd, J = 16.8, 6.1 Hz), 3.00 (1H, d, J = 16.8 Hz), 1.30 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 182.7, 149.7, 140.3, 133.6, 127.9, 126.8, 124.3, 66.7, 58.2, 48.9, 34.4, 23.3; HRMS-ESI (m/z) calcd for $C_{14}H_{19}NO_2S$ $[M + H]^+$ 266.1209, found 266.1212; optical rotation $[\alpha]^{20}_D$ 183.2 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-2-hydroxymethyl-6,7-dimethoxy-3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S,R)-**3d**).* Following the General Procedure, imine (S_S)-**1d** (89 mg, 0.29 mmol) was converted into (S_S,R)-**3d**. Purification of the crude product by column chromatography on silica gel using gradient elution from 30% EtOAc/Hex to EtOAc afforded (S_S,R)-**3d** as a beige amorphous solid (92 mg, 94% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.20; IR (film, cm^{-1}) 3359 (OH), 1559 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.57 (1H, s), 6.68 (1H, s), 4.34−4.26 (1H, m), 3.91−3.67 (8H, m), 3.64−3.53 (1H, m, overlapped with THF), 3.00 (1H, ddd, J = 18.0, 13.3, 5.2 Hz), 2.65 (1H, dd, J = 17.2, 5.2 Hz), 2.21−2.14 (1H, m), 2.02 (1H, tt, J = 13.2, 4.5 Hz), 1.30 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 177.3, 154.4, 149.3, 136.0, 125.9, 111.8, 110.4, 62.3, 58.1, 56.1, 55.9, 43.7, 25.5, 24.8, 23.1; HRMS-ESI (m/z) calcd for $C_{17}H_{25}NO_4S$ $[M + H]^+$ 340.1577, found 340.1586; optical rotation $[\alpha]^{20}_D$ −171.2 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-5-hydroxymethyl-6,7-dihydro-5H-benzofuran-(4E)-ylidene]-amide ((S_S,R)-**3e**).* A modified General Procedure was employed for conversion of imine (S_S)-**1e** (85 mg, 0.35 mmol) into (S_S,R)-**3e**. Thus, after addition of metoxymethanol at room temperature the reaction stirred for 60 min prior to the quench with saturated aqueous NH_4Cl solution. Separation of products by column chromatography on silica gel using gradient elution from 1% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2 provided recovered starting imine (S_S)-**1e** (38 mg, 0.16 mmol) and product (S_S,R)-**3e** as a yellow amorphous solid (42 mg, 44% yield, 89% based on recovered starting material): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.48; IR (film, cm^{-1}) 3366 (OH), 1603 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.28 (1H, m), 6.65−6.55 (1H, m), 4.70−4.57 (1H, m), 3.80−3.61 (3H, m), 2.93−2.80 (1H, m), 2.78−2.67 (1H, m), 2.25−2.03 (2H, m), 1.28 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 173.3, 160.0, 142.8, 119.8, 107.5, 62.1, 58.3, 42.5, 25.6, 22.9, 19.6; HRMS-ESI (m/z) calcd for $C_{13}H_{19}NO_3S$ $[M + H]^+$ 270.1158, found 270.1155; optical rotation $[\alpha]^{20}_D$ 80.5 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-5-hydroxymethyl-6,7-dihydro-5H-benzo[b]thiophen-(4E)-ylidene]-amide ((S_S,R)-**3f**).* A modified General Procedure was employed for conversion of imine (S_S)-**1f** (500 mg, 1.96 mmol) into (S_S,R)-**3f**. Thus, after addition of metoxymethanol at room temperature the reaction stirred for 30 min prior to the quench with saturated aqueous NH_4Cl solution. Purification of the crude product by column chromatography on silica gel using gradient elution from 50% EtOAc/Hex to EtOAc afforded (S_S,R)-**3f** as a yellow solid (524 mg, 94% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.30. Pure material was obtained by crystallization from Et_2O/hexanes: mp 70−71 °C; IR (film, cm^{-1}) 3375 (OH), 1580 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.33 (1H, d, J = 5.3 Hz), 7.18 (1H, d, J = 5.3 Hz), 4.32 (1H, dd, J = 6.3, 4.6 Hz), 3.84−3.75 (1H, m), 3.74−3.67 (1H, m), 3.61−3.56 (1H, m), 3.04 (1H, ddd, J = 17.6, 12.6, 5.0 Hz), 2.87 (1H, dd, J = 17.5, 5.5 Hz), 2.32−2.24 (1H, m), 2.17−2.06 (1H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 173.6, 149.5, 136.4, 126.1, 123.9, 62.5, 58.1, 43.4, 26.7, 23.0, 21.6; HRMS-ESI (m/z) calcd for $C_{13}H_{19}NO_2S_2$ $[M + H]^+$ 286.0930, found 286.0943; optical rotation $[\alpha]^{20}_D$ 2.8 (c 1, CH_2Cl_2). Anal. Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.71; H, 6.71; N, 4.91. Found: C, 54.80; H, 6.80; N, 4.85.

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-6-hydroxymethyl-5,6-dihydro-4H-benzo[b]thiophen-(7E)-ylidene]-amide ((S_S,R)-**3g**).* Following the General Procedure, imine (S_S)-**1g** (25 mg, 0.1 mmol) was converted into (S_S,R)-**3g**. Purification of the crude product by column chromatography on silica gel using gradient elution from 1% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2 afforded (S_S,R)-**3g** as a yellow oil (23 mg, 82% yield): analytical TLC on silica gel, 1:9 MeOH/CH_2Cl_2, R_f = 0.54; IR (film, cm^{-1}) 3366 (OH) 1576 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44 (1H, d, J = 5.0 Hz), 6.87 (1H, d, J = 5.0 Hz), 4.78−4.60 (1H, m), 3.81−3.75 (3H, m), 2.87−2.72 (2H, m), 2.27−2.18 (1H, m), 2.09−2.04 (1H, m), 1.32 (9H, s); $^{13}C\{^1H\}$ NMR (201.2 MHz, $CDCl_3$, ppm) δ 172.3, 146.1, 136.2, 132.0, 128.3, 62.0, 58.9, 42.6, 26.6, 22.9, 21.8; HRMS-ESI (m/z) calcd for $C_{13}H_{19}NO_2S_2$ $[M + H]^+$ 286.0930, found 286.0945; optical rotation $[\alpha]^{20}_D$ −120.9 (c 0.8, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-3-hydroxymethyl-chroman-(4E)-ylidene]-amide ((S_S,R)-**3h**).* Following the General Procedure, imine (S_S)-**1h** (100 mg, 0.4 mmol) was converted into (S_S,R)-**3h**. Purification of the crude product by column chromatography on silica gel using gradient elution from 30% diethylether/CH_2Cl_2 to 90% diethylether/CH_2Cl_2 afforded (S_S,R)-**3h** as a yellow amorphous solid (99 mg, 88% yield): analytical TLC on silica gel, 1:1 diethylether/CH_2Cl_2, R_f = 0.41; IR (film, cm^{-1}) 3390 (OH), 1612 (C═N), 1589 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 7.91 (1H, dd, J = 8.0, 1.7 Hz), 7.36 (1H, ddd, J = 8.3, 7.2, 1.7 Hz), 6.94 (1H, ddd, J = 8.1, c7.2, 1.1 Hz), 6.89−6.85 (1H, m), 4.54 (1H, dd, J = 11.5, 1.3 Hz), 4.34 (1H, dd, J = 7.1, 4.4 Hz), 4.24 (1H, dd, J = 11.6, 2.2 Hz), 3.87−3.79 (1H, m), 3.73−3.62 (2H, m), 1.30 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 171.0, 159.4, 134.7, 128.1, 121.9, 121.1, 118.5, 67.1, 61.1, 58.9, 44.2, 23.2; HRMS-ESI (m/z) calcd for $C_{14}H_{19}NO_3S$ $[M + H]^+$ 282.1158, found 282.1172; optical rotation $[\alpha]^{20}_D$ 11.9 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-3-hydroxymethyl-thiochroman-(4E)-ylidene]-amide ((S_S,R)-**3i**).* Following the General Procedure, imine (S_S)-**1i** (100 mg, 0.37 mmol) was converted into (S_S,R)-**3i**. Purification of the crude product by column chromatography on silica gel using gradient elution from 5% MeOH/CH_2Cl_2 to 15% MeOH/CH_2Cl_2 afforded product as a yellow oil (101 mg, 91% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.37; IR (film, cm^{-1}) 3366 (OH), 1595 (C═N), 1570 (C═N); ^1H NMR (400 MHz, THF-d_8, ppm) δ 8.12 (1H, dd, J = 8.2, 1.5 Hz), 7.30−7.25 (1H, m), 7.16−7.12 (1H, m), 7.10 (1H, ddd, J = 8.3, 7.2, 1.3 Hz), 4.20−4.03 (3H, m), 3.95−3.87 (1H, m), 3.57 (1H, dd, J = 13.9, 3.1 Hz), 2.98 (1H, dd, J = 13.9, 3.1 Hz), 1.37 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, THF-d_8, ppm) δ 173.5, 139.7, 132.4, 131.0, 130.2, 128.2, 125.2, 61.1, 58.9, 41.7, 27.9, 23.2; HRMS-ESI (m/z) calcd for $C_{14}H_{19}NO_2S_2$ $[M + H]^+$ 298.0930, found 298.0933; optical rotation $[\alpha]^{20}_D$ −22.8 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-3-hydroxymethyl-1-methyl-2,3-dihydro-1H-quinolin-(4E)-ylidene]-amide ((S_S,R)-**3j**).* Following the General Procedure, imine (S_S)-**1j** (320 mg, 1.21 mmol) was converted into (S_S,R)-**3j**. Purification of the crude product by column chromatography on silica gel using gradient elution from 2% MeOH/CH_2Cl_2 to 6% MeOH/CH_2Cl_2 afforded product as a yellow oil (321 mg, 90% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.32; IR (film, cm^{-1}) 3378 (OH), 1612 (C═N), 1569 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.94 (1H, dd, J = 8.0, 1.7 Hz), 7.32 (1H, ddd, J = 8.6, 7.1, 1.7 Hz), 6.71 (1H, ddd, J = 8.1, 7.2, 0.9 Hz),

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715−3724

6.68−6.63 (1H, m), 4.52−4.42 (1H, m), 3.91−3.77 (2H, m), 3.75−3.68 (1H, m), 3.56 (1H, dd, J = 12.7, 3.5 Hz), 3.22 (1H, dd, J = 12.7, 2.0 Hz), 2.95 (3H, s), 1.35 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 173.5, 149.4, 134.3, 128.6, 118.6, 117.4, 113.0, 61.5, 58.7, 52.7, 42.6, 39.4, 23.0; HRMS-ESI (m/z) calcd for $C_{15}H_{22}N_2O_2S$ $[M + H]^+$ 295.1475, found 295.1494; optical rotation $[\alpha]^{20}_D$ 227.7 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(R)-1-benzyl-3-hydroxymethyl-2,3-dihydro-1H-quinolin-(4E)-ylidene]-amide ((S_S,R)-**3k**).* Following the General Procedure, imine (S_S)-**1k** (221 mg, 0.65 mmol) was converted into (S_S,R)-**3k**. Purification of the crude product by column chromatography on silica gel using gradient elution from 50% EtOAc/Hex to EtOAc afforded product as a yellow amorphous solid (214 mg, 89% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.31; IR (film, cm^{-1}) 3366 (OH), 1611 (C═N), 1570 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97 (1H, dd, J = 8.0, 1.7 Hz), 7.36−7.31 (2H, m), 7.30−7.21 (4H, m, overlapped with chloroform), 6.73−6.65 (2H, m), 4.58−4.44 (3H, m), 3.94 (1H, q, J = 8.8 Hz), 3.82−3.67 (3H, m), 3.30 (1H, dd, J = 12.7, 1.5 Hz), 1.36 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 173.4, 148.5, 137.3, 134.3, 129.0, 128.9, 127.6, 126.9, 118.3, 117.5, 113.3, 61.7, 58.8, 55.4, 50.8, 42.4, 23.0; HRMS-ESI (m/z) calcd for $C_{21}H_{26}N_2O_2S$ $[M + H]^+$ 371.1788, found 371.1805; optical rotation $[\alpha]^{20}_D$ 121.5 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [(S)-2-hydroxymethyl-3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S,S)-**3a**).* A mixture of (S_S,R)-**3a** (1.1 g, 3.9 mmol) and TBAF·$3H_2O$ (2.85 g, 9.1 mmol) in anhydrous THF (50 mL) was stirred at ambient temperature for 1 h, whereupon aqueous saturated NH_4Cl solution (30 mL) was added. After stirring for 10 min, layers were separated. Aqueous layer was extracted with EtOAc (2 × 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). The residue was separated by column chromatography on silica gel using gradient elution from 50% EtOAc/Hex to EtOAc. Additional purification of the crude product by column chromatography on silica gel using gradient elution from 5% IPA/Hex to 10% IPA/Hex afforded (S_S,S)-**3a** as a yellow oil (347 mg, 32% yield): analytical TLC on silica gel, 1:1 EtOAc/Hex, R_f = 0.22; IR (film, cm^{-1}) 3340 (OH) 1610 (C═N), 1581 (C═N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09−8.05 (1H, m), 7.39−7.33 (1H, m), 7.25−7.20 (1H, m) 7.18−7.14 (1H, m), 4.44−4.29 (1H, m), 3.97−3.85 (1H, m), 3.82−3.73 (1H, m), 3.37−3.22 (1H, m), 2.98 (1H, ddd, J = 17.7, 13.1, 5.2 Hz), 2.75 (1H, ddd, J = 17.3, 5.1, 2.3 Hz), 2.23−2.14 (1H, m), 2.06 (1H, tt, J = 13.4, 4.9 Hz), 1.35 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 175.2, 140.8, 132.4, 131.9, 129.3, 127.7, 126.6, 62.3, 58.6, 39.8, 24.5, 24.2, 23.2; HRMS-ESI (m/z) calcd for $C_{15}H_{21}NO_2S$ $[M + H]^+$ 280.1366, found 280.1371; optical rotation $[\alpha]^{20}_D$ 114.5 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid [2-methylene-3,4-dihydro-2H-naphthalen-(1E)-ylidene]-amide ((S_S)-**4**).* To a solution of (S_S,R)-**3a** (100 mg, 0.36 mmol) and triethylamine (55 mg, 0.54 mmol) in anhydrous THF was added (iPrO)$_3$TiCl (104 mg, 0.4 mmol) at 0 °C under an argon atmosphere. After warming to ambient temperature and stirring for 12 h, the reaction mixture was poured into a mixture of brine (5 mL) and EtOAc (5 mL). The resulting slurry was filtered through a plug of Celite, and the filter cake was washed with EtOAc (15 mL). Organic layer from the filtrate was separated, washed with brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel using gradient elution from 10% EtOAc/Hex to 50% EtOAc/Hex afforded (S_S)-**4** as orange oil (84 mg, 88% yield): analytical TLC on silica gel, 4:10 EtOAc/Hex, R_f = 0.26; IR (film, cm^{-1}) 1605 (C═N) 1577 (C═N), 1555 (C═N); ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.24 (1H, dd, J = 8.0, 1.2 Hz), 7.44−7.35 (1H, m), 7.32−7.24 (1H, m), 7.22−7.15 (1H, m), 5.89 (1H, s), 5.65 (1H, s), 3.10−2.99 (2H, m), 2.78−2.60 (2H, m), 1.32 (9H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 174.5, 141.8, 141.5, 134.0, 132.3, 129.0, 127.4, 126.9, 121.9, 56.8, 34.1, 32.2, 22.5; HRMS-ESI (m/z) calcd for $C_{15}H_{19}NOS$ $[M + H]^+$ 262.1266, found 262.1261; optical rotation $[\alpha]^{20}_D$ 61.3 (c 1, CH_2Cl_2).

General Procedure A for Reduction of *tert*-Butanesulfinylketimines (S_S,R)-3 with BH_3-THF. Sulfinylketimine (S_S,R)-**3** (1.0 equiv) was dissolved in anhydrous THF (30 mL/mmol of imine **3**) and cooled to −15 °C under argon atmosphere. Borane-THF complex (1 M solution in THF, 1.2 equiv) was diluted with 3 volumes of anhydrous THF and added slowly to a solution of ketimine (S_S,R)-**3** within 3 h by syringe pump at −15 °C. After stirring for 1 h at −15 °C, the reaction was quenched by addition of MeOH. The mixture was then warmed to ambient temperature, stirred for 15 min and concentrated (rotary evaporator). The residue was suspended in THF (5 mL/mmol of imine (S_S,R)-**3**) and filtered through a plug of Celite. Filtrate was dried over Na_2SO_4 and concentrated (rotary evaporator). Product was purified by column chromatography on silica gel or by recrystallization.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1S,2R)-2-hydroxymethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amide ((S_S,R,S)-**5a**).* Following the General Procedure A for the reduction, sulfinylketimine (S_S,R)-**3a** (500 mg, 1.8 mmol) was converted into (S_S,R,S)-**5a**. Purification of the crude solid product by recrystallization from 1:1 THF/heptane afforded (S_S,R,S)-**5a** as a colorless needles (438 mg, 87% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.32; mp 123.5−124.5 °C; IR (film, cm^{-1}) 3445 (OH), 3160 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.59−7.53 (1H, m), 7.22−7.15 (2H, m), 7.12−7.06 (1H, m), 4.47 (1H, dd, J = 8.1, 4.6 Hz), 4.06 (1H, d, J = 4.5 Hz), 3.85−3.77 (1H, m), 3.71−3.62 (1H, m), 2.93−2.83 (1H, m), 2.77 (2H, dt, J = 16.8, 5.2 Hz), 2.33 (1H, s), 2.00−1.91 (1H, m), 1.63−1.52 (1H, m), 1.24 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 137.9, 136.4, 129.7, 129.1, 127.4, 126.5, 66.1, 58.0, 56.3, 43.6, 28.2, 23.9, 22.9; optical rotation $[\alpha]^{20}_D$ 121.4 (c 1, CH_2Cl_2). Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98. Found: C, 63.87; H, 8.33; N, 4.90.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1S,2R)-2-hydroxymethyl-indan-1-yl)-amide ((S_S,R,S)-**5b**).* Following the General Procedure A, ketimine (S_S,R)-**3b** (79 mg, 0.30 mmol) was reduced to (S_S,R,S)-**5b**. Crystallization from THF/heptane (1:1) afforded product as a crystalline material (70 mg, 88% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.29; mp 158.8−159.4 °C (dec.); IR (film, cm^{-1}) 3279 (OH), 3206 (NH), 3172 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.53−7.49 (1H, m), 7.25−7.18 (3H, m), 4.74 (1H, t, J = 7.9 Hz), 3.92 (1H, dd, J = 10.9, 5.2 Hz), 3.86−3.79 (2H, m), 3.09−2.99 (1H, m), 2.79−2.60 (3H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 143.1, 141.7, 128.2, 127.1, 125.0, 124.9, 64.8, 64.4, 56.3, 52.0, 33.3, 22.9; optical rotation $[\alpha]^{20}_D$ 13.8 (c 1, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.84; H, 8.17; N, 5.12.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1S,2R)-2-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-amide ((S_S,R,S)-**5d**).* Following the General Procedure A, ketimine (S_S,R)-**3d** (209 mg, 0.61 mmol) was reduced to (S_S,R,S)-**5d**. Crystallization from THF/heptane (1:1) afforded product as a crystalline solid (191 mg, 91% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.28; mp 142.7−143.5 °C; IR (film, cm^{-1}) 3418 (OH), 3274 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.14 (1H, s), 6.55 (1H, s), 4.40 (1H, dd, J = 8.1, 5.2 Hz), 4.05−3.97 (1H, m), 3.84 (3H, s), 3.83 (3H, s), 3.82−3.75 (1H, m), 3.71−3.63 (1H, m), 2.80 (1H, ddd, J = 15.7, 10.0, 5.2 Hz), 2.73−2.60 (2H, m), 2.29−2.19 (1H, m), 1.97−1.90 (1H, m), 1.60−1.49 (1H, m), 1.25 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 148.3, 147.7, 130.1, 128.2, 112.3, 111.2, 66.1, 58.2, 56.3, 56.1, 55.9, 44.0, 27.9, 24.3, 23.0; optical rotation $[\alpha]^{20}_D$ 118.7 (c 1, CH_2Cl_2). Anal. Calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 59.65; H, 8.07; N, 4.00.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((4S,5R)-5-hydroxymethyl-4,5,6,7-tetrahydro-benzofuran-4-yl)-amide ((S_S,S,R)-**5e**).* Following the General Procedure A, ketimine (S_S,R)-**3e** (229 mg, 0.85 mmol) was reduced to (S_S,R,S)-**5e**. Crystallization from THF/heptane (1:1) afforded product as a crystalline material (203 mg, 88% yield): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.31; mp 139.3−139.8 °C; IR (film, cm^{-1}) 3393 (OH), 3245 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26−7.24 (1H, m), 6.45 (1H, d, J = 1.8 Hz), 4.30−4.24 (1H, m), 3.96−3.90 (1H, m), 3.85−3.77 (1H, m),

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715−3724

3.75−3.65 (1H, m), 2.92−2.56 (3H, m), 2.19−2.09 (1H, m), 2.01−1.94 (1H, m), 1.69−1.56 (1H, m), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 152.2, 141.4, 118.7, 110.2, 65.9, 56.2, 54.8, 44.6, 25.0, 22.9, 22.2; optical rotation $[\alpha]^{20}_D$ 61.7 (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{13}H_{21}NO_3S$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.30; H, 7.99; N, 5.01.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((4S,5R)-5-hydroxymethyl-4,5,6,7-tetrahydro-benzo[b]thiophen-4-yl)-amide ((S_S,R,S)-**5f**).* Following the General Procedure A, ketimine (S_S,R)−**3f** (500 mg, 1.75 mmol) was reduced to (S_S,R,S)-**5f**. Crystallization from MeOH/EtOAc/heptane (1:3:3) afforded product as a colorless needles (448 mg, 89% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.26; mp 138.5−139.0 °C; IR (film, cm^{-1}) 3411 (OH), 3207 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.10 (1H, d, *J* = 5.3 Hz), 7.07 (1H, d, *J* = 5.3 Hz), 4.40−4.34 (1H, m), 4.10−4.04 (1H, m), 3.88−3.81 (1H, m), 3.70 (1H, dt, *J* = 11.0, 7.2 Hz), 2.86−2.80 (2H, m), 2.74−2.61 (1H, m), 2.32−2.21 (1H, m), 2.05−1.96 (1H, m), 1.65 (1H, dddd, *J* = 13.3, 11.0, 9.0, 6.8 Hz), 1.25 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 138.7, 136.0, 127.7, 122.9, 66.1, 56.9, 56.4, 44.1, 25.9, 24.1, 22.9; optical rotation $[\alpha]^{20}_D$ 98.4 (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{13}H_{21}NO_2S_2$: C, 54.32; H, 7.36; N, 4.87. Found: C, 54.56; H, 7.50; N, 4.77.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4S)-3-hydrox2ymethyl-chroman-4-yl)-amide ((S_S,R,S)-**5h**).* Following the General Procedure A, ketimine (S_S,R)-**3h** (202 mg, 0.72 mmol) was reduced to (S_S,R,S)-**5h**. Crystallization from THF/heptane (1:1) afforded product as a crystalline solid (193 mg, 95% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.28; mp 148.8−149.6 °C; IR (film, cm^{-1}) 3375 (OH), 3191 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 (1H, dd, *J* = 7.7, 1.4 Hz), 7.21−7.16 (1H, m), 6.96−6.90 (1H, m), 6.82 (1H, dd, *J* = 8.2, 1.0 Hz), 4.46 (1H, t, *J* = 4.0 Hz), 4.28−4.22 (1H, dd, *J* = 11.2, 2.9 Hz), 4.22−4.16 (1H, m), 3.75−3.61 (2H, m), 3.58−3.52 (1H, m), 2.60−2.45 (1H, br s), 2.35−2.27 (1H, m), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 154.9, 130.7, 129.6, 121.5, 121.4, 117.2, 63.9, 61.2, 56.1, 50.8, 41.8, 22.8; HRMS-ESI (*m*/*z*) calcd for $C_{14}H_{21}NO_3S$ $[M + H]^+$ 284.1315, found 284.1326; optical rotation $[\alpha]^{20}_D$ 8.0 (*c* 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4S)-3-hydroxymethyl-thiochroman-4-yl)-amide ((S_S,R,S)-**5i**).* Following the General Procedure A, ketimine (S_S,R)-**3i** (199 mg, 0.67 mmol) was reduced to (S_S,R,S)-**5i**. Crystallization from THF/heptane (1:1) afforded product as a crystalline solid (186 mg, 93% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.24; mp 157.4−158.2 °C; IR (film, cm^{-1}) 3338 (OH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37−7.31 (1H, m), 7.17−7.03 (3H, m), 4.48 (1H, t, *J* = 3.1 Hz), 3.74−3.64 (1H, m), 3.62−3.53 (1H, m), 3.39 (1H, dd, *J* = 12.8, 3.3 Hz), 3.30−3.23 (1H, m), 2.93 (1H, dd, *J* = 12.8, 4.2 Hz), 2.60−2.53 (1H, m), 2.22−2.12 (1H, m), 1.21 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 133.6, 132.4, 131.1, 128.5, 126.9, 125.1, 61.9, 55.9, 53.1, 39.3, 23.6, 22.8; optical rotation $[\alpha]^{20}_D$ −51.7 (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_2S_2$: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.16; H, 7.19; N, 4.52.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4S)-3-hydroxymethyl-1-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amide ((S_S,R,S)-**5j**).* Following the General Procedure A, ketimine (S_S,R)−**3j** (270 mg, 0.92 mmol) was reduced to (S_S,R,S)-**5j**. Purification of the crude product by column chromatography on silica gel using gradient elution from 3% $MeOH/CH_2Cl_2$ to 6% $MeOH/CH_2Cl_2$ afforded product as a yellow oil (250 mg, 92% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.30; IR (film, cm^{-1}) 3390 (OH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.27 (1H, m), 7.21−7.13 (1H, m), 6.73−6.66 (1H, m), 6.66−6.60 (1H, m), 4.38 (1H, s), 3.61−3.54 (2H, m), 3.48 (1H, s), 3.39−3.32 (2H, m), 3.21−3.12 (1H, m), 2.92 (3H, s), 2.32−2.24 (1H, m), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 146.3, 130.9, 129.4, 120.6, 117.1, 111.6, 62.6, 55.7, 52.7, 48.1, 41.1, 39.3, 22.9; HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{24}N_2O_2S$ $[M + H]^+$ 297.1631, found 297.1622; optical rotation $[\alpha]^{20}_D$ −57.0 (*c* 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4S)-1-benzyl-3-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amide ((S_S,R,S)-**5k**).* Following the General Procedure A, ketimine (S_S,R)−**3k** (201 mg, 0.54 mmol) was reduced to (S_S,R,S)-**5k**. Purification of the crude product by column chromatography on silica gel using gradient elution from 2% $MeOH/CH_2Cl_2$ to 5% $MeOH/CH_2Cl_2$ afforded product as a yellow amorphous solid (190 mg, 94% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.24; mp 169.4−170.6 °C; IR (film, cm^{-1}) 3390 (OH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34−7.29 (3H, m), 7.27−7.22 (3H, m), 7.08 (1H, ddd, *J* = 8.6, 7.3, 1.6 Hz), 6.69−6.64 (1H, m), 6.63−6.57 (1H, m), 4.52−4.48 (2H, m), 4.46−4.42 (1H, m), 3.62−3.57 (2H, m), 3.54 (1H, dd, *J* = 11.9, 3.4 Hz), 3.36 (1H, d, *J* = 2.4 Hz), 3.31−3.24 (1H, m), 2.37−2.29 (1H, m), 2.27−2.06 (1H, br s), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 145.3, 138.6, 131.1, 129.5, 128.8, 127.2, 126.7, 119.9, 117.0, 111.7, 62.4, 55.7, 55.2, 52.6, 46.2, 40.5, 22.9; HRMS-ESI (*m*/*z*) calcd for $C_{21}H_{28}N_2O_2S$ $[M + H]^+$ 373.1944, found 373.1934; optical rotation $[\alpha]^{20}_D$ −60.1 (*c* 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1S,2S)-2-hydroxymethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amide ((S_S,S,S)-**6a**).* Following the General Procedure A, ketimine (S_S,S)-**3a** (80 mg, 0.29 mmol) was reduced to (S_S,S,S)-**6a**. Crystallization from THF/heptane (1:1) afforded product as a colorless prisms (64 mg, 80% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.33; IR (film, cm^{-1}) 3261 (OH) 3156 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.55−7.52 (1H, m), 7.22−7.17 (2H, m), 7.11−7.09 (1H, m) 4.72 (1H, t, *J* = 4.6 Hz), 3.85−3.80 (1H, m), 3.69−3.64 (1H, m), 3.33−3.23 (1H, m), 2.89 (1H, ddd, *J* = 17.2, 5.9, 2.4 Hz), 2.79 (1H, ddd, *J* = 17.2, 11.5, 6.1 Hz), 2.07−1.99 (1H, m), 1.93−1.83 (1H, m), 1.78−1.72 (1H, m), 1.71−1.59 (1H, m), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 137.1, 136.8, 131.3, 129.1, 127.9, 126.8, 64.3, 56.5, 54.4, 42.4, 28.9, 23.0, 20.3; HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{23}NO_2S$ $[M + H]^+$ 282.1522, found 282.1547; optical rotation $[\alpha]^{20}_D$ −17.3 (*c* 0.8, CH_2Cl_2).

General Procedure B for Reduction of *tert*-Butanesulfinylketimines (S_S,R)-3 with $LiBHEt_3$. Sulfinylketimine (S_S,R)-**3** (1.0 equiv) was dissolved in anhydrous THF (10 mL/mmol of imine **3**) and cooled to −78 °C under argon atmosphere. $LiBHEt_3$ (1 M solution in THF; 1.2 equiv) was added slowly at a rate to keep the temperature below −75 °C. After stirring at −78 °C for 30 min, the mixture was gradually warmed to room temperature and left to stir for 12 h, whereupon it was quenched by addition of MeOH (5 mL/mmol of starting imine **3**). After stirring for 15 min, the mixture was concentrated to dryness, and the residue was suspended in $CHCl_3$ (5 mL/mmol of starting imine **3**) and filtered through a plug of Celite. Filtrate was dried over Na_2SO_4, filtered, and concentrated (rotary evaporator). The residue was purified by column chromatography on silica gel.

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1R,2R)-2-hydroxymethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amide ((S_S,R,R)-**7a**).* Following the General Procedure B for the reduction, sulfinylketimine (S_S,R)-**3a** (50 mg, 0.18 mmol) was converted to (S_S,R,R)-**7a**. Purification of the crude product by reverse phase column chromatography using 25% MeCN/aq. 0.1% HCOOH eluent afforded product as a colorless oil (31 mg, 62%): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.34; IR (film, cm^{-1}) 3375 (OH) 3254 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.28 (1H, m), 7.22−7.15 (2H, m), 7.13−7.08 (1H, m), 4.66 (1H, dd, *J* = 9.4, 4.5 Hz), 4.27−3.90 (2H, m), 3.82 (1H, dd, *J* = 11.9, 4.1 Hz), 3.74 (1H, dd, *J* = 11.9, 9.2 Hz), 2.89−2.74 (2H, m), 2.30−2.22 (1H, m), 1.79−1.72 (1H, m), 1.55 (1H, dddd, *J* = 13.7, 11.3, 10.3, 6.2 Hz), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 137.5, 136.3, 130.0, 129.1, 127.6, 126.2, 63.5, 57.2, 56.5, 40.9, 28.4, 23.0, 21.5; HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{23}NO_2S$ $[M + H]^+$ 282.1528, found 282.1510; optical rotation $[\alpha]^{20}_D$ 37.8 (*c* 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((1R,2R)-2-hydroxymethyl-indan-1-yl)-amide ((S_S,R,R)-**7b**).* Following the General Procedure B, ketimine (S_S,R)-**3b** (40 mg, 0.15 mmol) was reduced to (S_S,R,R)-**7b**. Purification of the crude product by column chromatography on silica gel using 6% $MeOH/CH_2Cl_2$ as eluent afforded product as a colorless oil (30 mg, 75% yield): analytical TLC on silica gel, 5:95 $MeOH/CH_2Cl_2$, R_f = 0.33; IR (film, cm^{-1}) 3367 (OH), 3246 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.18 (4H, m), 4.93 (1H, dd, *J* = 10.5,

dx.doi.org/10.1021/jo500506u | J. Org. Chem. 2014, 79, 3715−3724

7.0 Hz), 4.19−4.10 (1H, m), 4.09−3.94 (1H, br s), 3.89 (1H, dd, J = 12.0, 2,9 Hz), 3.73 (1H, dd, J = 11.5, 9.8 Hz), 2.99−2.92 (1H, m), 2.91−2.83 (1H, m), 2.71 (1H, dd, J = 15.4, 6.4 Hz), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 143.3, 141.9, 128.5, 127.0, 125.0, 64.4, 62.1, 56.5, 45.7, 33.6, 23.0; HRMS-ESI (m/z) calcd for $C_{14}H_{21}NO_2S$ $[M + H]^+$ 268.1366, found 268.1369; optical rotation $[\alpha]^{20}_D$ −54.8 (c 0.7, CH_2Cl_2)

*(S_S)-2-Methyl-propane-2-sulfinic acid ((4R,5R)-5-hydroxymethyl-4,5,6,7-tetrahydro-benzo[b]thiophen-4-yl)-amide ((S_S,R,R)-**7f**).* Following the General Procedure B, ketimine (S_S,R)-**3f** (50 mg, 0.18 mmol) was reduced to (S_S,R,R)-**7f**. Purification of the crude product by reverse phase column chromatography using 25% MeCN/aq. 0.1% HCOOH as eluent afforded product as a colorless oil (25 mg, 50%): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.32; IR (film, cm^{-1}) 3359 (OH), 3246 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.08 (1H, d, J = 5.2 Hz), 6.86 (1H, d, J = 5.2 Hz), 4.63 (1H, dd, J = 9.6, 4.6 Hz), 4.00 (1H, d, J = 9.7 Hz), 3.91−3.64 (3H, m), 2.87 (1H, ddd, J = 16.8, 5.5, 3.7 Hz), 2.73 (1H, ddd, J = 16.2, 10.0, 5.7 Hz), 2.28−2.18 (1H, m), 1.83−1.74 (1H, m), 1.68−1.56 (1H, m), 1.24 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 137.9, 136.6, 127.3, 123.2, 63.1, 56.6, 54.4, 41.1, 24.4, 22.9, 22.6; HRMS-ESI (m/z) calcd for $C_{13}H_{21}NO_2S_2$ $[M + H]^+$ 288.1092, found 288.1078; optical rotation $[\alpha]^{20}_D$ 46.1 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4R)-3-hydroxymethyl-chroman-4-yl)-amide ((S_S,R,R)-**7h**).* Following the General Procedure B, ketimine (S_S,R)-**3h** (50 mg, 0.18 mmol) was reduced to (S_S,R,R)-**7h**. Purification of the crude product by reverse phase column chromatography using 25% MeCN/aq. 0.1% HCOOH as eluent afforded product as a colorless oil (30 mg, 60%): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.32; IR (film, cm^{-1}) 3246 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.27 (1H, m), 7.20−7.16 (1H, m), 6.95−6.88 (1H, m), 6.81 (1H, dd, J = 8.2, 0.9 Hz), 4.69 (1H, dd, J = 9.6, 4.7 Hz), 4.55−4.46 (1H, m), 4.22 (1H, dd, J = 11.5, 2.8 Hz), 4.05 (1H, dd, J = 11.5, 8.1 Hz), 3.97 (1H, dd, J = 12.0, 3.7 Hz), 3.90−3.83 (1H, m), 3.20−2.62 (1H, br s), 2.55−2.48 (1H, m), 1.27 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 154.1, 129.7, 129.4, 122.7, 120.9, 117.0, 65.6, 61.0, 56.9, 54.8, 39.6, 23.0; HRMS-ESI (m/z) calcd for $C_{14}H_{21}NO_3S$ $[M + H]^+$ 284.1315, found 284.1299; optical rotation $[\alpha]^{20}_D$ 28.7 (c 1, CH_2Cl_2).

*(S_S)-2-Methyl-propane-2-sulfinic acid ((3R,4R)-3-hydroxymethyl-thiochroman-4-yl)-amide ((S_S,R,R)-**7i**).* Following the General Procedure B, ketimine (S_S,R)-**3i** (30 mg, 0.10 mmol) was reduced to (S_S,R,R)-**7i**. Purification of the crude product by reverse phase column chromatography using 25% MeCN/aq. 0.1% HCOOH as eluent afforded product as a colorless oil (22 mg, 73%): analytical TLC on silica gel, 5:95 MeOH/CH_2Cl_2, R_f = 0.32; IR (film, cm^{-1}) 3246 (NH); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32−7.28 (1H, m), 7.18−7.11 (2H, m), 7.09−7.03 (1H, m), 4.68 (1H, dd, J = 7.8, 3.1 Hz,), 4.52−4.38 (1H, m), 4.03−3.92 (1H, m), 3.90−3.80 (1H, m), 3.80−3.55 (1H, br s), 3.07−2.99 (1H, m), 2.93 (1H, dd, J = 12.7, 4.1 Hz), 2.52−2.45 (1H, m) 1.21 (9H, s); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, ppm) δ 133.7, 132.9, 130.7, 128.4, 126.7, 124.3, 64.2, 57.0, 56.4, 39.6, 24.6, 22.9; HRMS-ESI (m/z) calcd for $C_{14}H_{21}NO_2S_2$ $[M + H]^+$ 300.1092, found 300.1068; optical rotation $[\alpha]^{20}_D$ 87.4 (c 1, CH_2Cl_2).

■ ASSOCIATED CONTENT

Supporting Information

DFT computed relative energies of (S_S,R)-**3a** and its C2-epimer (S_S,S)-**3a**; X-ray crystallographic data for hydroxymethyl ketimines (E)-(S_S,R)-**3a**,**f** and sulfinamides (S_S,R,S)-**5a**,**f**,**h** and (S_S,S,S)-**6a** (CIF files); copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by European Social Fund (No. 2013/0026/1DP/1.1.1.2.0/13/APIA/VIAA/006). Authors thank Artis Kinens for DFT calculations, Dr. Sergey Belyakov for X-ray crystallographic analysis, and Dr. Ilva Nakurte (Universty of Latvia) for HRMS analyses.

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(14) A 0.1 M solution of anhydrous monomeric formaldehyde in THF was prepared by thermal cracking of paramormaldehyde, followed by condensation of gaseous HCHO in anhydrous THF; see Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704−704.

(15) Acid titration of formaldehyde-sodium sulfite adduct in aqueous medium was used; see Supporting Information page S2 for details.

(16) Methoxymethanol was prepared in situ by heating paraform in a mixture of anhydrous methanol and THF; see Experimental Section for details.

(17) Anhydrous monomeric formaldehyde has also been generated in situ from *N*-hydroxymethyl phthalimide or benzotriazolylmethanol; see Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. *Org. Lett.* **2007**, *9*, 1165−1167.

(18) See the Supporting Information for details.

(19) Ketimine (S_S,*S*)-**3a** was obtained by epimerization of diastereomerically pure (S_S,*R*)-**3a** with tetrabutylammonium fluoride, followed by chromatographic separation of diastereomers; see the Supporting Information for details.

(20) Similar four-membered chelates have been proposed for lithium *N*-sulfinyl enamides: (a) Wang, J.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X.; Liu, H. *Org. Lett.* **2013**, *15*, 1508−1511. (b) Zhao, C.-H.; Liu, L.; Wang, D.; Chen, Y.-J. *Eur. J. Org. Chem.* **2006**, *2006*, 2977−2986. (c) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 3792−3797.

(21) (a) Martjuga, M.; Shabashov, D.; Belyakov, S.; Liepinsh, E.; Suna, E. *J. Org. Chem.* **2010**, *75*, 2357−2368. (b) Martjuga, M.; Belyakov, S.; Liepinsh, E.; Suna, E. *J. Org. Chem.* **2011**, *76*, 2635−2647.

(22) Poor yields (5−10%) of hydroxymethylation products were observed in the reaction of lithium enamide (S_S)-**2a** with other aldehydes such as PhCHO and acetaldehyde. Although the yields could be improved to 18% for PhCHO and to 56% for MeCHO by using a large excess (>10 equiv) of the corresponding aldehyde, the developed hydroxymethylation conditions do not provide synthetically useful outcome with aldehydes other than formaldehyde. It should be also noted that the reaction of (S_S)-**2a** with acetaldehyde proceeded with excellent diastereoselectivity with respect to the a-center (99:1 dr), whereas the b-center was formed with poor diastereoselectivity (2:1 dr).