With compliments of the Author
Facile Synthesis of Enantiopure 1,1′-Spirobiindane-7,7′-dil and Its 4,4′-Derivatives: Application in Enantioselective Addition of Diethylzinc to Aromatic Aldehydes

Zhian Li, Xinmiao Liang,* Boshun Wan,* Fan Wu

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China, and Graduate School of Chinese Academy of Sciences, Beijing, P. R. China
Fax +86(411)84379260; E-mail: bswan@dicp.ac.cn
Received 7 June 2004; revised 23 July 2004

Abstract: The enantiopure 1,1′-spirobiindane-7,7′-dil (SPINOL) and its 4,4′-derivatives, 4,4′-diiodo-1,1′-spirobiindane-7,7′-dil (DISPINOL) and 4,4′-dimethyl-1,1′-spirobiindane-7,7′-dil (DMSPINOL) have been synthesized effectively via (1S)-(−)-4,4′-dibromo-1,1′-spirobiindane-7,7′-dil (BSPINOL) following the cleavage of the bismenthyl carbonate. Their absolute configurations were assigned by chemical correlation. They are also applied in the form of their Ti-alkoxides as catalysts for the addition of diethylzinc to aldehydes. The addition reactions proceeded with high conversions and enantioselectivities up to 88%. The effect of substitution of the substrate was studied.

Keywords: alkylation, aldehydes, stereoselectivity, spiro compounds, enantiomeric resolution, protecting groups

Lewis acid catalyzed enantioselective carbon–carbon bond formation is one of the most interesting challenges in catalytic asymmetric synthesis.1 A convenient route for this synthesis is the addition of diethylzinc to aldehydes.2 Titanium catalysts prepared in situ from titanium tetraisopropoxide and chiral diols have been proved to be highly effective for this type of reaction.2,3 Seebach and coworkers carried out in an extensive study in 1991 on using the titanium complexes of TADDOLs for the asymmetric organozinc addition. After that, BINOL-based ligands and H2-BINOL, two types of biphenyl with C2-symmetric chirality emerged.2 Most of them are axially chiral diols (Figure 1).

Recently, a newly reported C2 symmetrical diol, 1,1′-spirobiindane-7,7′-dil (SPINOL) has proven to be an excellent framework for chiral ligands in hydrogenation,4,5 conjugate addition of diethylzinc to enones4c and allylic alkylation.4d Enantiopure SPINOL has been prepared by Birman5 and Zhou6 and Zhou also described the synthesis of 4,4′-substituted SPINOL in hydrogenation.4e We have recently synthesized racemic 4,4′-dibromo-1,1′-spirobiindane-7,7′-dil (DBSPINOL) and developed a mild, rapid and convenient method to resolve it with crude (−)-menthyl chloroformate following the cleavage of the menthyl dicarbonates (Scheme 1).7 Herein we chose the easily prepared compounds 1 and 2 for the synthesis of (R)-(+)–SPINOL, (S)-(−)–SPINOL and some 4,4′-substituted enantiopure ligands for the enantioselective addition of diethylzinc to aldehydes, which has become a classical test in the design of new ligands for catalytic enantioselective synthesis.

Delogu and coworkers reported the bromination of biphenyl dicarbonates using BTEA–Br3 in the presence of acetic acid and ZnCl2 at 60 °C.5 Fortunately, we also found that menthyl dicarbonate in 1 was stable to BuLi at low temperature and stable to acid at room temperature. Herein it is successfully used as the protecting group to prepare enantiopure SPINOL and 4,4′-derivatives through replacing the two bromine atoms by electrophiles.9 The deprotection of the hydroxy group was performed via aqueous

Figure 1

SYNTHESIS 2004, No. 17, pp 2805–2808
Advanced online publication: 22.09.2004
© Georg Thieme Verlag Stuttgart · New York
KOH–EtOH solution. For the preparation of enantiopure SPINOL, compound I treated with BuLi (2.5 equiv; THF, −78 °C, 1 h) followed by acetic acid quench gave SPINOL bismenthyl carbonate (Scheme 2). Hydrolysis of the protecting group gave enantiomerically pure SPINOL. The optical rotation of SPINOL through this method \([\{\alpha\}^13\]D = −3.2 (c 1.0, CHCl3)) is unambiguously S configuration \([\{\alpha\}^15\]D = −3.27 (c 1.0, CHCl3)). Since the ste reogenic center was not modified in our synthesis, the absolute configuration of DBSPINOL formed from I was chemically correlated to be S. With similar treatment of diastereomers 1 and 2, another enantiopure SPINOL was obtained with \([\{\alpha\}^15\]D = +33.4 (c 1.0, CHCl3). Therefore, the absolute configuration of DBSPINOL formed from 2 was found to be R configuration \([\{\alpha\}^15\]D = +32.5 (c 1.0, CHCl3). The use of the diastereomers 1 and 2 from simple crystallization avoided the complicated column chromatography of the diastereomers of SPINOL. Under similar conditions, reaction of 1 or MeI as electrophiles on the pure form of diastereomer 1 led to the formation of 4,4’-derivatives, enantiopure DISPINOL and DM-SPINOL, in good yields. Their configurations prepared in this procedure were also S, based on apparent chemical correlation.

**Enantioselective Addition of Diethylzinc to Aromatic Aldehydes**

Since benzaldehyde has been most extensively studied, we focused our effort on the diethylzinc addition to benzaldehyde in our initial study (Scheme 2). By using the catalyst conveniently prepared in situ from Ti(OiPr)4 and \((R)-SPINOL\), benzaldehyde was smoothly alkylated to the secondary alcohol in high conversions (Table 1).

![Scheme 2](image)

The results in Table 1 show that the enantioselectivity of the reaction was insensitive to the temperature tested, and since the temperature of 0 °C was readily achieved in the laboratory, it was chosen to be the preferred condition for the rest of the study. The solvent effect was examined using commonly used organic solvents. Almost quantitative conversions were obtained when the reactions were carried out at 0 °C for 12 h. Enantioselectivity was found to be relatively independent on the solvents used, with the results of toluene (86% ee), dichloromethane (88% ee), THF (80% ee) and diethyl ether (84% ee). These observations were quite similar to those when BINOL was used as a chiral ligand. Since dichloromethane gave the best rate and enantioselectivity, it was chosen to be the preferred solvent for the rest of the study.

### Table 1 The Effect of Reaction Conditions on the Enantioselectivity of the Alkylation of Benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−15</td>
<td>toluene</td>
<td>&gt;99</td>
<td>87</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>toluene</td>
<td>&gt;99</td>
<td>86</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>+20</td>
<td>toluene</td>
<td>&gt;99</td>
<td>84</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>CH2Cl2</td>
<td>&gt;99</td>
<td>88</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>THF</td>
<td>88</td>
<td>80</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>Et2O</td>
<td>&gt;99</td>
<td>84</td>
<td>S</td>
</tr>
</tbody>
</table>

\(^a\)L/Ti(OiPr)4–Et2Zn–aldehyde, 0.2:1:4:3:1; reaction time = 12 h; \((R)-SPINOL\) was used as ligand.

\(^b\)The ee values were determined by chiral GLC (cyclodex β-2,3,6-M, 30 m × 0.32 mm capillary column from National Chromatographic Research and Analysis Center, Chinese Academy of Sciences). Conversions are calculated based on GC analysis using naphthalene as the internal standard.

\(^c\)The absolute configurations of the products were estimated based on the comparison of GLC traces and the specific rotation with known compounds.

The optimized conditions were then used in the addition of diethylzinc to a variety of aromatic aldehydes and the synthesized derivatives; the results are summarized in Table 2. It is clearly observed that ligands \((S)-DB-SPINOL, (S)-DMSPINOL and (S)-DISPINOL\) give the product in 84, 84 and 83% ee, respectively (entries 2–4), which are slightly lower than those that obtained with the ligand SPINOL. The enantioselectivities catalyzed by Ti-SPINOL results are similar to those from the same reactions catalyzed by Ti-BINOL. A comparison of the results from the entries reveals the detrimental effect on enantioselectivity of ortho-substituents. This is probably due to the strong steric hindrance effect of the ortho-substituent, which significantly weakens the coordination of the aldehyde and consequently lowers the enantioselectivity of the reaction. The electronic effects from substrates are less significant as compared with the steric hindrance effect in influencing the enantioselectivity of the reaction.

In summary, we have developed a simple, inexpensive and potentially general method to synthesize enantiopure SPINOL and its 4,4’-substituted enantiopure ligands by combining resolution and protection of DBSPINOL with menthol chloroformate. By this method, we also determined their configurations. For the first time, \((S)-SPINOL\) and its 4,4’-derivatives, \((S)-DBSPINOL, (S)-DMSPINOL and (S)-DISPINOL\) with C2-symmetric spirocyclic framework, were applied in Lewis acid catalyzed asymmetric synthesis, which induced high conversions and a moderate to high enantioselectivity for the production of chiral secondary alcohols from the diethylzinc addition to aromatic aldehydes, except for the ortho-substituted aldehydes. Further work is underway to develop other new SPINOL-based ligands and investigate the effect of substitution of the ligand in catalyzed asymmetric synthesis.
Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a HORIBA SEPA-200 highly sensitive polarimeter. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 MHz). HRMS were recorded on a Mariner-TOF 5303 (Applied Biosystems, USA). Flash chromatography was performed with silica-gel GF254 plates. All the solvents used were A.R. grade and used as received, except that CH₂Cl₂ was distilled from CaH₂ and toluene, and THF and Et₂O were distilled from sodium and benzophenone, respectively. The solutions were quenched, except that CH₂Cl₂ was distilled from CaH₂ and toluene, and THF and Et₂O were distilled from sodium and benzophenone for the diethylzinc addition to aldehydes, respectively.

### Table 2 Addition of Et₂Zn to Aldehydes Catalyzed by SPINOL and 4,4’-Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Aldehyde</th>
<th>Conversion(%)</th>
<th>Ee (%), config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-SPINOL</td>
<td>benzaldehyde</td>
<td>&gt;99</td>
<td>88, S</td>
</tr>
<tr>
<td>2</td>
<td>(S)-DBSPINOL</td>
<td>benzaldehyde</td>
<td>&gt;99</td>
<td>84, R</td>
</tr>
<tr>
<td>3</td>
<td>(S)-DMSPINOL</td>
<td>benzaldehyde</td>
<td>&gt;99</td>
<td>84, R</td>
</tr>
<tr>
<td>4</td>
<td>(S)-DISPINOL</td>
<td>benzaldehyde</td>
<td>&gt;99</td>
<td>83, R</td>
</tr>
<tr>
<td>5</td>
<td>(R)-SPINOL</td>
<td>o-chlorobenzaldehyde</td>
<td>&gt;99</td>
<td>19, S</td>
</tr>
<tr>
<td>6</td>
<td>(R)-SPINOL</td>
<td>o-bromobenzaldehyde</td>
<td>&gt;99</td>
<td>2, S</td>
</tr>
<tr>
<td>7</td>
<td>(R)-SPINOL</td>
<td>o-fluorobenzaldehyde</td>
<td>&gt;99</td>
<td>66, S</td>
</tr>
<tr>
<td>8</td>
<td>(R)-SPINOL</td>
<td>p-fluorobenzaldehyde</td>
<td>&gt;99</td>
<td>88, S</td>
</tr>
<tr>
<td>9</td>
<td>(R)-SPINOL</td>
<td>p-methoxybenzaldehyde</td>
<td>&gt;99</td>
<td>81, S</td>
</tr>
<tr>
<td>10</td>
<td>(R)-SPINOL</td>
<td>p-chlorobenzaldehyde</td>
<td>&gt;99</td>
<td>88, S</td>
</tr>
<tr>
<td>11</td>
<td>(R)-SPINOL</td>
<td>m-chlorobenzaldehyde</td>
<td>&gt;99</td>
<td>86, S</td>
</tr>
</tbody>
</table>

*CH₂Cl₂ as solvent; reaction temperature = 0 °C; for other conditions, see Table 1.

### Notes

1. CH₂Cl₂ as solvent; reaction temperature = 0 °C; for other conditions, see Table 1.

2. Yields: 0.43 g (77% overall yield); >99% ee; mp 158–159 °C; [α]₂0D +33.2 (c 1.0, CHCl₃).

(R)-(+)-SPINOL

A solution of 2 (mp 49–53 °C, 1.7 g, 3.1 mmol) in THF (25 mL) in a flame-dried flask, under nitrogen, was cooled to –78 °C and treated with BuLi (2.7 mL, 2.89 M solution in hexanes, 2.5 equiv). After 1 h, the reaction mixture was quenched by addition of AcOH (1.0 mL), worked up with CH₂Cl₂ and H₂O, and dried (MgSO₄). The solution was evaporated to give the crude (R)-(+)-SPINOL bismenthyl carbonate (1.3 g, 2.2 mmol), which was dissolved in a solution of degassed H₂O–EtOH (15%; 180 mL) containing KOH (2.7 g, 48 mmol) and refluxed for 2 h. The mixture then cooled and evaporated to add H₂O (2 × 30 mL) and the mixture was extracted with hexane (2 × 30 mL). The ether layer was separated and neutralized with aq HCl (18%) producing a white precipitate which was extracted with Et₂O (2 × 30 mL). The ether layer was dried (MgSO₄), filtered and the solvent was evaporated in vacuo to give (S)-(−)-SPINOL.

Yield: 0.52 g (98%); mp 155–156 °C; >99% ee; [α]₂0D +37.3 (c 1.0, CHCl₃).

HRMS: m/z calcd for C₁₇H₁₆O₂ (M – 1) –: 251.10775; found: 251.10744.

(S)-(−)-DISPINOL

To a solution of KOH (8.7 g, 155 mmol) in degassed H₂O–EtOH (15%; 180 mL), purified SPINOL bismenthyl carbonate (1.0 g, 1.3 mmol) was added and the mixture was refluxed for 2 h. The mixture then cooled and evaporated. To add water H₂O (20 mL), and the mixture was extracted with hexane (2 × 30 mL). After simple work-up, enantiomerically pure (−)-menthol was obtained (0.40 g, 97.6% recovered yield). The aq layer was separated and neutralized with aq HCl (18%), producing a white precipitate which was extracted with Et₂O (2 × 30 mL). The ether layer was dried (MgSO₄), filtered and the solvent was evaporated in vacuo to give (S)-(−)-DISPINOL bismenthyl carbonate.
Sphere. After stirring for 1 h at –78 °C, the reaction was carried out with BuLi (1.4 mL, 2.88 M) in hexane at –78 °C under Ar atmosphere.

**Analytical Data**

**Yield:** 0.35 g (96% yield); white solid; mp 91–92 °C; >99% ee; [α]D20 +89.0 (c 0.5, THF).

**1H NMR (CDCl3):** δ = 2.12–2.31 (m, 4 H), 3.00 (m, 4 H), 4.64 (s, 2 H), 6.48 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.4 Hz, 2 H).

**13C NMR (CDCl3):** δ = 36.45, 36.74, 61.29, 83.39, 117.18, 132.00, 138.81, 149.64, 153.20.

**HRMS:** m/z calcd for C17H14I2O2 (M – 1) –: 502.90106; found: 502.90238.

Enantiomerically pure (–)-menthol was obtained from hexane solution (0.23 g; 100% recovery yield).

**Synthesis of (S)-(-)DIPSINOL**

A solution of 2 (0.78 g, 1.0 mmol) in TFH (20 mL) was charged with Buli (1.4 mL, 2.88 M) in hexane at –78 °C under Ar atmosphere. After stirring for 1 h at –78 °C, the reaction was carried out in the same way described above by using iodomethane as a electrophile reagent to give 5.

**Yield:** 0.44 g (68.0%); mp 215–216 °C.

**IR (KBr):** 2951, 1753, 1489, 1262, 1238, 1181, 965, 781 cm⁻¹.

**1H NMR (CDCl3):** δ = 0.67 (d, J = 6.9 Hz, 6 H), 0.78–0.94 (m, 18 H), 1.25–1.40 (m, 4 H), 1.58–1.64 (m, 6 H), 1.82 (d, J = 12.0 Hz, 2 H), 2.21–2.26 (m, 10 H), 2.86–2.93 (m, 4 H), 4.35 (ddd, J = 4.4 Hz, 2 H), 6.82 (d, J = 8.0, 2 H), 6.99 (d, J = 8.0, 2 H).

**13C NMR (CDCl3):** δ = 13.02, 20.97, 22.12, 23.84, 26.29, 31.47, 34.17, 37.03, 38.42, 40.37, 46.80, 62.64, 79.46, 89.99, 122.90, 137.49, 140.01, 148.04, 149.80, 164.82.

**Anal. Calcd for C22H32O6: C, 61.82; H, 7.97; found: C, 61.72, H, 8.01.**

Enantiomerically pure (–)-menthol was obtained from hexane solution (0.21 g, 100% recovery yield).

**Enantioselective Addition of Diethylzinc to Aldehydes: General Procedure**

Titanium tetraisopropoxide (240 mL, 0.8 mmol) was added to a solution of (R)-SPINOL (25.2 mg, 0.1 mmol) in CH2Cl2 (4.0 mL) at r.t. and stirred for 15 min followed by the addition of a solution of diethylzinc (1 M; 1.5 mL, 1.5 mmol) in hexane and continued stirring for 15 min. The solution was then cooled to 0 °C, benzaldehyde (51.0 μL, 0.5 mmol) was added and the mixture was allowed to stir at 0 °C for 12 h. The reaction was quenched with aq HCl (1.0 M; 8.0 mL), and the product was extracted with Et2O (8.0 mL) and dried (MgSO4). After removal of the solvent at r.t., the residue was purified by column chromatography (silica gel; EtOAc–hexanes, 1:5). The conversion and enantioselectivity of the reaction were determined by GLC.

**Acknowledgment**

We are particularly grateful to Prof. Lefeng Zhang for his useful discussions on this paper.

**References**


