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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 12 Nov 2009.

To cite this article: Minoo Dabiri, Peyman Salehi, Seddigheh Heydari & Gholamreza Kozehgary (2009) Enantioselective Diethylzinc Addition to Aromatic Aldehydes Catalyzed by Novel Ti(IV) Complex of Three-Dentate Chiral Sulfonamide Ligands, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:24, 4350-4361, DOI: 10.1080/00397910902900688

To link to this article: http://dx.doi.org/10.1080/00397910902900688

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Synthetic Communications®, 39: 4350–4361, 2009
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902900688

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Enantioselective Diethylzinc Addition to Aromatic Aldehydes Catalyzed by Novel Ti(IV) Complex of Three-Dentate Chiral Sulfonamide Ligands

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Abstract: The synthesis of several novel three-dentate sulfonamide alcohol ligands is described, starting from camphorsulfonyl chloride. The influence of temperature and ligand structure on the asymmetric addition of dietylzinc to aromatic aldehydes has been studied. Enantioselectivities up to 76% have been obtained.

Keywords: Aldehydes, diethylzinc, enantioselectivity, sulfonamide alcohols

INTRODUCTION

The development of stereoselective asymmetric reactions using organocatalysts has become a research area of great importance, and a number of new organocatalysts have been devised for this purpose.[1] In recent years, there has been great interest in the synthesis of chiral sulfonamide ligands both as auxiliaries and catalysts for a wide variety of asymmetric transformations.[2] An easy-to-perform and well-documented reaction for testing the catalytic reactivity and enantio-differentiating ability of

Received January 5, 2009.

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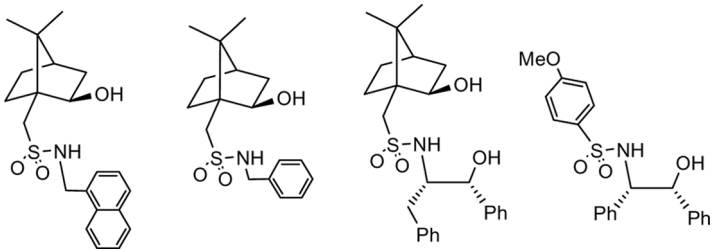

Figure 1. Sulfonamide alcohols used as ligands in the enantioselective addition of dialkylzinc to aldehydes.

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certain catalytic systems is the addition of diethylzinc to aromatic aldehydes.[3] In particular, many chiral sulfonamide ligands have been tested in this addition with varying success (Fig. 1).[4]

Chiral bidentate and tetradentate camphorsulfonamide ligands[4] have been used in the catalytic enantioselective addition of dialkylzinc to aldehydes, but to the best of our knowledge, few reports have emerged about tridentate camphor sulfonamide derivatives for this reaction.[5]

In this article, the enantioselective alkylation of aromatic aldehydes by diethylzinc in the presence of catalytic amounts of novel chiral sulfonamide ligands is reported.

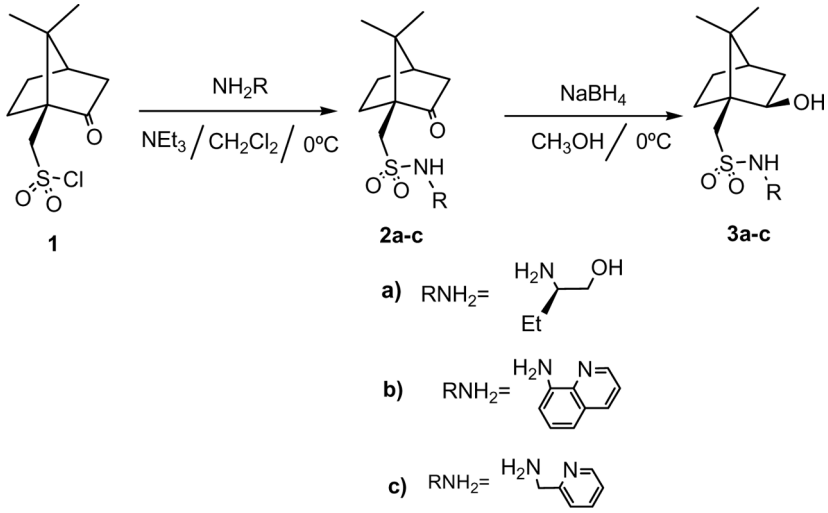
RESULTS AND DISCUSSION

A series of novel chiral ligands were synthesized by the reaction of camphorsulfonyl chloride (**1**) with the appropriate amines and reduction of the produced ketones, **2a–c**, with sodium borohydride[6] (Scheme 1). After purification, rotating frame Overhauser effect spectroscopy (ROESY) spectroscopic study showed that the *exo*-alcohol was the major product (**3a–c**).

To evaluate the catalytic activity of chiral sulfonamide ligands, we examined camphor-based tridentate sulfonamides (**3a–c**) and their ketone precursors (**2a–c**) as catalysts in the presence of titanium tetraisopropoxide (Scheme 2) for the enantioselective addition of diethylzinc to benzaldehyde. The results are summarized in Table 1.

First, we started with reactions catalyzed by ligands **2a–c**. Because of lack of other strongly binding sites, we could expect that only sulfonamide nitrogen atoms and the carbonyl group of the ketone chelated the metal center. Not surprisingly, almost racemic products for ligands **2b**,**c** were obtained, and ligand **2a** gave very modest enantioselectivitiy (Table 1, entries 1–3).

Then we turned our attention to the synthesized tridentate ligands **3a–c**, which had the ability to coordinate to the central metal atom by



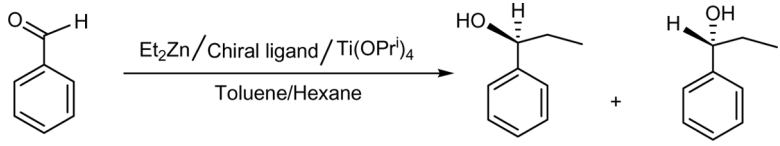
Scheme 1. The synthesis of tridentate chiral sulfonamide ligands.

an extra hydroxy group manipulated in the camphor ring. Increasing the enantioselectivity indicated that the hydroxy groups on isoborneol-10-sulfonamide moieties had a great impact on the enantioselectivity of the reaction (Table 1, entries 7, 11, and 12).

To evaluate the asymmetric induction by camphor moiety, we also synthesized and examined β-sulfonamide alcohols **5a**,**b** as catalysts in the presence of titanium tetraisopropoxide (Scheme 3) (Table 1, entries 15–20).

The comparison of ligands **3a** and **5a**,**b** again showed that the camphor moiety had an important role in the enantioselectivity of the reaction (Table 1, entries 7, 15, and 18).

Addition of catalytic amounts (10 mol%) of benzoic acid in the reaction of diethylzinc to benzaldehyde with **3a** led to a moderate increase in the enantiomeric excess (ee) and yield of the reaction (Table 1, entry 10, and Table 2, entry 2).



Scheme 2. Enantioselective addition of diethylzinc to benzaldehyde in the presence of chiral ligands.

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Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral ligands (**2, 3**, and **5**)

Entry	Ligand (mol %)	T (°C)	Time (h)	Yield (%)[a]	Ee (%)[b]	Configuration[c]
1	**2a** (20)	−20	24	52	17	(S)
2	**2b** (20)	−20	24	32	9	(R)
3	**2c** (12)	−20	24	57	3	(R)
4	**3a** (5)	−20	40	41	11	(S)
5	**3a** (10)	−20	20	79	54	(S)
6	**3a** (15)	−20	40	88	57	(S)
7	**3a** (20)	−20	20	80	57	(S)
8	**3a** (20)	+25	40	100	36	(S)
9[d]	**3a** (20)	−20	20	65	31	(R)
10[e]	**3a** (20)	−20	20	87	59	(S)
11	**3b** (20)	−20	20	80	36	(S)
12	**3c** (20)	−20	24	41	23	(S)
13	**3c** (20)	+25	40	100	8	(S)
14	**3c** (20)	−20	40	58	8	(S)
15	**5b** (10)	−20	24	62	8	(S)
16	**5b** (10)	+10	40	84	9	(S)
17[d]	**5b** (10)	+10	40	64	20	(R)
18	**5a** (20)	−20	24	62	9	(S)
19	**5a** (10)	+10	40	80	7	(S)
20[d]	**5a** (10)	+10	40	53	9	(R)

[a]GC yield on the mixture of the two enantiomers.

[b]Ee was determined by GC using a chiral capillary column (HP-chiral).

[c]Absolute configuration of the major enantiomer was determined by comparison with an authentic sample.

[d]Without any $Ti(OPr^i)_4$.

[e]With 10 mol% of benzoic acid.

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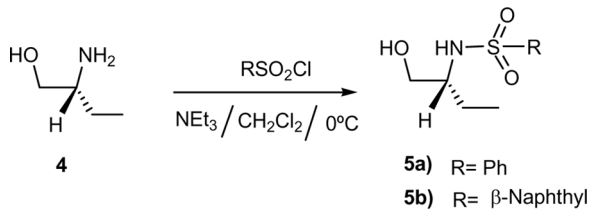

Scheme 3. The synthesis of bidentate chiral sulfonamide ligands.

Table 2. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by chiral ligand **3a**[a]

Entry	Aldehyde	Yield (%)[b]	Ee (%)[c,d]
1	*p*-FC_6H_4CHO	94	56
2[e]	*p*-FC_6H_4CHO	93	58
3	*p*-ClC_6H_4CHO	97	52
4	*p*-BrC_6H_4CHO	98	56
5	*p*-MeC_6H_4CHO	89	59
6	*p*-$MeOC_6H_4CHO$	87	54
7	*o*-$MeOC_6H_4CHO$	96	76
8	*o*-ClC_6H_4CHO	95	73

[a]Condition: −20°C, 40 h, and 15 mol% of **3a**.

[b]Measured as conversion percentage by GC.

[c]Determined by capillary chiral GC analysis using the chiral column (HP-chiral).

[d]Absolute configuration was determined by comparing the sign of specific rotation.[7–10] The major enantiomer in all cases had the *S* configuration.

[e]With 10 mol% of benzoic acid.

Increasing the ratio of ligand **3a** to benzaldehyde increased the enantioselectivity for production of (S)-1-phenyl-1-propanol, and the best enantioselectivity (57% ee) was obtained when 15 mol% of **3a** was used (Table 1, entries 4–7).

We observed that lower temperatures favored the enantioselectivity of the reaction; thus, when the reactions were carried out at +25°C with 20 mol% of **3a**, lower ee values were obtained than when −20°C was used (Table 1, entries 7 and 8). When we considered the mechanism reported by Yus et al.,[5a,11] we introduced an additional sp^2 nitrogen binding site in the ligand, which retarded the interaction of aldehyde with titanium and reduced the Lewis acidity of titanium, reflected in reduction of ee and yield of the reactions (Table 1, entries 11–14) (Fig. 2b). On the other hand, introduction of an additional oxygen in ligand **3a** resulted in a more rigid transition state and therefore improved the ee of the reaction (Table 1, entries 4–8) (Fig. 2a). For ligand **3a**, in absence of titanium tetraisopropoxide, lower ee values and also product with opposite configuration were obtained (Table 1, entry 9).

Once the optimal ligand **3a** was found, different aromatic aldehydes were tested as substrates in the enantioselective addition of diethylzinc under the same conditions described in entry 6 (Table 1). The results are summarized in Table 2. For substituted aromatic aldehydes, moderate to good enantioselectivities were obtained.

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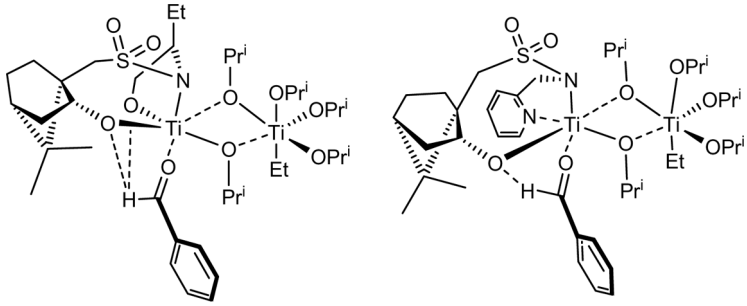

(a) (b)

Figure 2. Proposed mechanism of (a) **3a** and (b) **3c**.

Substituents at the *ortho* position of the substrate had a favorable effect on the enantioselectivity. Both 2-methoxy- and 2-chlorobenzaldehyde gave good enantioselectivities (Table 2, entries 7 and 8). The best enantioselectivity, up to 76%, was obtained for 2-methoxybenzaldehyde (Table 2, entry 7).

EXPERIMENTAL

General

Melting points were obtained in open capillary tubes and measured on an electrothermal 9200 apparatus. Mass spectra (MS) were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. Infrared (IR) spectra were recorded as KBr pellets on a Nicolet Impact 400D spectrophotometer. Conversions were determined with a Hewlett-Packard HP-5890 gas chromatography (GC) instrument equipped with a flame ionization detector and a 30-m HP-1 capillary column, using nitrogen (2 mL/min) as carrier gas. The enantiomeric ratio were determined with the aforementioned apparatus using a 30-m WCOT fused silica capillary column (HP-chiral). ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300.13 and 75.47 MHz, respectively.

Synthesis of Ligands 2a–c and 5a,b

A solution of amine (10 mmol) and triethylamine (12 mmol) in dry CH_2Cl_2 (10 ml) at 0°C was slowly added to a solution of camphorsulfonyl chloride (2.5 g, 10 mmol) in dry CH_2Cl_2 (10 ml) over 0.5 h. The resulting mixture was stirred at room temperature for another 15 h. When the

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reaction was completed, the mixture was poured into a 0.5 M HCl solution (50 ml), and the obtained mixture was extracted with ethyl acetate (3×50 ml). The organic layer was washed with HCl solution and water and dried over anhydrous Na_2SO_4. The desired products were obtained after concentration under reduced pressure. In some cases, the residue was purified by flash-column chromatography. The desired camphorsulfonamides were obtained in 85–95% yields.

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Synthesis of Ligands 3a–c

The sulfonamides (9 mmol) were dissolved in methanol (30 ml) at 0°C. Sodium borohydride (30 mmol) was added, with vigorous stirring, to this solution over 120 min. The resulting mixture was stirred for 5 min to 1 h until thin-layer chromatography (TLC) showed that the ketone was consumed completely. Methanol was removed under reduced pressure, and the residue was added to water (25–30 ml) and extracted with ethyl acetate (3×40 ml). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. The crude product was purified by flash-column chromatography to afford the expected *exo*-borneol derivatives in 85–91% yields.

Data

(1S,2R,4S)-N-(R)-1-Hydroxybutan-2-yl-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonamide) (**2a**)

Yield 95% as colorless oil; $[\alpha]_D^{25} = +24.5$ (c = 1.02, $CHCl_3$); IR (KBr) 3506, 3299, 2966, 1740, 1328, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.70–0.88 (m, 9H), 1.25–1.40 (m, 4H), 1.70–192 (m, 6H), 2.16 (m, 2H), 2.38–2.41 (m, 1H), 2.88 (d, $J = 15.3$Hz 1H), 3.2 (bs, 1H), 3.34 (d, $J = 15.3$Hz, 1H), 3.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 10.3, 19.5, 19.6, 24.9, 25.6 (2C), 26.7, 42.5, 45.7, 48.0, 57.1, 58.7, 64.0, 215.9; MS (EI) 304 ($M^+ + 1$, 28), 286 (25), 272 (23), 215 (31), 151 (22), 109 (63), 58 (100), 41 (72).

(1S,2R,4S)-N-(R)-1-Hydroxybutan-2-yl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-methanesulfonamide) (**3a**)

Yield 87%; mp 89–91°C; $[\alpha]_D^{25} = -29.4$ (c = 1.0, $CHCl_3$); IR (KBr) 3506, 3464, 3177, 2937, 1305, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ, ppm)

0.81 (s, 3H), 0.88–1.09 (m, 6H), 1.47–1.58 (m, 4H), 1.70–1.76 (m, 5H), 2.15 (s, 1H), 2.89 (d, $J = 13.7$ Hz, 1H), 3.40 (bs, 1H), 3.50 (d, $J = 13.7$ Hz, Hz, 1H), 3.68 (m, 1H), 4.06 (bs, 1H), 5.33 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 10.56, 19.8, 20.5, 25.2, 27.3, 30.4, 30.9, 38.9, 44.3, 48.6, 50.4, 53.5, 57.5, 64.6; MS (EI) 306 ($M^+ + 1$, 5), 288 (27), 274 (5), 256 (72), 58 (100), 41 (32).

(1S,2R,4S)-N-Quinolin-8-yl-(7,7-dimethyl-2-oxobicyclo[2.2.1] heptane-1-methanesulfonamide) (**2b**)

Yield 96%; mp 120–121°C; $[\alpha]_D^{25} = +25.5$ (c = 0.98, $CHCl_3$); IR (KBr) 3246, 2958, 1739, 1503, 1372, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.82 (s, 3H), 1.10 (s, 3H), 1.42–1.46 (m, 1H), 1.81–1.94 (m, 4 H), 2.30–237 (m, 1H), 2.56 (m, 1H), 3.05 (d, $J = 14.85$ Hz, 1H), 3.65 (d, $J = 14.85$ Hz, 1H), 7.27–7.55 (m, 3H), 7.94 (t, $J = 4.26$Hz, 1H), 8.15 (dd, $J = 8.29$ Hz, 1H), 8.80 (m, 1H), 9.11 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 19.7, 19.9, 25.2, 26.9, 42.5, 42.8, 48.0, 48.6, 58.5, 114.4, 122.0, 122.0, 127.1, 128.3, 134.3, 136.3, 138.4, 148.7; MS (EI) 358 (M^+, 27), 277 (26), 144 (100), 116 (22), 81 (24), 41 (40).

(1S,2R,4S)-N-Quinolin-8-yl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-methanesulfonamide) (**3b**)

Yield 88%; mp 98–99°C; $[\alpha]_D^{25} = -23$ (c = 1.0, $CHCl_3$); IR (KBr) 3543, 3296, 1952, 1505, 1369, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.69 (s, 3H), 0.97 (s, 3H), 1.09–1.26 (m, 2H), 1.63–1.81 (m, 5 H), 3.03 (d, $J = 13.8$ Hz, 1H), 3.23 (bs, 1H), 3.57 (d, $J = 13.8$ Hz, 1H), 4.09–4.20 (m, 1H), 7.46–7.55 (m, 3H), 7.81 (d, $J = 6.80$ Hz, 1H), 8.16 (d, $J = 8.29$ Hz, 1H), 8.82 (m, 1H), 9.00 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 19.8, 20.4, 27.3, 30.3, 39.1, 44.3, 48.8, 50.4, 51.1, 60.3, 114.1, 122.2, 122.2, 127.0, 128.4, 134.0, 136.4, 138.3, 148.8; MS (EI) 360 (M^+, 25), 342 (2), 190 (73), 144 (100), 116 (25), 43 (26), 55 (25), 31 (75).

(1S,2R,4S)-N-Pyridin-2-ylmethyl-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonamide) (**2c**)

Yield 87% as colorless oil; $[\alpha]_D^{25} = +14$ (c = 1.02, $CHCl_3$); IR (KBr) 3290, 2958, 1740, 1595, 1328, 1148 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.71 (s, 3H), 0.9 (s, 3H), 1.29 (m, 1H), 1.74–2.26 (m, 6H), 2.80 (d,

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$J = 13.7$ Hz, 1H), 3.34 (d, $J = 13.7$ Hz, 1H), 4.38 (m, 2H), 6.52 (t, $J = 5.13$Hz, 1H), 7.08 (t, $J = 5.88$ Hz, 1H), 7.30 (d, $J = 7.94$ Hz, 1H), 7.57 (t, $J = 7.63$Hz, 1H), 8.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 19.4, 19.7, 25.9, 26.8, 42.5, 42.6, 48.2, 48.3, 49.8, 58.8, 122.1, 122.5, 136.9, 149.0, 156.4, 216.0; MS (EI) 323 ($M^+ + 1$, 15), 171 (76), 155 (73), 107 (100), 79 (26), 41 (36).

(1S,2R,4S)-N-Pyridin-2-ylmethyl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-methanesulfonamide) (**3c**)

Yield 85%; mp 59–61°C; $[\alpha]_D^{25} = -28$ (c = 1.0, $CHCl_3$); IR (KBr) 3529, 3299, 2933, 1594, 1322, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.62 (s, 3H), 0.87 (s, 3H), 1.12 (m, 1H), 1.34 (m, 1H), 1.55–1.65 (m, 5 H), 2.67 (d, $J = 15$ Hz, 1H), 3.28 (d, $J = 15$ Hz, 1H), 3.87–3.99 (m, 2H), 4.33 (s, 1H), 6.56 (bs, 1H), 7.11 (t, $J = 6.3$ Hz, 1H), 7.24 (d, $J = 7.47$ Hz, 1H), 7.58 (t, $J = 706$Hz, 1H), 8.42 (d, $J = 4.43$Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 19.7, 20.4, 27.2, 30.1, 39.2, 44.2, 47.8, 48.5, 50.2, 52.2, 75.8, 122.4, 122.8, 137.2, 149.1, 156.1; MS (EI) 325 ($M^+ + 1$, 24), 306 (8), 172 (45), 155 (23), 108 (100), 79 (50), 41 (53).

(R)-2-(2-Naphthalensulfonylamino)-2-ethyl-1-ethanol (**5b**)

Yield 96%; mp 118–121°C; $[\alpha]_D^{25} = +10.4$ (c = 0.97, $CHCl_3$); IR (KBr) 3514, 3281, 1427, 1311, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm) 0.61 (t, $J = 7.29$ Hz, 3H), 1.16–1.25 (m, 1H), 1.48–1.56 (m, 1H), 3.01–3.28 (m, 2H), 3.36 (bs, 1H), 4.63 (bs, 1H), 7.63–7.72 (m, 2H), 7.84–8.16 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 10.3, 24.3, 57.1, 63.6, 122.9, 127.3, 127.9, 128.2, 128.9, 129.6 (2C), 134.4, 139.4; MS (EI) 280 ($M^+ + 1$, 12), 262 (12), 248 (24), 191 (22), 127 (100), 31 (21).

(R)-2-(2-Benzensulfonylamino)-2-ethyl-1-ethanol (**5a**)

Yield 92%; mp 57°C; $[\alpha]_D^{25} = +19.6$ (c = 1.02, $CHCl_3$); IR (KBr) 3514, 3281, 1447, 1321, 1161 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz, δ, ppm) 0.69 (t, $J = 7.47$ Hz, 3H), 1.35–1.50 (2H, m), 2.84 (bs, 1H), 3.17 (m, 1H), 3.47–3.56 (m, 2H), 5.53 (bs, 1H), 7.27–7.59 (m, 3H), 7.90–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ, ppm) 10.1, 24.5, 57.2, 64.3, 127.0 (2C), 129.0 (2C), 132.6, 140.6; MS (EI) 230 ($M^+ + 1$, 23), 212 (19), 198 (64), 170 (14), 141 (43), 125 (17), 77 (100), 51 (33), 31 (26).

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General Procedure for the Enantioselective Addition of Diethylzinc to Benzaldehyde

The ligand (0.11 mmol) was placed in a test tube and dissolved in dry toluene (2 mL). The solution was stirred for 5 min. A 1.0 M solution of diethylzinc in *n*-hexane (2.2 mmol, 2.2 mL) was then added, and after the mixture was stirred for 5 min, a solution of benzaldehyde (1.11 mmol) in dry toluene (1 mL) was added by a syringe. The mixture was stirred at the appropriate temperature for the time reported in the Table 1. Saturated aqueous NH_4Cl was added (10 mL), and the mixture was extracted with ethyl acetate (3×20 mL). The collected organic phases were washed with water, dried over Na_2SO_4, and analyzed by GC, after suitable dilution.

CONCLUSION

In conclusion, we have shown that three-dentate sulfonamide alcohol ligand **3a**, which is easily prepared from (R)-2-amino-1-butanol and camphorsulfonyl chloride, can be successfully used as a ligand in the enantioselective addition of diethylzinc to aryl aldehydes.

ACKNOWLEDGMENTS

Financial support from the Research Council of Shahid Beheshti University and the Catalyst Center of Excellence (CCE) is gratefully acknowledged.

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