Stereocontrolled Synthesis of 1,3-Amino Alcohols by Reduction of Substituted 2-[1-[(tert-Butylsulfinyl)amino]alkyl]cyclohexanones
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Abstract: Assembly of diethylzinc, cyclohex-2-en-1-one, and a chiral N-tert-butylsulfinyl imine in the presence of an appropriate phosphoramidite ligand yields a β-sulfinylamino cyclohexanone, which on reduction with sodium borohydride or lithium triethylborohydride provides access to a wide range of enantiomerically pure N-tert-butylsulfinyl 1,3-amino alcohols with five stereogenic centers.

Key words: amino alcohols, ketones, reduction, phosphoramidites, multicomponent reaction, stereoselectivity

Chiral amino alcohols are useful as building blocks in asymmetric synthesis, where they can function as ligands or auxiliaries. Although less common than 1,2-amino alcohols, 1,3-amino alcohols have been used extensively in asymmetric synthesis.1

After the seminal contribution of He and Eliel in 1987,2 more work has been published on the chemistry of (–)-8-aminomenthol [(1S,2S,5R)-2-(2-aminopropan-2-yl)-5-methylcyclohexanol] and its derivatives than on any other single 1,3-amino alcohol.1 This is probably because such compounds can be readily prepared in three steps from natural (+)-pulegone (Scheme 1, a). To the best of our knowledge, and despite the prevalence of (–)-8-aminomenthol as a source of chirality in asymmetric synthesis, no work on any other stereoisomer has been reported. Undoubtedly, this is because of the lack of affordable enantioselectively pure precursors and routes for the efficient syntheses of these chiral building blocks.4

We have recently reported that enantiomerically pure β-amino cycloalkanones can be readily prepared by trapping by chiral N-tert-butylsulfinyl imines of the chiral enolates formed by asymmetric conjugate addition of dialkylzinc reagents to cyclic enones.5 These enantiomerically pure β-amino cycloalkanones, which contain three consecutive stereogenic centers, offer a good platform for the stereo-selective synthesis of syn- and anti-1,3-amino alcohols (Scheme 1, b).

Although a broad range of substrates could be used for the preparation of β-aminocycloalkanones by our tandem procedure, we selected diethylzinc, cyclohex-2-en-1-one, and sulfinimine 2 (or its enantiomer ent-2) for the sake of simplicity in this study. In our previous study, we used the phosphoramidite ligand L2, because it permits the generation of highly enantioenriched enolates (ee > 98%) through a copper-catalyzed addition of dialkylzinc reagents to cyclic enones.6 We decided to re-examine the tandem reaction by using phosphoramidite ligand L1, in which the binaphthyl moiety is the sole source of chirality, and which has been reported to afford only modest enantioselectivity (60% ee) in the conjugate addition.7

Our studies in which we used ligand L1 in the tandem copper-catalyzed addition of diethylzinc to cyclohex-2-en-1-one and Mannich reaction with sulfinimine 2 (or ent-2) are summarized in Table 1. Interestingly, better diastereoselection was obtained when the (R)-sulfinimine 2 was added before the conjugate addition occurred (entries 1 and 3), and the opposite was observed with ent-2 (entries 2 and 4). A greater excess of the enolate afforded similar results, suggesting that kinetic resolution of the homo-chiral enolate is not a good explanation for this matched/mismatched combination. It is more likely that the (R)-sulfinimine 2 cooperates with phosphoramidite Sa-L1 in the copper-catalyzed addition of diethylzinc; however, we lack firm evidence to support this hypothesis. Importantly, diastereoisomers 3a and 3b could be easily separated by normal flash chromatography (FC). Nevertheless, the use of the phosphoramidite ligand L2 is still more practical, because compound 3a is obtained as a single isomer (entry 5). Unfortunately, a rather low selectivity was observed when the combination of ligand L2 and sulfinimine 2 (or its enantiomer ent-2) for the sake of simplicity in this study. In our previous study, we used the phosphoramidite ligand L2, because it permits the generation of highly enantioenriched enolates (ee > 98%) through a copper-catalyzed addition of dialkylzinc reagents to cyclic enones.6 We decided to re-examine the tandem reaction by using phosphoramidite ligand L1, in which the binaphthyl moiety is the sole source of chirality, and which has been reported to afford only modest enantioselectivity (60% ee) in the conjugate addition.7
and sulfinimine ent-2 was used, compounds ent-3b and ent-3c being obtained as an inseparable 71:29 mixture (entry 6). The stereochemical information present in cyclohexanones 3 suggests that a stereoselective reduction is possible. However, because control can be exerted by the cyclohexanone moiety as well as by the sulfinylamino group, the stereochemical outcome was not completely apparent at the outset of this work. Moreover, the repulsive gauche interaction between the C(2) and C(3) substituents of the cyclohexanone moiety could favor the diaxial conformer over the usual diequatorial one, further complicating the result.

Reduction of compound 3a with sodium borohydride gave the crystalline amino alcohol 4a exclusively in almost quantitative yield. When the 71:29 mixture of compounds 3b and 3c was reduced by sodium borohydride, diastereoisomers 4c and 4d were isolated as pure compounds after FC. To confirm the stereochemical assignment, the sulfinyl group in compounds 4a and 4d was oxidized with 3-chloroperoxybenzoic acid to give the sulphonamides 4f and ent-4f, respectively. This result clearly supports the view that the formation of the minor β-amino cycloalkanone 3c is a consequence of poor diastereomeric control in the reaction of the chiral enolate with the chiral sulfinimine (Scheme 2).

Interestingly, reduction of 3a with lithium triethylborohydride at −78 °C gave the syn-amino alcohol 4b, whereas anti-amino alcohols are formed preferentially by reduction of acyclic N-sulfinyl β-amino ketones. More surprisingly, when the mixture of compounds 3b + 3c was submitted to reduction under the same conditions, syn-amino alcohols 4e and 4e were isolated after FC (Scheme 2).

Table 1  Syntheses of 2-[(tert-Butylsulfinyl)amino]methyl]cyclohexanone 3a–c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Method</th>
<th>Imine</th>
<th>Products (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>A</td>
<td>2</td>
<td>ent-3a + ent-3b (77:23)</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>A</td>
<td>ent-2</td>
<td>ent-3a + ent-3b + ent-3c (27:67:6)</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>B</td>
<td>2</td>
<td>3a + 3b (86:14)</td>
</tr>
<tr>
<td>4</td>
<td>L1</td>
<td>B</td>
<td>ent-2</td>
<td>ent-3a, ent-3b, ent-3c (49:48:3)</td>
</tr>
<tr>
<td>5</td>
<td>L2</td>
<td>B</td>
<td>2</td>
<td>3a (&gt;98)</td>
</tr>
<tr>
<td>6</td>
<td>L2</td>
<td>B</td>
<td>ent-2</td>
<td>ent-3b + ent-3c (71:29)</td>
</tr>
</tbody>
</table>

Method A: The sulfinimine (2) or ent-2 was added 5 h after the addition of Et2Zn.
Method B: Et2Zn was added to the mixture of cyclohex-2-en-1-one, ligand, Cu(OTf)2, and sulfinimine 2.
Relative amounts of each diastereomeric product as determined by 1H NMR of the crude reaction mixture.

Figure 1  X-ray crystal structure of compound 4a

Importantly, because both enantiomers of the phosphoramidite ligand and tert-butylsulfinamides were available, enantiomers of amino alcohols 4a–e were also prepared from ent-L2 and ent-2 (see below). Moreover, the N-sulfinyl group can be easily oxidized to a sulphonamide group (e.g., 4f) or removed with methanolic hydrogen chloride to give the free amine, which can be further alkylated. We hope that this ability to modify the electronic nature of the amino group could be useful in finding future applications.

The absolute configuration of compound 4a was determined by single-crystal X-ray analysis. The observed stereochemistry was consistent with an axial hydride delivery from sodium borohydride to the diequatorial conformer of cyclohexanone 3a (Figure 1).
for these chiral 1,3-amino alcohols in asymmetric synthesis.

In conclusion, the stereoselective reduction of easily available 2-{[(tert-butylsulfinyl)amino]alkyl}cyclohexanones with sodium borohydride or lithium triethylborohydride gives access to a wide range of enantiomerically pure 1,3-amino alcohols. Only two synthetic operations are required to build these amino alcohols, which have five stereogenic centers.

TLC was performed on Merck silica gel 60 F254, using aluminum plates and visualized by staining with phosphomolybdic acid. Flash chromatography (FC) was carried out on hand-packed columns of Merck silica gel 60 (0.040–0.063 mm) with hexane–EtOAc as the eluent. IR spectra were recorded on a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus using open glass capillaries and are reported without corrections. 1H NMR spectra were recorded with a Bruker AC-300 using CDCl3 (δ = 7.27) or CD2OD (δ = 4.84) as the solvent and internal standard. 13C NMR spectra were recorded with a Bruker 75-MHz spectrometer, and DEPT-135 experiments were performed to assign the CH, CH2, and CH3 protons. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HRMS (El) were recorded on a Finnigan MAT 95S. N-Sulfinyl imine 2 and phosphoramidite ligands L1 and L2 were prepared according to the reported procedures. The properties of known compounds matched those reported in the corresponding references.

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(R)-N-{[(1R)-1-[(1R,2S)-2-Ethyl-6-oxocyclohexyl]-3-phenylpropyl]-2-methylpropane-2-sulfonamide (3a) and (R)-N-{[(1R)-1-[(1R,2S)-2-Ethyl-6-oxocyclohexyl]-3-phenylpropyl]-2-methylpropane-2-sulfonamide (3b); Typical Procedure A

C2H5OH (22 mg, 0.06 mmol), phosphoramidite L1 (66 mg, 0.12 mmol), and enone 1 (230 mg, 240 μL, 2.40 mmol) were suspended in CH2Cl2 (8.0 mL) and stirred at r.t. for 15 min before cooling to −40 °C. A 1.0 M soln of Et2Zn in toluene (9.0 mL, 9 mmol) was added dropwise and the mixture was allowed to reach −20 °C while being stirred for 5 h. A soln of sulfimine 2 (482 mg, 2.00 mmol) in CH2Cl2 (6.0 mL) was then added dropwise, and the mixture was stirred overnight at −20 °C. The reaction was quenched at −20 °C by addition of a sat. soln of NH4Cl in 1:1 H2O–MeOH (3.0 mL), and the mixture was stirred for 15 min at r.t. The resulting precipitate was filtered off on a short pad of Celite and, after evaporation of solvents, the crude sample was analyzed by 1H NMR spectroscopy to determine the imine conversion and the diastereomeric ratio of the products. The sample was then purified by column chromatography (silica gel, EtOAc–hexane, 75:25 to 70:30) to give pure 3a and 3b as colorless oils; yield: 3a: 474 mg (66%); 3b: 144 mg (20%).

Compounds 4a: [α]D20 20 –30 (c 2.5, CHCl3).

IR (KBr): 2957, 2868, 1698, 1454, 1069 cm−1.

1H NMR (300 MHz, CDCl3): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 4.71 (d, J = 7.2 Hz, 1 H), 3.40 (m, 1 H), 2.83 (m, 1 H), 2.55 (m, 1 H), 2.30 (m, 4 H), 2.10 (m, 1 H), 1.92 (m, 1 H), 1.80–1.60 (m, 3 H), 1.40 (m, 2 H), 1.26 (s, 9 H), 0.87 (t, J = 7.2 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 9.46 (CH3), 23.1 (CH3), 25.1 (CH3), 25.6 (CH2), 26.4 (CH2), 33.1 (CH2), 38.5 (CH2), 41.4 (CH2), 43.0 (CH3), 55.2 (CH3), 56.4 (q), 58.8 (CH2), 125.9 (CH), 128.3 (CH), 128.4 (CH), 141.6 (q), 215.0 (q).

HRMS–MALDI: m/z [M + Na]+ calc for C21H33NNaO2S: 386.2130; found: 386.2139.

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(R)-N-([1R,2S,6R]-2-Ethyl-6-hydroxyhexylcyclohexyl)-3-phenylpropyl)-2-methylpropane-2-sulfonamide (4a); Typical Procedure for Reduction with NaBH₄

NaBH₄ (100 mg, 2.6 mmol) was added to a soln of 3a (492 mg, 1.36 mmol) in 95% EtOH (7 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h (TLC monitoring; hexane–EtOAc, 1:1). Sat. aq NH₄Cl was then carefully added (5 mL). When gas evolution ceased, the mixture was partitioned between EtOAc (50 mL) and H₂O (20 mL). The aq phase was extracted with more EtOAc (2 × 20 mL), and the combined organics extracts were washed with brine (10 mL) and dried (MgSO₄). The filtered soln was concentrated in vacuo to give pure 4a as a colorless solid; yield: 471 mg (96%); mp 175–178 °C; [α]D²⁰ = –5.2 (c 1.0, EtOH).

IR (KBr): 3374, 2928, 1455, 1362, 1033 cm⁻¹.

¹H NMR (400 MHz, CD₃OD): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 3.56 (td, J = 10.1, 3.9 Hz, 1 H), 3.36 (m, 1.8 H), 2.83 (dt, J = 13.3, 5.9 Hz, 1 H), 2.55 (dt, J = 13.3, 8.2 Hz, 1 H), 1.75 (m, 3 H), 1.65–1.45 (m, 3 H), 1.72 (m, 2 H), 1.24 (s, 9 H), 1.15–0.80 (m, 4 H), 0.67 (t, J = 7.2 Hz, 3 H).

¹³C NMR (100 MHz, CD₃OD): δ = 9.9 (CH₃), 35.7 (CH₃), 58.3 (CH), 73.1 (CH), 126.9 (CH).


Crystal Structure: C₁₇H₂₇NO₂S, M = 356.57; triclinic, a = 9.5123(11) Å, b = 9.7013(11) Å, c = 13.3333(15) Å, α = 94.474(2), β = 110.126(2), γ = 105.743(2); V = 1091.8(2) Å³; space group P1; Z = 2; d = 0.71125 g cm⁻³; μ = 0.161 mm⁻¹; F(000) = 400; T = 23 ± 1 °C. Data collection was performed on a Bruker Smart CCD diffractometer, based on three o-scans (ranging from 0° to 34°) at values of φ = 0°, 120°, and 240° with the detector at 2θ = –32°. For each of these runs, 606 frames were collected at 0° intervals and 20 s per frame. An additional run at 0°, 120°, and 240° with SADABS. The structure was solved by direct methods and refined to all 7190 unique F² by full-matrix least-squares refinements. All the hydrogen atoms were placed at idealized positions and refined as rigid atoms. Final wR² = 0.1484 for all data and 467 parameters; R = 0.0613 for 4885 F > 4σ(Fo).

(S)-N-([1S,2R,6S]-2-Ethyl-6-hydroxyhexylcyclohexyl)-3-phenylpropyl)-2-methylpropane-2-sulfonamide (ent-4a)

By following the typical procedure starting from ent-3a (616 mg, 1.70 mmol) and NaBH₄ (120 mg), pure compound ent-4a was obtained as a colorless solid; yield: 565 mg (92%); [α]D²⁰ +5.0 (c 1.00, EtOH).

(R)-N-([1R,2R,6S]-2-Ethyl-6-hydroxyhexylcyclohexyl)-3-phenylpropyl)-2-methylpropane-2-sulfonamide (4d)

By following the typical procedure, a 2:4:1 mixture of 3b and 3c (550 mg, 1.50 mmol) was reduced by NaBH₄ (110 mg, 2.9 mmol). After solvent evaporation, the residue was purified by FC (hexane–EtOAc, 3:2 to 1:1) to give pure compounds 4c and 4d as colorless foams; yield: 4c: 244 mg (44%); 4d: 116 mg (21%).
HRMS–EI: m/z cale for C_{11}H_{17}NO_{3}S [M – C_{4}H_{8}]^{+}: 309.1762; found: 309.1780.

(S)-N-[(1R)-1-[(1S,2S,6S)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl]-2-methylpropane-2-sulfonamide (ent-4b)

By following the typical procedure, ent-3a (556 mg, 1.53 mmol) was reduced with a 1 M soln of LiBH_{4} in THF (9 mL, 9 mmol) to give pure ent-4b; yield: 444 mg (80%); [α]_{D}^{20} = −55.0 (c 0.90, MeOH).

(R)-N-[(1S)-1-[(1R,2R,6R)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl]-2-methylpropane-2-sulfonamide (ent-4e)

By following the typical procedure, a 2:4:1 mixture of 3b and 3c (570 mg, 1.57 mmol) was stirred for 30 min at 0 °C until the starting material was consumed, and then the mixture was warmed to 20 °C and stirred for 30 min. After aqueous workup and solvent evaporation, the residue was purified by FC (hexane–EtOAc, 3:2 to 1:1) to give pure 4c and 4e as colorless foams; yield: 4c: 256 mg (45%); 4e: 139 mg (24%).

Compound 4c: [α]_{D}^{20} = −124.0 (c 0.50, EtOH).

IR (KBr): 3471, 1415, 1297, 1342, 1035 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.66 (m, 1 H), 7.34 (m, 1 H), 7.26 (m, 1 H), 7.22 (m, 1 H), 5.29 (m, 1 H), 3.27 (m, 1 H), 2.06 (m, 1 H), 1.81 (m, 1 H), 1.43 (m, 1 H), 1.30 (m, 1 H), 0.90 (m, 3 H), 0.70 (m, 1 H), 0.65 (m, 1 H); J_{HH} = 7.1 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 135.5 (CH₂), 52.4 (CH), 57.0 (q), 66.7 (CH), 126.8 (CH), 128.3 (CH), 128.5 (CH), 142.3 (q).

13C NMR (75 MHz, CDCl₃): δ = 25.3 (CH₂), 32.1 (CH₂), 33.9 (CH₂), 34.7 (CH₂), 34.8 (CH), 35.5 (CH₂), 52.4 (CH), 57.0 (q), 58.6 (CH), 126.8 (CH), 129.3 (CH), 130.0 (CH), 143.6 (q).

MS (EI, 70 eV): m/z (%) = 139.10 (100), 181.0 (42), 227 (20), 309 (21) [M – C₄H₈]^{+}.

HRMS–EI: m/z cale for C_{11}H_{17}NO_{3}S [M – C_{4}H_{8}]^{+}: 309.1762; found: 309.1780.

N-[(1R)-1-[(1S,2S,6S)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl]-2-methylpropane-2-sulfonamide (ent-4d)

By following the typical procedure from 4d (55 mg, 0.15 mmol) and MCPBA (70%, 55 mg, 0.23 mmol), pure ent-4f was isolated as a colorless foam; yield: 39 mg (71%); [α]_{D}^{20} = −29.0 (c 2.5, CHCl₃).

Acknowledgment

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References

(6) Closely related examples are described in references 5a and 5b.
(8) Closely related examples are described in references 5a and 5b.
(9) Synthetic (−)-pulegone is about ten times more expensive than its natural enantiomer.
(17) Sulfinimines 2 and ent-2 were prepared from phenylpropyl and (R, S)- and (S, S)-2-methylpropane-2-sulfonamide (>99% ee) by using CuSO₄ as described in: Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. J. Org. Chem. 1999, 64, 1278.
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