Journal of Molecular Catalysis A: Chemical 286 (2008) 106–113

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

C_2-symmetrical bis(camphorsulfonamides) as chiral ligands for enantioselective addition of diethylzinc to benzaldehyde

Anna Kozakiewicz, Małgorzata Ullrich, Mirosław Wełniak, Andrzej Wojtczak*

Faculty of Chemistry, N. Copernicus University, Gagarina 7, 87-100 Toruń, Poland

ARTICLE INFO

Article history:
Received 5 December 2007
Received in revised form 10 February 2008
Accepted 11 February 2008
Available online 16 February 2008

Keywords:
Bis(ketosulfonamide)
Bis(hydroxysulfonamide)
Camphor derivatives
Activity
Diethylzinc addition

ABSTRACT

Purpose of the research was to determine the activity of chiral bis(sulfonamide) ligands derived from camphor in the addition of diethylzinc to benzaldehyde. Chiral bis(ketosulfonamides) and bis(hydroxysulfonamides), have been synthesized in a reaction of diamines with camphorsulfonic acid chloride. Their activity in a reaction of asymmetric addition of dialkylzinc to benzaldehyde in a presence of titanium(IV) tetraisopropoxide was determined. The bis(ketosulfonamide) ligands reveal low enantioselectivity, with the ee% not exceeding 12%. The bis(hydroxysulfonamides) reveal much higher asymmetric induction in the investigated $ZnEt_2$ addition. The best enantiomeric excess (62%) has been observed for bis(hydroxysulfonamide) obtained from 1,3-diamine propane. The yields of the reaction obtained after 18 h are 92–96%. Crystal structures have been solved for bis(ketosulfonamide) ligands obtained from diamines based on C_2 to C_4 chain. The (2R) configuration in the rings systems of bis(hydroxysulfonamide) containing the C_3 bridge was also determined by the crystal structure analysis. The sulfonamides have been characterized by IR, ^1H and ^{13}C NMR.

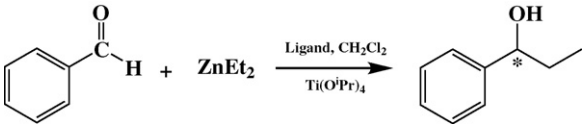
1. Introduction

Catalytic asymmetric addition of dialkyl zinc to aldehydes and ketones is intensively studied in the recent years being one of the methods of the C–C bond formation. This idea was derived from the paper of Oguni and Omi [1] who described a process of this type using (*S*)-leucinol as a catalyst. The enantiomeric excess attained 49% in this case. Much better result (95% ee) was achieved by Noyori and co-workers [2] with 3-dimethylaminoisoborneol (DAIB). The addition of diethyl zinc to benzaldehyde is a model reaction of this type simultaneously serving for estimation of the efficiency of the used catalyst (Scheme 1).

Currently, several hundreds of the similarly acting catalysts such as various chiral amino alcohols, amino tiols, amines, diols and bis(sulfonamides) are known. The addition of this type is usually conducted in the presence of $Ti(O^iPr)4$. The role of bis(sulfonamides) is based on the formation of the ligand–titanium complex having the Lewis acid character which activates the aldehyde molecule. An idea of the use of bis(sulfonamides) as ligands in the asymmetric addition of dialkyl zinc to aldehydes was formulated for the first time by Yoshioka et al. [3]. Hwang and Uang [4] described a synthesis and application of C_2-symmetric bis(camphorsulfonamide) ligands in the addition reaction under consideration containing the trans-1,2-diaminocyclohexane fragment. In this case enantioselectivity up to 80% was observed. The next work concerning the enantioselective addition of Et_2Zn to benzaldehyde in the presence of bis(camphorsulfonamides) as promoters has been published by Bauer and Gajewiak [5]. The authors linked two isoborneol fragments by means of 1,2-ethylenediamine, 1,2- or 1,3-phenylenediamine to receive the best results in the last case (67% ee). Yus et al. [6] reported a synthesis and the use of ligands based on a reaction of camphorsulfonic acid chloride with 1,2-, 1,3- and 1,4-xylylenediamines or (+)-2,2-diamino-1,1′-binaphthyl and further reduction of the resulted bis(ketosulfonamides) by means of DIBAL. These ligands have been used with success (90% ee) in the addition of Et_2Zn to acetophenone and its derivatives. An interesting paper [7] concerning a synthesis of bis(sulfonamides) has been published containing only one terpene fragment to be proved an excellent ligands for the addition of Me_2Zn and Et_2Zn to acetophenone leading to the near completely enantioselective course. The next work concerning the same reaction was the paper of Wang and co-workers [8] where the unit of L-tartatic acid was used as a link between two sulfonamide fragments. Especially good results have been obtained for the selected ketones, as for example, acetophenone, where enantiomeric excess reached 94%. The use of bis(sulfonamide) containing the bornane fragment connected with the polymeric matrix has also been reported [9]. In this case various enantioselectivity (42–90%) of an addition of Et_2Zn to *p*-substituted derivatives of acetophe-

* Corresponding author. Tel.: +48 56 6114506; fax: +48 56 6542477.
E-mail address: awojt@chem.uni.torun.pl (A. Wojtczak).

1381-1169/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2008.02.006



Scheme 1. Asymmetric addition of diethylzinc to benzaldehyde.

none has been observed. The overview of bissulfonamides and other classes of catalysts has been published by Ramon and Yus [10].

The qualitative model of the enantioselectivity was published by Qiu et al. [11]. The molecular level model might be helpful in establishing the basis for rational control of the product. Several crystal structures of the $Ti(NR_2)_2(L)_{1-2}$, where L is a sulfonamide ligand, have been reported, giving an insight into the architecture of the catalyst. The structures revealed different modes of the sulfonamide coordination to Ti. The bis(sulfonamide) ligands can coordinate with either η^2-*N,N*, η^3-N_2O or η^4-N_2O_2 modes [12–16]. The monosulfonamides reveal η^2-*N,O* [17]. In all cases the ligands are coordinated *via* the atoms of the sulfonamide groups. However, there is a possibility of forming the different coordination pattern involving the other donor group occurring in the functionalized ligand molecule. Different architecture of Ti_{1-3} complexes assisting the catalysis has been discussed [18–20]. However, most of the literature reports consider the heterodinuclear Ti–Zn complexes as the catalytically active species.

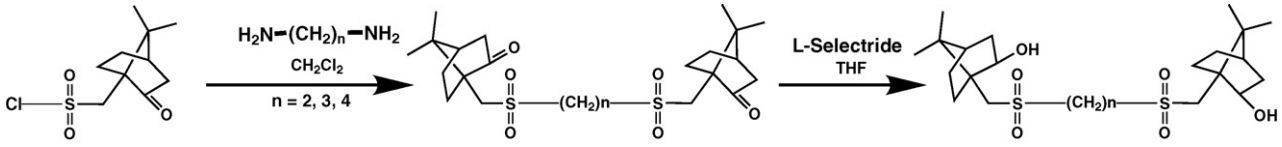
The aim of the reported research was to test the activity of new chiral ligands belonging to the group of bis(sulfonamides) and to rationalize the effect of their architecture on the catalytic performance in the reaction of $ZnEt_2$ addition to benzaldehyde.

2. Experimental

Melting points for **1–7** were determined using Boetius' table. Rotations were measured on Lot-Oriel S-2 automatic polarimeter. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer using $CDCl_3$ solutions. The IR spectra were recorded on a PerkinElmer Spectrum RX I spectrophotometer. Elemental analyses were performed on Elementary Analysensysteme GmbH Vario MACRO CHN analyzer. GC analyses were performed on a PerkinElmer chromatograph using a Supelco β-Dex 325 column (30 m × 0.25 mm, isothermal conditions, T = 100 °C). The crystals suitable for the diffraction experiments were obtained by vapor diffusion method from the ethanol solution. X-ray diffraction data were measured using Oxford Sapphire CCD diffractometer with Mo Kα radiation, λ = 0.71073 Å at 293(2) K. The numerical absorption correction was applied, based on the crystal shape [21]. For all crystals, the absolute structure was determined by the Flack method [22]. Structures were solved and refined with the full-matrix least-squares procedure using SHELX-97 program package [23]. The structures **1**–**3** and **6** have been deposited with CCDC, the deposition numbers are CCDC 670434 to 670437, respectively.

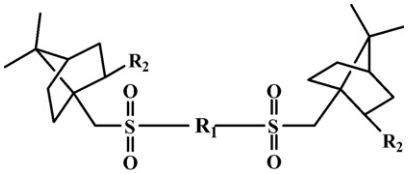
2.1. Preparation of bis(ketosulfonamides) *1–3*

General procedure of synthesis of the investigated sulfonamides is shown on Scheme 2. The molecular composition of the investigated keto- and hydroxysulfonamides is presented in Table 1. Diamine (29.8 mmol) was added into CH_2Cl_2 (15 ml). A solution of (+)-10-camphorsulfonic acid chloride (15.00 g, 59.8 mmol) in CH_2Cl_2 (75 ml) was dropped into cooled (0 °C) solution of amines and stirred for about 20 min (colorless precipitate of triethylammonium hydrochloride was formed). The reaction mixture was stirred



Scheme 2. Synthesis of bis(sulfonamide) ligands derived for camphor.

Table 1
Addition of diethylzinc to benzaldehyde using bis(sulfonamide) ligands



Entry	Ligand	*R*1	*R*2	Addition order	Time (h)	Yield (%)	ee (%)[a]	Configuration
1	1	$HN(CH_2)_2NH$	=O	Ti/Zn	17	82	5.8	*R*
2	1	$HN(CH_2)_2NH$	=O	Zn/Ti	18	84	1.3	*R*
3	2	$HN(CH_2)_3NH$	=O	Ti/Zn	18	98	2.2	*R*
4	2	$HN(CH_2)_3NH$	=O	Zn/Ti	18	82	1.3	*R*
5	3	$HN(CH_2)_4NH$	=O	Ti/Zn	18	93	12	*R*
6	3	$HN(CH_2)_4NH$	=O	Zn/Ti	18	89	6.2	*R*
7	4	Piperazine	=O	Ti/Zn	17	50	2.3	*R*
8	4	Piperazine	=O	Zn/Ti	18	59	0.9	*R*
9	5	$HN(CH_2)_2NH$	–OH	Ti/Zn	18	93	31	*S*
10	5	$HN(CH_2)_2NH$	–OH	Zn/Ti	18	92	21	*S*
11	6	$HN(CH_2)_3NH$	–OH	Ti/Zn	18	96	62	*S*
12	6	$HN(CH_2)_3NH$	–OH	Zn/Ti	18	93	52	*S*
13	7	$HN(CH_2)_4NH$	–OH	Ti/Zn	18	92	40	*S*
14	7	$HN(CH_2)_4NH$	–OH	Zn/Ti	18	94	58	*S*

[a] Determined by GC analysis using a Supelco β-Dex column, the absolute configuration assigned by comparison to literature values [21].

at the same temperature for 2h and subsequently at 20 °C for 1 h. It was then quenched by pouring it into 1 M aqueous HCl (50 ml). After separation of layers, the residual was dissolved with CH_2Cl_2. The combined organic layers were washed successively with the saturated solution of $NaHCO_3$ (25 ml) and water (2× 50 ml). After drying over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under vacuum. The oily residue was dissolved in CH_2Cl_2, a solid product was precipitated with a mixture of EtOAc and hexane. The obtained precipitate was crystallized from EtOAc. The preparation procedure for **4** was described by Ullrich et al. [24].

*2.1.1. (+)-N,N′-(ethane-1,2-diyl)bis((7,7-dimethyl-2-oxobicyclo [2.2.1]heptan-1-yl) methanesulfonamide) (**1**)*

Colorless solid (69.5%), mp 130–132 °C, $[\alpha]_D^{20}$ = 32.2 [*c* = 5.45 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.61 (bs, 2H, 2*x*NH), 3.45, 2.94 (2d, *J* = 15.1 Hz, 4H, 2*x*CH_2S), 3.40 (t, *J* = 2.7 Hz, 4H, 2*x*CH_2N), 2.40 (ddd, *J* = 18.7 Hz, *J* = 4.9 Hz, *J* = 3.0 Hz, 2H, 2*x*CH), 2.25 (m, 2H, 2*x*CH), 2.12 (t, *J* = 4.3 Hz, 2H, 2*x*CH), 2.10 – 1.87 (m, 6H, 6*x*CH), 1.45 (ddd, *J* = 12.3 Hz, *J* = 8.6 Hz, *J* = 3.6 Hz, 2H, 2*x*CH), 1.02 (s, 6H, 2*x*CH_3), 0.91 (s, 6H, 2*x*CH_3). ^{13}C NMR (75 M Hz, $CDCl_3$) δ (ppm): 216.86 (2*x*C=O), 58.97 (2*x*C), 49.59 (2*x*CH_2S), 48.78 (2*x*C), 43.65 (2*x*CH_2N), 42.85 (2*x*CH_2), 42.70 (2*x*CH), 26.98 (2*x*CH_2), 26.07 (2*x*CH_2), 19.84 (2*x* CH_3), 19.46 (2*x*CH_3). IR (KBr): 3285, 2958, 1734, 1333, 1147, 778 cm^{-1}. Anal. Calcd for $C_{22}H_{36}N_2O_6S_2$: C, 54.05; H, 7.43; N, 5.74. Found: C, 54.05; H, 7.21; N, 5.65.

*2.1.2. (+)-N,N′-(propane-1,3-diyl)bis((7,7-dimethyl-2-oxobicyclo [2.2.1]heptan-1-yl) methanesulfonamide) (**2**)*

Colorless solid (73.9%), mp 140–142 °C, $[\alpha]_D^{20}$ = 28.0 [*c* = 5.25 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.35 (t, *J* = 6.3 Hz, 2H, 2*x*NH), 3.42, 2.91 (2d, *J* = 15.0 Hz, 4H, 2*x*CH_2S), 3.31 (q, *J* = 6.3 Hz, 4H, 2*x*CH_2N), 2.39 (ddd, *J* = 18.5 Hz, *J* = 4.6 Hz, *J* = 3.3 Hz, 2H, 2*x*CH), 2.26 (t, m, *J* = 12.4 Hz, 2H, 2*x*CH), 2.12 (t, *J* = 4.5 Hz, 2H, 2*x*CH), 2.10–1.81 (m, 8H, 6*x*CH, CH_2), 1.44 (ddd, *J* = 12.6 Hz, *J* = 8.9 Hz, *J* = 3.6 Hz, 2H, 2*x*CH), 1.03 (s, 6H, 2*x*CH_3), 0.91 (s, 6H, 2*x*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 216.70 (2*x*C=O), 58.97 (2*x*C), 49.17 (2*x*CH_2S), 48.67 (2*x*C), 42.85 (2*x*CH_2), 42.72 (2*x*CH), 40.42 (2*x*CH_2N), 30.61 (CH_2), 26.97 (2*x*CH_2), 26.17 (CH_2) 19.83 (2*x*CH_3), 19.49 (2*x*CH_3). IR (KBr): 3337, 2965, 1729, 1419, 1324, 1144, 1096, 1054, 777 cm^{-1}. Anal. Calcd for $C_{23}H_{38}N_2O_6S_2$: C, 54.93; H, 7.63; N, 5.58. Found: C, 55.03; H, 7.57; N, 5.79.

*2.1.3. (+)-N,N′-(butane-1,4-diyl)bis((7,7-dimethyl-2-oxobicyclo [2.2.1]heptan-1-yl) methanesulfonamide) (**3**)*

Colorless solid (65.2%), mp 95–98 °C, $[\alpha]_D^{20}$ = 12.3 [*c* = 4.60 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.26 (*t*, *J* = 6.1 Hz, 2H, 2*x*NH), 3.39, 2.90 (2d, *J* = 15.1 Hz, 4H, 2*x*CH_2S), 3.25–3.15 (m, 4H, 2*x*CH_2N), 2.40 (ddd, *J* = 18.6 Hz, *J* = 2.9 Hz, *J* = 4.5 Hz, 2H, 2*x*CH), 2.27–1.89 (m, 10H, 8*x*CH, 2*x*CH), 1.71 (qw, *J* = 3.0 Hz, 4H, 2*x*CH_2), 1.50–1.39 (m, 2H, 2*x*CH), 1.01 (s, 6H, 2*x*CH_3), 0.92 (s, 6H, 2*x*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 217.09 (2*x*C=O), 59.15 (2*x*C), 49.16 (2*x*CH_2S), 48.82 (2*x*C), 43.93 (2*x*CH_2N), 43.03 (2*x*CH_2), 42.73 (2*x*CH), 26.99 (2*x*CH_2), 26.96 (2*x*CH_2), 26.57 (2*x*CH_2), 19.89 (2*x*CH_3), 19.45 (2*x*CH_3). IR (KBr): 3291, 2961, 1734, 1319, 1146 cm^{-1}. Anal. Calcd for $C_{24}H_{40}N_2O_6S_2$: C, 55.76; H, 7.81; N, 5.42. Found: C, 55.74; H, 7.64; N, 5.65.

*2.1.4. (+)-N,N′-(piperazine)bis((7,7-dimethyl-2-oxobicyclo [2.2.1]heptan-1-yl) methanesulfonamide) (**4**)*

Colorless solid (95.3%), mp 294.5–295 °C, $[\alpha]_D^{20}$ = 38.7 [*c* = 3.60 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.50–3.37 (m, 8H, 4*x*CH_2(piperazine)), 3.34, 2.76 (2d, *J* = 14.7 Hz, 2H, 2*x*CH_2S), 2.53–2.32 (m, 4H, 4*x*CH), 2.11 (t, *J* = 4.3 Hz, 2H, 2*x*CH), 2.10–1.99 (m, 2H, 2*x*CH), 1.94 (d, *J* = 18.3 Hz, 2H, 2*x*CH), 1.64 (ddd, *J* = 13.8 Hz, *J* = 9.5 Hz, *J* = 4.5 Hz, 2H, 2*x*CH), 1.44 (ddd, *J* = 12.6 Hz, *J* = 9.7 Hz, *J* = 3.5 Hz, 2H, 2*x*CH), 1.11 (s, 6H, 2*x*CH_3), 0.87 (s, 6H, 2*x*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 214.82 (2*x*C=O), 58.11 (2*x*C), 47.98 (2*x*C), 45.80 (2*x*CH_2S), 45.56 (4*x*CH_2N piperazine), 42.72 (2*x*CH), 42.49 (2*x*CH_2), 26.86 (2*x*CH_2), 25.07 (2*x*CH_2), 19.82 (2*x*CH_3), 19.70 (2*x*CH_3).IR (KBr): 2970, 1734, 1340, 1158, 1089, 946 cm^{-1}. Anal. Calcd for $C_{24}H_{38}N_2O_6S_2$: C, 55.98; H, 7.45; N, 5.45. Found: C, 55.94; H, 7.54; N, 5.53.

*2.2. Preparation of bis(hydroxysulfonamides) **5–7***

The general procedure of reduction of **1–3** to obtain **5–7** is as follows. The solution of corresponding diketone (1.5 mmol) in THF (10 ml) was cooled to −50 °C under argon atmosphere. L-Selectride (12 mmol, 1 M solution in THF) was then slowly added. The mixture was stirred at this temperature for 1 h, allowed to warm up to the room temperature, and stirred for 4 days. Then reaction mixture was cooled to 0 °C, quenched by addition of water (1 ml), EtOH (8 ml), 3 M NaOH (10 ml) and 30% H_2O_2 (8 ml). The solution was saturated with K_2CO_3 and extracted with CH_2Cl_2 (3× 20 ml). Combined organic phase was washed with water, brine and dried over $MgSO_4$. The drying agent was filtered out, solvent was evaporated in vacuo. The obtained precipitate was crystallized from ethanol.

*2.2.1. (+)-N,N′-(ethane-1,2-diyl)bis((2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptan-1-yl)methanesulfonamide) (**5**)*

Colorless solid (68.5%), mp 180–184 °C, $[\alpha]_D^{20}$ = −52.10 [*c* = 1.0 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.70 (bs, 2H, 2*x*NH), 4.07–4.03 (m, 2H, 2*x*CHOH), 3.67 (t, *J* = 5.7 Hz, 2H, 2*x*OH), 3.49, 2.93 (2d, *J* = 13.8 Hz, 2 × 2H, 2*x*CH_2S), 3.33 (s, 4H, 2*x*CH_2N), 1.83–1.64 (m, 12H, 6*x*CH_2), 1.51–1.43 (m, 2H, 2*x*CH), 1.05, 0.82 (2s, 2*x*6H, 2*x*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 76.25 (2*x*CHOH), 52.22 (2*x*CH_2S), 50.34 (2*x*C), 48.81 (2*x*C), 44.36 (2*x*CH), 43.59 (2*x*CH_2N), 39.27 (2*x*CH_2), 30.36 (2*x*CH_2), 27.33 (2*x*CH_2), 20.52 (2*x*CH_3), 19.88 (2*x*CH_3). IR (Nujol): 3535, 3256, 1314, 1142, 1075, 880, 790, cm^{-1}. Anal. Calcd for $C_{22}H_{40}N_2O_6S_2$: C, 53.61; H, 8.19; N, 5.69. Found: C, 53.65; H, 8.11; N, 5.65.

*2.2.2. (+)-N,N′-(propane-1,3-diyl)bis((2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptan-1-yl)methanesulfonamide) (**6**)*

Colorless solid (77.5%), mp 184–188 °C, $[\alpha]_D^{20}$ = −50.04 [c = 1.0 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.11 (t, *J* = 6.3 Hz, 2H, 2*x*NH), 4.08–4.04 (m, 2H, 2*x*CHOH), 3.45, 2.89 (2d, *J* = 13.8 Hz, 2*x*2H, 2*x*CH_2S), 3.33–3.27 (m, 6H, 3*x*CH_2), 1.85–1.64 (m, 12H, 6*x*CH_2), 1.55–1.45 (m, 2H, 2*x*CH), 1.06, 0.83 (2s, 12H, 4*x*CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 76.32 (2*x*CHOH), 52.04 (2*x*CH_2), 50.34 (2*x*C), 48.78 (2*x*C), 44.37 (2*x*CH), 39.95 (2*x*CH_2), 39.15 (2*x*CH_2), 31.02 (CH_2), 30.44 (2*x*CH_2), 27.33 (2*x*CH_2), 20.54 (2*x*CH_3), 19.88 (2*x*CH_3). IR (HCB): 3448, 3270, 2954, 1452, 1400, 1311, 1079, 1048, 1018 cm^{-1}. Anal. Calcd for $C_{23}H_{42}N_2O_6S_2$: C, 54.50; H, 8.36; N, 5.53. Found: C, 54.43; H, 8.28; N, 5.64.

*2.2.3. (+)-N,N′-(butane-1,4-diyl)bis((2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptan-1-yl)methanesulfonamide) (**7**)*

Colorless solid (91.8%), mp 125–130 °C, $[\alpha]_D^{20}$ = −42.91 [c = 1.0 ($CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.87 (t, *J* = 6.3 Hz, 2H, 2*x*NH), 4.07 (q, *J* = 4.2 Hz, 2H, 2*x*CHOH), 3.45, 2.89 (2d, *J* = 13.8 Hz, 2*x*2H, 2*x*CH_2S),3.28 (d, *J* = 3.9 Hz, 2H, 2*x*OH), 3.25–3.10 (m, 4H, 2*x*CH_2N), 1.84–1.65 (m, 16H, 8xCH_2), 1.55–1.45 (m, 2H, 2*x*CH), 1.06, 0.83 (2s, 12, 4xCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 76.57 (2*x*CHOH), 52.01 (2*x*CH_2), 50.35 (2*x*C), 48.76 (2*x*C), 44.39 (2*x*CH), 42.77 (2*x*CH_2), 39.10 (2*x*CH_2), 30.45 (2*x*CH_2), 27.35 (2*x*CH_2), 27.12 (2*x*CH_2), 20.56 (2*x*CH_3), 19.90 (2*x*CH_3). IR(Nujol): 3271, 2359, 1454, 1377, 1310, 1141, 780 cm^{-1}. Anal. Calcd for $C_{24}H_{44}N_2O_6S_2$: C, 55.34; H, 8.52; N, 5.38. Found: C, 55.29; H, 8.47; N, 5.41.

2.3. Enantioselective of addition diethylzinc to benzaldehyde

The reaction of $ZnEt_2$ addition was performed according to Scheme 1, under dry argon. Titanium tetraisopropoxide (0.42 ml, 1.4 mmol) was added to the ligand **1–7** (0.2 mmol) dissolved in methylene chloride (5 ml). The mixture was stirred for 1h at room temperature, cooled to −50 °C, and diethylzinc (3 ml of 1 M hexane solution, 3 mmol) was added. Stirring was continued at this temperature, and benzaldehyde (0.1 ml, 1 mmol) was added. The mixture was allowed to warm up to the room temperature and stirred for the period of time indicated in Table 1. The reaction was quenched with 1 M HCl (10 ml), and insolubles were filtered out. The organic layer was separated, and the aqueous layer was extracted three times with 5 ml of ethyl acetate. Combined organic extracts were washed with brine, dried over $MgSO_4$ and purified by column chromatography (hexane–ethyl acetate, 5:1) to give 1-phenylpropanol. The enantiomeric excess was determined by GC analysis using a β-Dex column.

3. Results and discussion

Bis(ketosulfonamide) ligands **1–3** were synthesized from diamines and (+)-10-camphorsulfonic acid chloride. Hydroxy ligands **5–7** were obtained by the reduction of the carbonyl group in **1–3** ligands with L-Selectride (Scheme 2). The bis(sulfonamide) ligands were applied in the asymmetric addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide. The enantiomeric excess ee% was determined by GC method using a Supelco β-Dex column, while the reaction yield was determined gravimetrically, the respective data are presented in Table 1. First series of processes was performed for the **1–7** ligands dissolved in CH_2Cl_2, and bound to $Ti(O^iPr)_4$, with $ZnEt_2$ added after pre-equilibration of the system. Finally, freshly distilled benzaldehyde was added and the mixture was stirred for the time indicated in Table 1. The stereoselective reduction of the ligands resulted in the R-enantiomers of the 2-hydroxy ligands **5–7**, as determined by X-ray structural analysis for **6**.

The absolute configuration of the product of the catalyzed reaction depends on the nature of the ligand used. The obtained results indicated that ligands possessing the carbonyl group (**1–4**) gave (*R*)-1-phenylpropanol as a major product, but revealed only weak asymmetric induction in the investigated process. The enantiomeric excess ee% obtained for ligands **1**, **2** and **4** was very small, while ligand **3** gave only modest enantioselectivity (Table 1, entries 1, 3, 7 and 5, respectively). Bis(hydroxysulfonamides) **5–7** gave significantly higher enantiomeric excesses and (*S*)-1-phenylpropanol as a major product. The best results were obtained for ligand **6** (Table 1, entry 11). The observed difference between the two groups of sulfonamide ligands might be explained based on the hypothesis, that oxygen atom bound to C_2 might participate in the ligand coordination to Ti, therefore affecting the position of bulky norbornyl moiety. Also the η^2-*N*,*N* coordination of bis(ketosulfonamide) ligands similar to that found in Ref. [15,18], with the norbornyl moiety distant from the substrate position, would be consistent with the small ee% values and slight preference for the *R* product.

On the other hand, the enantiomeric excesses 31 to 62% of *S* product (Table 1) obtained with the use of ligands **5–7** might be rationalized consistently with the explanation presented above. The *R* configuration on C_2 results in the norbornyl moiety position closer to the axial bond between the substrate and Ti, than that postulated for carbonyl ligands. Consequently, the steric effect of bulky norbornyl causes positioning of the substrate phenyl ring away from the camphor moiety, and addition of ethyl to the *Si* side of the benzaldehyde, giving the excess of the *S* product.

We have found, that the reversed sequence of the reagent addition ($ZnEt_2$ followed by $Ti(O^iPr)_4$, Zn/Ti series) had not changed the configuration of the product, when compared to the primary $ZnEt_2$ addition procedure described above. Also, the yield of the reaction was not affected. However, the ee% values obtained in that series were slightly lower from those determined for the Ti/Zn series. The product of the $ZnEt_2$ addition was not detected, when the reaction was conducted in an absence of $Ti(O^iPr)_4$. Those observations might be coupled to the change of the ligand coordination and consequently different architecture of the catalytically active heterodinuclear complex.

Bauer and Gajewiak had investigated the catalytic activity for the ligand identical to our bis(hydroxysulfonamide) **5** [5], with the reported ee value of 12% for the product of the *R* configuration. Our experiment gave 31% ee but with *S* configuration of the obtained product (Table 1). In both cases the reaction was conducted under identical conditions and the same order of metal compounds dosage Ti/Zn. The only difference was the reaction time for our experiment, longer by 2 h than that reported by Bauer and Gajewiak. Therefore, comparison of the reaction conditions does not explain that difference in the absolute configuration of the product. In our procedure, the absolute configuration of the product was determined by GC based on the literature data [25] and the retention time for all the ligands used. For both the Zn/Ti and Ti/Zn series with bis(hydroxysulfonamides) we consistently detected the *S* configuration of the formed asymmetric center, and that seems to reflect the stereochemical restraints within the molecule of the heterodinuclear complex catalyst. Bauer and Gajewiak [5] had coupled the inversion of the product absolute configuration for that ligand with the *N*,*N* coordination of the ligand to the same metal site, with the camphorsulfonyl moiety not involved. Contrary, our data discussed above indicate that the presence of the additional asymmetric center at position 2 of the norbornyl moiety affects the position of the ring system in the coordination sphere and determines the positioning of the substrate.

The absolute configuration of the product of the catalyzed reaction depends on the nature of the ligand used. The mode of coordination of the sulfonamides to Ti center in the catalyst molecule affects the enantioselectivity of the addition and the substrate specificity [4,5]. Therefore the crystal structure determination for the bis(sulfonamides) was carried out. The details of the data collection and structure refinement are presented in Table 2. The geometry of the bicyclo[2.2.1]heptan ring system is similar in all the structures. The only changes are caused by the presence of either carbonyl oxygen or hydroxyl group bound to the C2 carbon. In the investigated structures the C2=O and C2–OH distances are 1.196(5)–1.220(3) Å and 1.41(2)–1.437(9) Å, respectively, the values typical for these types of bonds. Table 3 presents the details of the H-bonds.

The asymmetric part of the crystal structure of **1** is presented in Fig. 1. The central CH_2–CH_2 bridge has a trans conformation, the N1–C11–C12–N1A torsion angle being 178.0(2)°. Position of the SO_2 groups relative to the camphor moieties is described with the C1–C10–S1–N1 and C1A–C10A–S1A–N1A torsion angles being 158.2(2) and −166.0(2)°, respectively. Position of the sulfonamide moiety is different in the two parts of the molecule. The values of O1–C2–C1–C10, C2–C1–C10–S1 and O1A–C2A–C1A–C10A, C2A–C1A–C10A–S1A are 16.9(3), −92.8(2)° and 12.5(4), 78.3(2)°, respectively. The observed difference is caused by the non-equivalent H-bonds involving the carbonyl O1 atoms and the sulfonamide N–H groups (Table 3). Such a conformation results in the intramolecular O1...O2 and O1A...O2A distances being 3.199(3) Å and 3.177(3) Å. These pairs of atoms might be involved in a coordination to Ti(IV) center for a heterodinuclear complex catalyst. However, the X-ray structures of the catalytically active

Table 2
Crystallographic data for bis(sulfonamide) ligands: **1**,**2**,**3** and **6**

	1	**2**	**3**	**6**
Formula sum	$C_{22}H_{36}N_2O_6S_2$	$C_{23}H_{38}N_2O_6S_2$	$C_{25}H_{42}N_2O_6S_2Cl_2$	$C_{23}H_{42}N_2O_6S_2$
Formula weight	488.65	502.67	601.63	506.71
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12$	$P1$
Unit cell dimensions				
a (Å)	9.408 (1)	6.832 (5)	17.249 (3)	7.117(1)
b (Å)	10.746 (1)	8.743 (6)	7.119 (1)	11.989(1)
c (Å)	24.699 (2)	42.590 (3)	12.397 (2)	15.781(2)
α (°)				93.060(8)
β (°)				102.22(1)
γ (°)				99.71(1)
V (Å^3)	2497.0(4)	2544.0(5)	1522.3(4)	1291.6(3)
Z	4	4	2	2
Density (calculated) (mg/m^3)	1.300	1.312	1.313	1.303
Absorption coefficient (mm^{-1})	0.252	0.249	0.390	0.246
F(000)	1048	1080	640	548
Crystal size (mm)	0.37 × 0.24 × 0.23	0.35 × 0.34 × 0.09	0.27 × 0.22 × 0.22	0.35 × 0.29 × 0.10
θ range for data collection (°)	2.72–31.36	2.87–31.38	2.88–31.21	2.08 to 31.32
Index ranges	$-13 <= h <= 13$, $-12 <= k <= 15$, $-32 <= l <= 34$	$-9 <= h <= 7$, $-12 <= k <= 12$, $-59 <= l <= 62$	$-24 <= h <= 24$, $-10 <= k <= 10$, $-14 <= l <= 17$	$-10 <= h <= 8$, $-17 <= k <= 17$, $-21 <= l <= 22$
Reflections collected	24821	25250	15061	12873
Independent reflections	7600 [R(int) = 0.0625]	7775 [R(int) = 0.0916]	4649 [R(int) = 0.0572]	9599 [R(int) = 0.0583]
Transmission (max/min)	0.9443/0.9125	0.9779/0.9178	0.9205/0.9020	0.9761/0.9188
Data/restraints/parameters	7600/0/293	7775/0/302	4649/0/179	9599/7/616
Goodness-of-fit on F^2	0.977	1.088	1.015	0.913
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0540	$R1$ = 0.1084	$R1$ = 0.0614	$R1$ = 0.0805
	w$R2$ = 0.1134	w$R2$ = 0.1996	w$R2$ = 0.1449	w$R2$ = 0.2074
R indices (all data)[a]	$R1$ = 0.0834, w$R2$ = 0.1268	$R1$ = 0.1417, w$R2$ = 0.2181	$R1$ = 0.0791, w$R2$ = 0.1547	$R1$ = 0.1473, w$R2$ = 0.2560
Largest diff. peak and hole (e Å^{-3})	0.301 and −0.383	0.650 and −0.462	0.268 and −0.387	0.604 and −0.316
Flack (x)	0.02 (7)	0.1 (1)	−0.1 (1)	0.0 (1)

[a] $R1 = \Sigma||F_0|-|F_c||/\Sigma|F_0|$; $wR2 = [\Sigma w(F_0^2 - F_c^2)^2 / \Sigma(w|F_0|^2)^2]^{1/2}$.

Table 3
Hydrogen bonds in crystal structures of **1–3** and **6**

D–H	d(D–H)	d(H...A)	<DHA	d(D...A)	A
1					
N1–H1N	0.900	2.275	130.00	2.935(2)	O1A [$x+1/2, -y+3/2, -z$]
N1A–H1NA	0.900	2.374	121.01	2.941(3)	O1 [$x-1/2, -y+1/2, -z$]
2					
N1A–H3NA	0.984	1.919	170.66	2.894(6)	O3 [$x+1, y, z$]
3					
N1–H1N	0.833	2.094	169.30	2.917(2)	O2[$-x+1/2, -y-1/2, -z$]
6					
O5–H5A	0.820	2.301	139.05	2.969(8)	O1
N1–H1B	0.900	2.097	151.90	2.922(8)	O12 [$x-1, y-1, z$]
N2–H2C	0.900	2.233	154.71	3.07(1)	O1 [$x+1, y, z$]
O7–H7A	0.820	2.175	133.98	2.807(7)	O5
N3–H3D	0.860	2.376	148.54	3.142(8)	O7 [$x+1, y, z$]
N4–H4C	0.860	2.363	144.59	3.105(9)	O8 [$x+1, y, z$]
O12–H12A	0.820	2.143	139.95	2.820(7)	O10

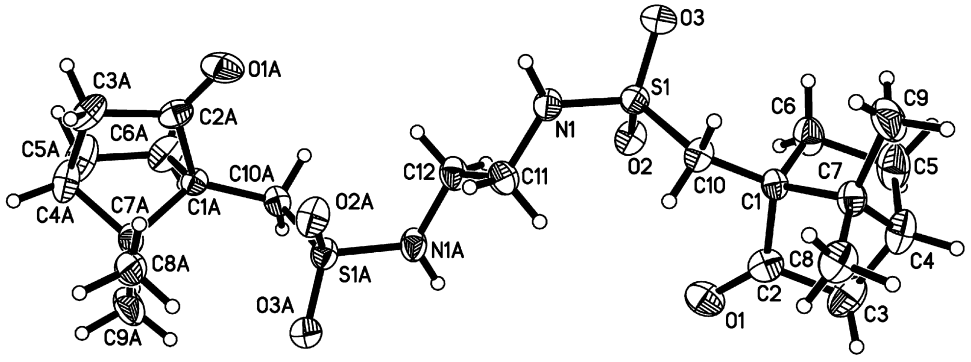


Fig. 1. Structure of (+)-*N*,*N*′-(ethane-1,2-diyl)bis((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methanesulfonamide) (**1**). The thermal ellipsoids displayed at 30% probability level.

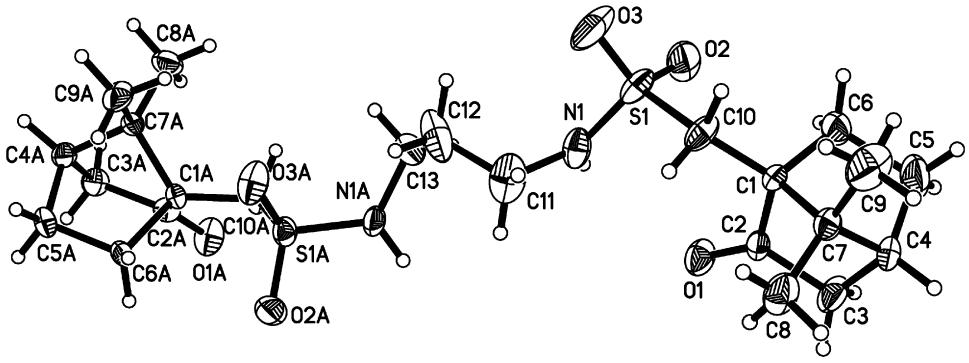


Fig. 2. Structure of (+)-*N*,*N*′-(propane-1,3-diyl)bis((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methanesulfonamide) (**2**), the thermal ellipsoids displayed at 30% probability level.

complexes revealed either η^2-*N*,*N* [15] or η^2-*N*,*O* coordination involving atoms of the sulfonamide moiety [12].

The molecule of **2** constituting the asymmetric part of the crystal structure is presented in Fig. 2. The C_3 bridge conformation is described with the S–N–C–C and N–C–C–C torsion angles being 95.6(7), 70.4(9)° and 93.8(8), 74.6(8)° for S1…C13 and S1A…C11 parts of the molecule, respectively. Position of the sulfonamide moieties relative to the camphor fragment is different in two parts of molecule, as described by the torsion angles N1–S1–C10–C1 and S1–C10–C1–C2: 85.0(5), −61.2(6)° and those −176.3(3) and −148.4(3)° for the corresponding part of molecule. The structure reveals the presence of a single intermolecular N1A…O3[*x* + 1,*y*,*z*] H-bond of 2.894(6) Å. An intramolecular interaction is found between O1…H–N1 groups, the O1…N1 distance being 2.884(6) Å. That interaction causes the molecular conformation appropriate for either *N*,*N* or *N*,*O* coordination to Ti. The η^3-N_2O coordination involving the ring-bound oxygen, analogous to that suggested in [11] is possible. That indicates the flexibility of the camphor–sulfonamide fragment, what would enable different coordination modes.

The complete molecule of **3** is presented in Fig. 3. The overall shape of the molecule similar to the C letter, with the central C13–C13A bond by the 2-fold axis relating two halves of the molecule. The CH_2Cl_2 solvent molecule was found in the structure. The crystal structure reveals the conformational disorder of the C_4 central bridge. The major population (56%) is in the trans conformation, while in the alternative conformation (population of 44%) the C11–C12–C12A–C11A torsion angle is −98.1(9)°. The orientation of sulfonamide moiety relative to the ring system is described with C1–C10–S1–N1 and C2–C1–C10–S1 being 55.7(2) and −90.8(3)°,

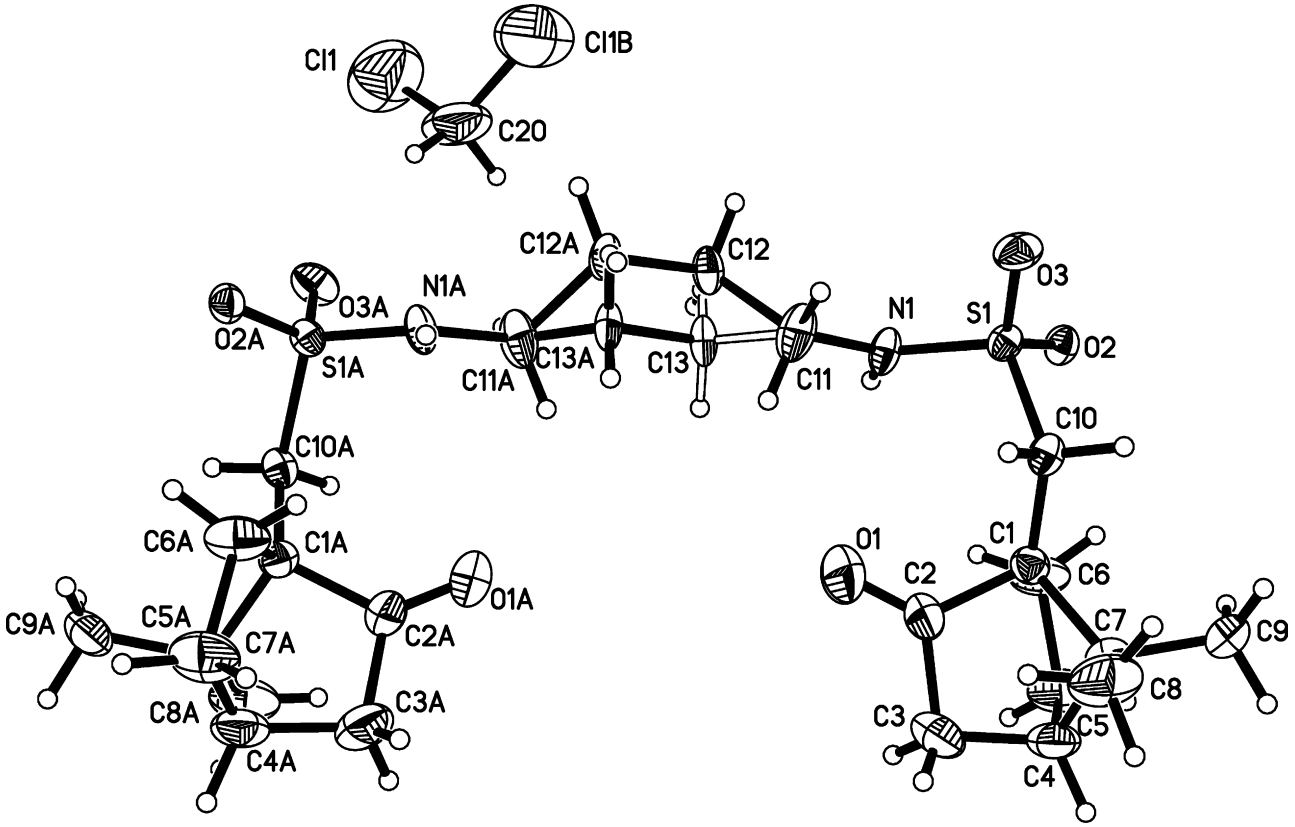


Fig. 3. Structure of (+)-*N*,*N*′-(butane-1,4-diyl)bis((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methanesulfonamide) (**3**). The thermal ellipsoids ploted at 30% probability level.

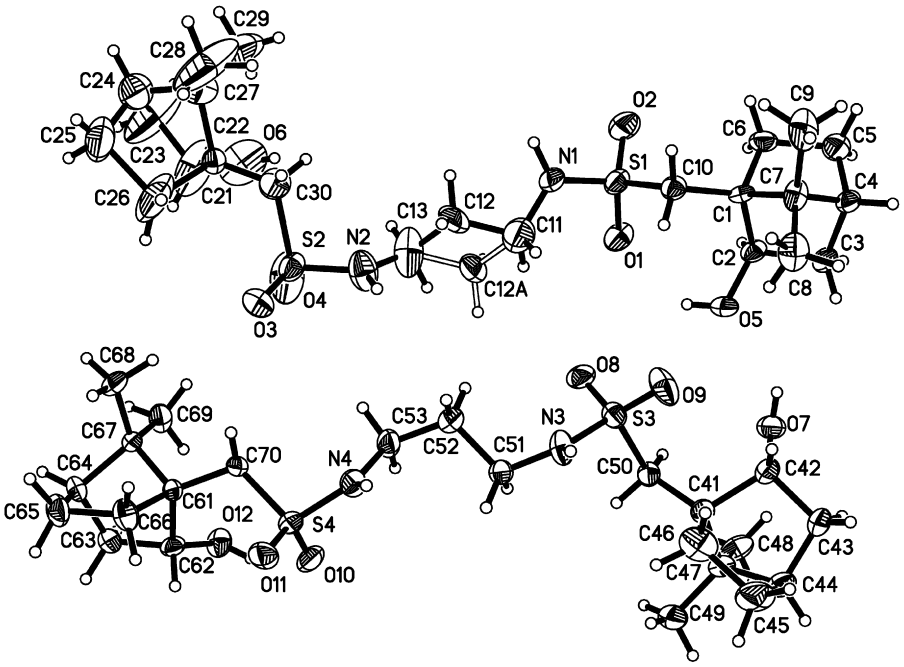


Fig. 4. Structure of (+)-*N*,*N*′-(propane-1,3-diyl)bis((2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptan-1-yl)methanesulfonamide) (**6**), with thermal ellipsoids displayed at 30% probability level.

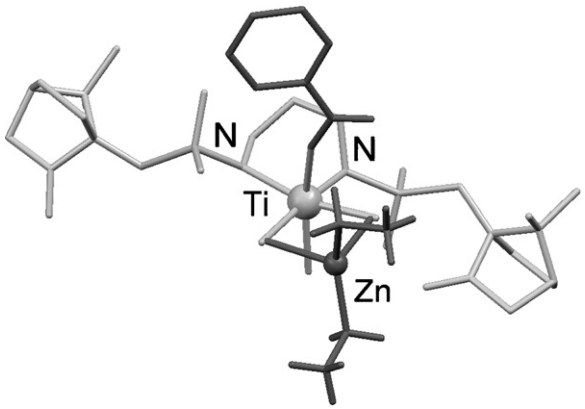
respectively. In that conformation the O1...N1 intramolecular distance is 3.234(4) Å. The intermolecular N1...O2[-*x* + 1/2,*y*-1/2,-*z*] H-bond exists, the N...O distance being 2.917(2) Å (Table 3). With the conformation found in the structure, such ligands might play a role of bi-, tri- or even four-dentate ligands, similar to [11,12,15].

Crystal structure of **6** is presented in Fig. 4. The reduction of **2** with L-Selectride resulted in the (2*R*) configuration of the formed chiral centers as confirmed by the Flack method [22]. The major $ZnEt_2$ addition product obtained in the reaction has the reversed configuration of the chiral center (1(*S*)-phenylpropanol). The structure consists of two molecules in the asymmetric unit. The central C_3 bridge in both molecules of **6** has conformation similar to that found in **2**, one of them revealing the conformational disorder. The torsion angles C1–C10–S1–N1 describing the spatial relation between the ring system and the sulfonamide moiety are close to 180° for three fragments and −83.7(6) for the fragment containing N3, while the C2–C1–C10–S1 angles vary between −52.2(6) and 72.9(7)°. Comparison of these molecules with **2** reveals the slight elongation of the intramolecular N...N distance being 4.54(1) and 4.384(8) Å for two molecules of **6**, while for **2** it is 3.970(6) Å. That would exclude the possibility of the η^2-*N*,*N* ligand coordination with no significant conformational changes. The structure reveals an existence of intra- and intermolecular H-bonds (Table 3). Of those, the single intramolecular OH...O(sulfo) found in each molecule strongly affects the molecular conformation, what results in the O...O(sulfo) distances being 2.820(7) and 2.969(8) Å (Table 3) for two moieties.

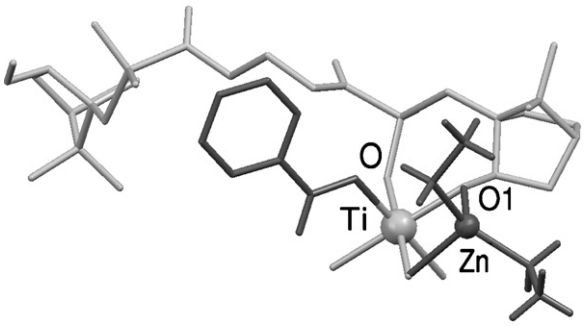
Crystal structure of **1** suggests the possible formation of the complex with the η^2-*N*,*N* coordination. The activity data reported here suggest, that this mode of coordination is consistent with the formation of (*R*)-1-phenylpropanol and the low ee% of 5.8% (Table 1). This mode of ligand binding to Ti is in accordance with the observed deprotonation of the sulfonamide NH upon the complex formation.

For **2**, the η^2-*N*,*O*1 or η^3-N_2O coordination analogous to that reported by Pritchett et al. [12] would be consistent with the observed *R* configuration of the major product, but should result in the ee% value higher than the observed 2%. The molecular conformation found in the crystal structure results in position of two N atoms enabling their participation in a formation of two Ti–N bonds analogous to Armistead et al. [15]. The N1...N1A distance of 3.970 Å is slightly too large and η^2-*N*,*N* coordination and same conformational adjustments would be required, compared to the free sulfonamide structure **2**. The η^2-*N*,*N* geometry of the catalyst would be consistent with the observed *R* configuration of the addition product and relatively low ee% (Table 1, Scheme 3).

Conformation found in the structure of **3** suggests the possible coordination η^4-N_2O_2, analogous to that suggested by Qui et al. [11], consistent with the reported chirality of the product and the ee%. However, such mode of ligand binding would prevent the formation of Ti–$ZnEt_2$ heterodinuclear complex required for the catalysis. The possible coordination η^2-*N*,*N* would explain 12 ee% of the (*R*)-1-phenylpropanol product observed in the experiment reported here.



Scheme 3. Hypothetic structure of the active complex of Ti(sulfonamide)–$ZnEt_2$ for **2**. The proposed η^2-*N*,*N* coordination results in only little steric control of the substrate orientation, what is consistent with the low ee% values and main *R* product determined for ligand **1–3**. The substrate molecule and $ZnEt_2$ displayed in black. Model obtained by optimization with molecular mechanics as implemented in Arguslab program [26] using UFF forcefield.



Scheme 4. Hypothetic orientation of the substrate in the Ti(sulfonamide)–$ZnEt_2$ active complex with the η^2-*O,O* coordination of ligand **6**. The proposed orientation of benzaldehyde is consistent with the reported *S* configuration of the product and observed high enantiomeric excess. Model obtained by molecular mechanics minimization with the UFF forcefield implemented in Arguslab [26].

The structure of bis(ketosulfonamide) **4**, containing the piperazine bridge, was reported previously [24]. The piperazine bridge present in the molecular architecture prevents the η^2-*N,N* mode of coordination, possible for other bis(sulfonamides) reported here. The reasonable mode of coordination seems to be the η^2-*O,O via* the sulfonamide oxygen atoms. The determined activity of the catalytic complex with that sulfonamide ligand is relatively low, and the small excess of the *R* product has been found (Table 1).

The conformation of **6** indicates the possibility of η^2-*O,O* coordination to Ti *via* O1 and O(sulfo) atoms, analogous to the intramolecular H-bond. Such a conformation would be consistent with the observed (1*S*) configuration of the product and high ee% values found in the reported experiments (Scheme 4).

4. Conclusions

We report the synthesis of C_2-symmetrical ligands derived from achiral 1,2-, 1,3- and 1,4-diamines and (+)-10-camphorsulfonic acid chloride. The (*R*)-1-phenylpropanol produced in the reaction conducted in a presence of investigated bis(ketosulfonamides) **1–3** suggests that the probable mode of their coordination is η^2-*N,N*. That seems to correspond to the conformational flexibility found in the reported crystal structures. The ligand containing the piperazine bridge might coordinate to Ti in the η^2-*O,O* mode, *via* the sulfonamide oxygen atoms. Both these coordination modes are consistent with the ee% and the product configuration reported in this paper. The inverted configuration of the product detected after use of bis(hydroxysulfonamides) suggests the participation of the hydroxyl oxygen in the ligand coordination to Ti.

In a group of bis(ketosulfonamides), the best catalytic efficiency found for the ligand with C_4 bridge separating the sulfonamide moieties suggests the η^2-*N,N* coordination. For the bis(hydroxysulfonamides), the most efficient ligand possesses the C_3 bridge. Its activity might result from the η^2-*O,O* coordination, suggested by the crystal structure and the activity data.

Acknowledgements

The research was partly supported by 526-Ch grant of the Rector of N. Copernicus University and by ZPORR grant (AK).

References

[1] N. Oguni, T. Omi, Tetrahedron Lett. 25 (1984) 2823.
[2] M. Kitamura, S. Suga, K. Kawai, R. Noyori, J. Am. Chem. Soc. 108 (1986) 6071.
[3] M. Yoshioka, T. Kawakita, M. Ohno, Tetrahedron Lett. 30 (1989) 1657.
[4] C.-D. Hwang, B.-J. Uang, Tetrahedron: Asymmetry 9 (1998) 3979.
[5] T. Bauer, J. Gajewiak, Tetrahedron 59 (2003) 10009.
[6] M. Yus, D.J. Ramon, O. Prieto, Tetrahedron: Asymmetry 14 (2003) 1103.
[7] V.J. Forrat, D.J. Ramon, M. Yus, Tetrahedron: Asymmetry 16 (2005) 3341.
[8] A. Hui, J. Zhan, J. Fan, Z. Wang, Tetrahedron: Asymmetry 17 (2006) 2101.
[9] V.J. Forrat, D.J. Ramon, M. Yus, Tetrahedron: Asymmetry 17 (2006) 2054.
[10] D.J. Ramon, M. Yus, Synlett 15 (2007) 2309.
[11] J. Qiu, Ch. Guo, Z. Xumu, J. Org. Chem. 62 (1997) 2665.
[12] S. Pritchett, P. Gantzel, P.J. Walsh, Organometallics 16 (1997) 5130.
[13] S. Pritchett, D.H. Woodmansee, P. Gantzel, P.J. Walsh, J. Am. Chem. Soc. 120 (1998) 6423.
[14] S. Pritchett, P. Gantzel, P.J. Walsh, Organometallics 18 (1999) 823.
[15] L.T. Armistead, P.S. White, M.R. Gagné, Organometallics 17 (1998) 216.
[16] E. Royo, J.M. Betancort, T.J. Davis, P. Carroll, P.J. Walsh, Organometallics 19 (2000) 4840.
[17] S. Hamura, T. Oda, Y. Shimizu, K. Matsubara, H. Nagashima, J. Chem. Soc., Dalton Trans. (2002) 1521.
[18] G. Pescitelli, L. Di Bari, P. Salvadori, Organometallics 23 (2004) 4223.
[19] K.-H. Wu, H.-M. Gau, Organometallics 23 (2004) 580.
[20] S. Kii, K. Maruoka, Chirality 15 (2003) 68.
[21] Oxford Diffraction, CrysAlis CCD and CrysAlis RED software, Oxford Diffraction, Abingdon, Oxfordshire, England, 2000.
[22] H.D. Flack, Acta Cryst. A 39 (1983) 876.
[23] G.M. Sheldrick, SHELX97, University of Göttingen, Germany, 1997.
[24] M. Ullrich, A. Kozakiewicz, M. Wełniak, A. Wojtczak, Acta Cryst. E 62 (2006) o3750.
[25] D. Steiner, S.G. Sethofer, Ch.T. Goralski, B. Singaram, Tetrahedron: Asymmetry 13 (2002) 1477.
[26] M.A. Thompson, ArgusLab 4.0.1, Planaria Software LLC, Seattle, WA, http://www.arguslab.com.