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# Synthesis, structure and activity of sulfonamides derived from (+)-camphor in the enantioselective addition of diethylzinc to benzaldehyde

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ABSTRACT

New chiral sulfonamides derived from (+)-camphor, with different substituents on camphor C2 and sulfonamide N, were synthesized. Their activity was tested in the reaction of $Et_2Zn$ addition to benzaldehyde. The yield of the reaction was 44–96%, the enantiomeric excess was 1–69%. Sulfonamides possessing the 2-hydroxyl group gave an excess of 1-(*S*)-phenylpropanol, while catalysts containing other sulfonamides gave 1-(*R*)-phenylpropanol as a major product. The best catalytic efficacy was observed for sulfonamides with (*R*)-C2–OH group, while the use of thioketo- and mercaptosulfonamides resulted in low enantiomeric excess and yields not exceeding 60%. Crystal structures have been determined for sulfonamides with N-benzyl moiety and different substituents on the C2 atom. The structural analysis revealed the presence of intramolecular N···O(C2) and $O_{sulfo}$···O(C2) H-bonds, what confirms the ability of these molecules to adopt the conformation required for their bidentate coordination to Ti(IV) *via* the sulfonamide group and substituent at C2. The coordination mode for investigated sulfonamides was determined with the IR spectra for five obtained Ti(IV) complexes and crystal structure analysis of the ligands. The 3D structures of Ti(IV) complex catalysts containing investigated sulfonamides were postulated, which are consistent with the reported chirality of the addition product and observed % ee.



## 1. Introduction

Catalytic synthesis is currently one of the most intensely developing fields in the organic chemistry. Currently, the asymmetric addition of organometallic compounds to one of the heterotopic sides of the carbonyl group is extensively investigated topic. Numerous catalytic systems are currently tested for an addition of organozinc compounds to aldehydes and ketones [1–5]. The prototypic reaction of that kind is an addition of diethylzinc to benzaldehyde (Scheme 1), which is usually used for testing the efficacy of the developed catalysts. The addition is usually performed in a presence of $Ti(O^iPr)_4$ which forms complexes with different organic auxiliaries, such as 1,2-, 1,3- and 1,4-aminoalcohols, aminotiols, diamines, diols and also sulfonamides, and subsequently activates the substrate molecule [6,7]. Usually the excess of $Ti(O^iPr)_4$ is used, what enhances the transfer of the alkyl group to aldehyde or ketone.

The use of monosulfonamide ligands derived from borneol in the enantioselective $Et_2Zn$ addition to benzaldehyde was reported for the first time by Ramón and Yus [8]. The highest catalytic efficiency was obtained for the sulfonamide with N-benzyl moiety and the (*R*)-C2–OH group in the camphor ring, with 71% ee for the synthesis of (*S*)-1-phenylpropanol [8]. The use of the same ligand in the asymmetric addition to acetophenone led to the tertiary (*S*)-alcohol with 84% ee [3].

Hui et al. [9] investigated the effects of substitution in the aromatic ring of monosulfonamides on the enantioselectivity of the $Et_2Zn$ addition to different aldehydes. Results indicated that the electron-withdrawing substituents make a reaction more difficult, while the presence of electron-donating substituents enhances the reaction and increases the reaction rate. It was found that the *para*-substituted ligands gave higher enantioselectivity of addition (66–72% ee) than those found for *meta*- and *ortho*- (37–68% ee) [9]. Authors also investigated the role of the solvent. The highest catalytic efficiency was observed for the reaction conducted in toluene, while the use of MeCN gave the worst results [9]. Authors suggested that polar media enhanced the solvolysis and decomposition of $Et_2Zn$. The highest ee of 72% has been achieved in a synthesis of (*S*)-1-phenylpropanol with the ligand possessing the *para*-phenyl substituent. The use of the same ligand in the $Et_2Zn$ addition to other aldehydes resulted in the enantiomeric excess 2–83% ee [9].

Architecture of Ti(IV) complexes with the auxiliary ligands affects the catalytic efficacy. There are no reports on the structure of the catalyst molecules containing the ligands derived from camphor. The structure of $TiL_2$ complex with monosulfonamides was investigated by Hamura et al. [10]. That structure revealed the bidentate coordination of the ligand *via* O and N of the sulfonamide moiety, what resulted in positioning of the organic part of sulfonamide distant from the expected position of the substrate

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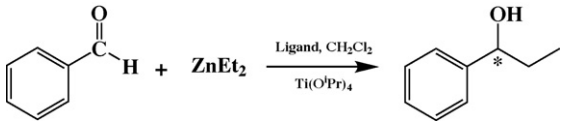
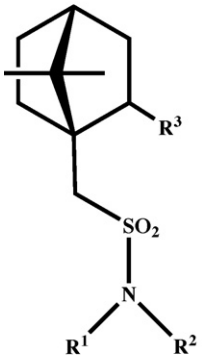



**Scheme 1.** Asymmetric addition of $Et_2Zn$ to benzaldehyde.

in the Ti(IV) coordination sphere. The research on $Ti_2L_2$ type complexes has been conducted for several sulfonamide ligands with the additional hydroxyl group in the amine moiety [11]. Structural results revealed the $\eta^2$ –NO coordination *via* the sulfonamide N and the hydroxyl O atom, with that atom bridging two Ti centers in a dimeric molecule. The Ti coordination sphere was a trigonal bipyramid.

Wu and Gau investigated the catalytic activity of $Ti_2$(monosulfonamide)$_2$ with similar ligands in the $Et_2Zn$ addition to benzaldehyde, obtaining (*R*)-1-phenylpropanol with 92–100% yields and 67–96% ee [12]. Their structural data showed different coordination sphere of two Ti ions in the dimeric complex. One Ti atom had the octahedral coordination sphere formed by N, O atoms of sulfonamide, hydroxyl O and the O$^i$Pr groups, while for the second Ti ion the sulfonamide oxygen does not participate in the formation of trigonal bipyramidal sphere. The binuclear complex $Ti_2L$ was also obtained with the single monosulfonamide ligand coordinating *via* N, O atoms of sulfonamide and hydroxyl O, which acted as a bridge [13]. The structural results on both types of complexes indicated that the additional donor group of the monosulfonamide ligand or the alkoxy ligand can act as the group bridging two metal centers.

The aim of the research reported here was to synthesize new ligands derived from camphor, including those containing sulfur atom at C2 position (Scheme 2). The catalytic efficacy of these chiral auxiliaries in the stereoselective addiction of $Et_2Zn$ to benzaldehyde was also determined. Crystal structures of selected ligands were investigated to find the relation between the molecular architecture and the observed catalytic properties of their Ti(IV) complexes.




| | $R^3$ | $R^1$ | $R^2$ |
|---|---|---|---|
| **1** | =O | H | Bn |
| **2** | =O | H | 4-$C_6H_4Me$ |
| **3** | =O | H | 2-$C_6H_4Me$ |
| **4** | =O | H | 2,4-$C_6H_3Me_2$ |
| **5** | =O | H | 3,4-$C_6H_3Me_2$ |
| **6** | =O | Me | Ph |
| **7** | =O | $^i$Bu | $^i$Bu |
| **8** | =O | morpholine | |
| **9** | =S | H | Bn |
| **10** | =S | H | 2-$C_6H_4Me$ |
| **11** | -SH | H | Bn |
| **12** | -SH | morpholine | |
| **13** | -OH | H | Bn |
| **14** | -OH | H | 4-$C_6H_4Me$ |
| **15** | -OH | H | 2-$C_6H_4Me$ |
| **16** | -OH | H | 2,4-$C_6H_3Me_2$ |
| **17** | -OH | H | 3,4-$C_6H_3Me_2$ |
| **18** | -OH | Me | Ph |
| **19** | -OH | $^i$Bu | $^i$Bu |
| **20** | -OH | morpholine | |

**Scheme 2.** Ligands **1**–**20** investigated in the enantioselective addition of $Et_2Zn$ to benzaldehyde.

## 2. Experimental

Melting points for **1**–**20** were determined using Boetius table. Rotations were measured on a Lot-Oriel S-2 automatic polymeter. 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 Perkin Elmer Spectrum RX I spectrophotometer. Elemental analyses were performed on ELEMENTARY Analysensysteme GmbH Vario MACRO CHN analyzer. GC analyses were performed on a Perkin Elmer 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 [14]. The absolute structure was determined by the Flack method [15]. Structures were solved and refined with the full-matrix least-squares procedure using SHELX-97 program package [16]. The structures **1**, **9**, **11** and **13** have been deposited with CCDC, the deposition numbers are CCDC 767832 to 767835, respectively.

### 2.1. Preparation of ketosulfonamides *1*–*8*

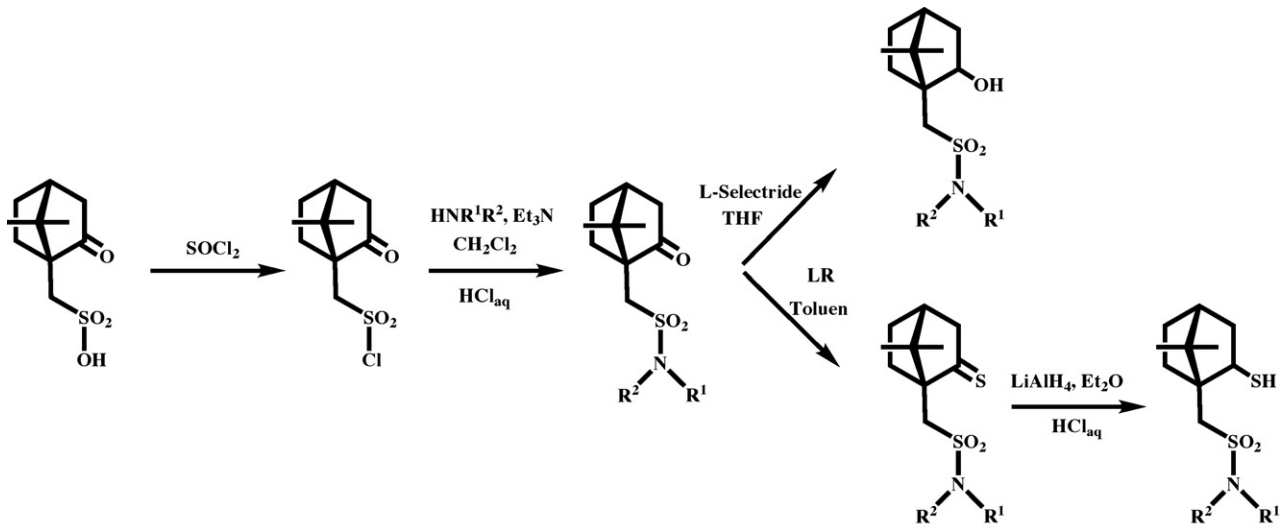
General procedure of synthesis of the investigated sulfonamides is shown on Scheme 3. Initially, the (+)-10-camphorsulfonic acid chloride was obtained from the respective sulfonic acid. The investigated ketosulfonamides were obtained as follows. The respective amine (97.1 mmol) was added into $CH_2Cl_2$ (350 ml) and 65.2 mmol of $Et_3N$. 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 the reaction mixture was stirred for 2.5 h. Subsequently 600 ml AcOEt was added to precipitate triethylammonium hydrochloride. The reaction mixture was then quenched by adding 200 ml water, 1 M aqueous HCl (200 ml) and brine (200 ml). After drying over anhydrous $Na_2SO_4$ and filtering, the solvent was evaporated under vacuum. The residue was dissolved in $CH_2Cl_2$, a solid product was precipitated with EtOH.

#### 2.1.1. *(1S,4S)-(N-benzyl)-(2-keto-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**1**)*

Colorless solid (90.0%), mp 52–53 °C, $[\alpha]_D^{20}$ = 7.7 [$c$ = 1.70 ($CHCl_3$)]. $^1H$ NMR (200 MHz, $CDCl_3$) δ (ppm): 7.43–7.22 (m, 5H, CH), 5.75 (t, $J$ = 5.8 Hz, 1H, NH), 4.36 (d, $J$ = 5.8 Hz, 2H, $CH_2$(Bn)), 3.13, 2.86 (2d, $J$ = 15.0 Hz, 2H, $CH_2S$), 2.41–2.25, 2.18–1.90, 1.50–1.35 (3m, 1, 5, 1H, $CH_2CH(CH_2)_2$), 0.94, 0.74 (2s, 6H, 2 × $CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$) δ (ppm): 216.65 (C=O), 136.89(C), 128.52 (2 × CH), 128.15 (2 × CH), 127.60 (CH), 59.03 (C), 50.37 ($CH_2$), 48.48 (C), 47.20 ($CH_2$), 42.70 ($CH_2$), 42.52 (CH), 26.79 ($CH_2$), 26.53 ($CH_2$), 19.57 ($CH_3$), 19.21 ($CH_3$). IR(KBr): 3246 (NH), 1728 (C=O), 1496 (HC=C), 1329, 1150 ($SO_2N$) cm$^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_3S_1$: C, 63.52; H, 7.21; N, 4.36. Found (%): C, 63.31; H, 7.11; N, 4.49.

#### 2.1.2. *(1S,4S)-N-(4-methylphenyl)-(2-keto-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**2**)*

Colorless solid (90.2%), mp 144–145 °C, $[\alpha]_D^{20}$ = 67.1 [$c$ = 1.75 ($CHCl_3$)]. $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm): 7.67 (s, 1H, NH), 7.21–7.10 (m, 4H, 4 × CH), 3.36, 2.83 (2d, $J$ = 15.3 Hz, 2H, $CH_2S$), 2.32 (s, 3H, $CH_3$), 2.49–2.41, 2.23–1.96, 1.55–1.42 (3m, 1, 5, 1H, $CH_2CH(CH_2)_2$), 0.95, 0.86 (2s, 6H, 2 × $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm): 217.34 (C=O), 135.39(C), 134.92 (C), 129.91




**Scheme 3.** Scheme of the synthesis of sulfonamide ligands derived from camphor.

(2 × CH), 122.55 (2 × CH), 59.67 (C), 49.04 (C), 48.61 ($CH_2$), 43.04 ($CH_2$), 42.77 (CH), 27.57 ($CH_2$), 27.02 ($CH_2$), 20.81 ($CH_3$), 19.83 ($CH_3$), 19.31 ($CH_3$). IR(KBr): 3305(NH), 1739 (C=O), 1442 (HC=C), 1334, 1162 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_3S_1$: C, 63.52; H, 7.21; N, 4.36. Found (%): C, 63.58; H, 7.19; N, 4.36.

*2.1.3. (1S,4S)-N-(2-methylphenyl)-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl) methanesulfonamide (**3**)*

Colorless solid (85.3%), mp 116–118 °C, $[\alpha]_D^{20}$ = 56.0 [*c* = 1.85 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.8 Hz, 1H, CH), 7.33 (s, 1H, NH), 7.25–7.08 (m, 3H, 3 × CH), 3.55, 2.99 (2d, *J* = 15.3 Hz, *J* = 15.0 Hz, 2H, $CH_2S$), 2.37 (s, 3H, $CH_3$), 2.50–2.39, 2.29–1.93, 1.53–1.43 (3m, 1, 5, 1H, $CH_2CH(CH_2)_2$), 1.03, 0.91 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 216.73 (C=O), 135.47(C), 131.41 (C), 131.19 (CH), 126.86 (CH), 125.66 (CH), 122.66 (CH), 59.48 (C), 50.23 ($CH_2$), 48.70 (C), 42.84 ($CH_2$), 42.79 (CH), 26.98 ($CH_2$), 26.93 ($CH_2$), 19.85 ($CH_3$), 19.47 ($CH_3$), 18.23 ($CH_3$). IR(KBr): 3291 (NH), 1734 (C=O), 1458 (HC=C), 1319, 1146 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_3S_1$: C, 63.52; H, 7.21; N, 4.36. Found (%): C, 63.50; H, 7.24; N, 4.41.

*2.1.4. (1S,4S)-N-(2,4-dimethylphenyl)-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl) methanesulfonamide (**4**)*

Colorless solid (55.6%), mp 100–102 °C, $[\alpha]_D^{20}$ = 39.8 [*c* = 1.55 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.28–7.22 (m, 1H, CH), 7.23 (s, 1H, NH), 7.05–6.96 (m, 2H, 2 × CH), 3.53, 2.96 (2d, *J* = 15.3 Hz, 2H, $CH_2S$), 2.34 (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 2.49–2.39, 2.24–1.94, 1.52–1.42 (3m, 1, 5, 1H, $CH_2CH(CH_2)_2$), 1.02, 0.92 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 216.72 (C=O), 135.75(C), 132.70(C), 132.34 (C), 131.88 (CH), 127.33 (CH), 123.67 (CH), 59.46 (C), 49.91 ($CH_2$), 48.64 (C), 42.82 ($CH_2$), 42.76 (CH), 26.96 ($CH_2$), 26.90 ($CH_2$), 20.72 ($CH_3$), 19.82 ($CH_3$), 19.46 ($CH_3$), 18.22 ($CH_3$). IR(KBr): 3249 (NH), 1739 (C=O), 1418 (HC=C), 1333, 1150 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{25}N_1O_3S_1$: C, 64.45; H, 7.51; N, 4.18. Found (%): C, 63.50; H, 7.46; N, 4.11.

*2.1.5. (1S,4S)-N-(3,4-dimethylphenyl)-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl) methanesulfonamide (**5**)*

Colorless solid (92.2%), mp 139–141 °C, $[\alpha]_D^{20}$ = 60.9 [*c* = 1.60 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.61 (s, 1H, NH), 7.10–7.05 (m, 2H, 2 × CH), 7.03–6.97 (m, 1H, CH), 3.38, 2.83 (2d, *J* = 15.3 Hz, 2H, $CH_2S$), 2.24 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 2.51–2.41, 2.19–1.94, 1.55–1.43 (3m, 1, 5, 1H, $CH_2CH(CH_2)_2$), 0.95, 0.87 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 217.26 (C=O), 137.74 (C), 135.13 (C), 134.06 (C), 130.32 (CH), 123.87 (CH), 119.87 (CH), 59.65 (C), 49.01 (C), 48.54 ($CH_2$), 43.03 ($CH_2$), 42.77 (CH), 27.56 ($CH_2$), 27.01 ($CH_2$), 19.81 ($CH_3$), 19.78 ($CH_3$), 19.31 ($CH_3$), 19.12 ($CH_3$). IR(KBr): 3221 (NH), 1735 (C=O), 1484 (HC=C), 1324, 1150 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{25}N_1O_3S_1$: C, 64.45; H, 7.51; N, 4.18. Found (%): C, 64.33; H, 7.40; N, 4.30.

*2.1.6. (1S,4S)-N-methyl-N-phenyl-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl) methanesulfonamide (**6**)*

Colorless solid (65.0%), mp 104–105 °C, $[\alpha]_D^{20}$ = 27.6 [*c* = 1.65 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44–7.34 (m, 4H, 4 × CH), 7.31–7.24 (m, 1H, CH), 3.48, 2.86 (2d, *J* = 14.7 Hz, 2H, $CH_2S$), 3.38 (s, 3H, $CH_3N$), 2.55–2.44, 2.42–2.31, 2.09–1.86, 1.61–1.49 (4m, 1, 1, 3, 2H, $CH_2CH(CH_2)_2$), 1.10, 0.84 (1s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 215.16 (C=O), 141.50 (C), 129.16 (2 × CH), 127.03 (CH), 126.14 (2 × CH), 58.26 (C), 47.70 (C), 45.12 ($CH_2$), 42.83 (CH), 42.48 ($CH_2$), 38.29 ($CH_3N$), 26.77 ($CH_2$), 25.15 ($CH_2$), 20.02 ($CH_3$), 19.66 ($CH_3$). IR(KBr): 1729 (C=O), 1457 (HC=C), 1325, 1152 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_3S_1$: C, 63.52; H, 7.21; N, 4.36. Found (%): C, 64.02; H, 7.15; N, 4.35.

*2.1.7. (1S,4S)-N,N-di-iso-butyl-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl) methanesulfonamide (**7**)*

Colorless solid (60.1%), mp 104–106 °C, $[\alpha]_D^{20}$ = 26.4 [*c* = 4.95 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.31, 2.77 (2d, *J* = 14.4 Hz, 2H, $CH_2S$), 2.99 (ddd, *J* = 24.0 Hz, *J* = 13.8 Hz, *J* = 7.5 Hz, 4H, 2 × $CH_2$), 2.59–2.49, 2.42–2.31, 2.10–1.84 (3m, 1, 1, 5H, $CH_2CH(CH_2)_2$), 1.68–1.56 (m, 1H, CH), 1.44–1.34 (m, 1H, CH), 1.15, 0.88 (2s, 6H, 2 × $CH_3$), 0.94 (dd, *J* = 6.9 Hz, 12H, 4 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 215.49 (C=O), 58.40(C), 56.83 (2 × $CH_2$), 47.67 (C), 46.45 ($CH_2$), 42.92 (CH), 42.57 ($CH_2$), 27.42 (2 × CH), 26.84 ($CH_2$), 25.31 ($CH_2$), 20.16(4 × $CH_3$), 20.13 ($CH_3$), 19.78 ($CH_3$). IR(KBr): 1734 (C=O), 1458 (HC=C), 1319, 1146 ($SO_2N$) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{33}N_1O_3S_1$: C, 62.94; H, 9.68; N, 4.08. Found (%): C, 63.50; H, 9.52; N, 4.55.

*2.1.8. (1S,4S)-(2-keto-7,7-dimethylbicyclo [2.2.1]hept-1-yl)morpholinesulfonmethane (**8**)*

Colorless solid (91.9%), mp 144–147 °C, $[\alpha]_D^{20}$ = 32.3 [*c* = 4.40 ($CHCl_3$)]. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.74 (t, *J* = 6.0 Hz, 4H, 2 × $CH_2$), 3.30–3.26 (m, 4H, 2 × $CH_2$), 3.32, 2.72 (2d, *J* = 14.7 Hz, *J* = 11.1 Hz, 2H, $CH_2S$), 2.56–2.32, 2.12–1.90, 1.68–1.57, 1.46–1.37

(4m, 2, 3, 1, 1H, $CH_2CH(CH_2)_2$), 1.11, 0.86 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 215.08 (C=O), 66.47 (2 × $CH_2$), 58.07 (C), 47.88 (C), 45.71 (2 × $CH_2$), 44.40 ($CH_2$), 42.71 (CH), 42.50 ($CH_2$), 26.83 ($CH_2$), 25.06 ($CH_2$), 19.90 ($CH_3$), 19.69 ($CH_3$). IR(KBr): 1734 (C=O), 1319, 1146 ($SO_2N$) cm$^{-1}$. Anal. Calcd (%) for $C_{14}H_{23}N_1O_4S_1$: C, 55.79; H, 7.69; N, 4.65. Found (%): C, 55.50; H, 7.61; N, 4.55.

### 2.2. Preparation of thioketosulfonamides **9**–**10**

The ketosulfonamide **1** (5.00 g, 15.55 mmol), $Na_2SO_4$ (5.00 g) and Lawesson reagent (11.78 g, 29.12 mmol) were dissolved in 250 ml of toluene and molecular sieves 4A (3.00 g) added. The reaction mixture was heated under reflux for 50 h. After cooling, the resulted crystals were separated by suction. Then silica gel (70–100 mesh) deactivated with $Et_3N$ was added to a filtrate. The product was deposited on silica by evaporation of toluene with a rotary evaporator. A residue was placed on a chromatographic column with silica gel and eluted with toluene (I CC). The orange product was repeatedly purified using chromatography (eluent $CH_2Cl_2$-petroleum ether 1:1, II CC) (eluent $CH_2Cl_2$-petroleum ether 1:4, III CC) and (eluent EtOAc:petroleum ether 1:20, IV CC) and additional crystallization from petroleum ether (acetone bath) giving 2.58 g (44% yield) of the pure thioketosulfonamide **9**. TLC: eluent: $CH_2Cl_2$ $R_f$ = 0.56, eluent: toluene $R_f$ = 0.18, eluent: petroleum ether-EtOAc $R_f$ = 0.56 orange spot, vanillin as a developer.

#### 2.2.1. (1S,4S)-(N-benzyl)-(7,7-dimethylbicyclo[2.2.1]hept-1-yl-2-thione) methanesulfonamide (**9**)

Orange solid (44%), mp 91–95 °C, $[\alpha]_D^{20}$ = 156.7 [$c$ = 2.00 ($CHCl_3$)]. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ (ppm): 7.42–7.26 (m, 5H, 5 × CH), 4.57 (t, $J$ = 5.6 Hz, 1H, NH), 4.37 (d, $J$ = 6.2 Hz, 2H, $CH_2$(Bn)), 3.99, 3.00 (2d, $J$ = 15.0 Hz, 2H, $CH_2S$), 2.90–2.40, 2.20–1.98, 1.70–1.99 (3m, 3, 2, 2H, $CH_2CH(CH_2)_2$), 1.16, 0.80 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ (ppm): 265.08 (C=S), 136.84(C), 128.70 (2 × CH), 128.02 (2 × CH), 127.85 (CH), 69.65 (C), 54.98 ($CH_2$), 52.67 ($CH_2$), 50.49 (C), 47.43 ($CH_2$), 44.88 (CH), 29.27 ($CH_2$), 27.18 ($CH_2$), 20.29 ($CH_3$), 19.69 ($CH_3$). IR(KBr): 3316 (NH), 1454 (HC=C), 1325, 1136 ($SO_2N$), 1249 (C=S) cm$^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_2S_2$: C, 60.50; H, 6.87; N, 4.15. Found (%): C, 60.39; H, 6.73; N, 4.29.

#### 2.2.2. (1S,4S)-(2-methylphenyl)-(7,7-dimethylbicyclo[2.2.1]hept-1-yl-2-thione) methanesulfonamide (**10**)

Orange solid (24%), mp 112.5–114 °C, $[\alpha]_D^{20}$ = 123.7 [$c$ = 2.00 ($CHCl_3$)]. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ (ppm): 7.55 (d, $J$ = 8.0 Hz, 1H, CH), 7.26–7.11 (m, 3H, 3 × CH), 6.64 (s, 1H, NH), 4.17, 3.19 (2d, $J$ = 14.8 Hz, 2H, $CH_2S$), 2.75–2.41, 2.17–1.98, 1.70–1.37 (3m, 3, 2, 2H, $CH_2CH(CH_2)_2$), 2.35 (s, 3H, $CH_3$), 1.20, 0.83 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ (ppm): 265.10 (C=S), 135.16(C), 131.12 (CH), 129.86 (C), 127.17 (CH), 125.54 (CH), 122.20 (CH), 69.61 (C), 54.81 ($CH_2$), 52.32 ($CH_2$), 50.22 (C), 44.99 (CH), 29.42 ($CH_2$), 27.06 ($CH_2$), 20.38 ($CH_3$), 19.70 ($CH_3$), 18.17 ($CH_3$). IR(KBr): 3412 (NH), 1444 (HC=C), 1316, 1125 ($SO_2N$), 1252 (C=S) cm$^{-1}$. Anal. Calcd (%) for $C_{17}H_{23}N_1O_2S_2$: C, 60.50; H, 6.87; N, 4.15. Found (%): C, 60.32; H, 6.78; N, 4.21.

### 2.3. Preparation of mercaptosulfonamides **11** and **12**

A solution of thioketosulfonamide **9** (0.10 g, 2.37 mmol) in $Et_2O$ (5 ml) was quickly added to a suspension of $LiAlH_4$ (0.10 g, 2.63 mmol) in $Et_2O$ at room temperature. The reaction was conducted for 5 min and carefully quenched with water (5 ml). The organic layer was separated, whereas an aqueous one was extracted with $Et_2O$ (3 × 10 ml). The combined organic layers were rinsed with water (5 ml), brine (2 × 5 ml) and then dried over anhydrous $Na_2SO_4$. After the removal of $Et_2O$, a crude product was crystallized from EtOH to obtain 11 (0.089 g, 89% yield).

#### 2.3.1. (1S,2R,4S)-(N-benzyl)-(7,7-dimethylbicyclo[2.2.1]hept-1-yl-2-thiol) methanesulfonamide (**11**)

Colorless solid (89%), mp 134–136 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 7.42–7.28 (m, 5H, 5 × CH), 4.58 (t, $J$ = 6.0 Hz, 1H, NH), 4.35 (ddd, $J$ = 21.6 Hz, $J$ = 14.1 Hz, $J$ = 6.3 Hz, 2H, $CH_2$(Bn)), 3.88, 2.82 (2d, $J$ = 13.8 Hz, 2H, $CH_2S$), 3.49–3.36 (m, 1H, CHS), 2.52 (d, $J$ = 7.5 Hz, 1H, SH), 2.20–1.90, 1.75–1.69, 1.63–1.49, 1.33–1.19 (4m, 2, 3, 1, 1H, $CH_2CH(CH_2)_2$), 0.93, 0.79 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 136.84(C), 128.89 (2 × CH), 128.10 (CH), 128.05 (2 × CH), 53.43 ($CH_2$), 49.80 (C), 49.52 (C), 47.32 ($CH_2$), 45.13 (CH), 43.78 (CH), 39.94 ($CH_2$), 33.02 ($CH_2$), 27.26 ($CH_2$), 20.86 ($CH_3$), 19.88 ($CH_3$). IR(KBr): 3269 (NH), 2567 (SH), 1460 (HC=C), 1317, 1147 ($SO_2N$) cm$^{-1}$. Anal. Calcd (%) for $C_{17}H_{25}N_1O_2S_2$: C, 60.14; H, 7.42; N, 4.13. Found (%): C, 60.19; H, 7, 35; N, 4.19.

#### 2.3.2. (1S,2R,4S)-(7,7-dimethylbicyclo[2.2.1]hept-1-yl-2-thiol)morpholinesulfonmethane (**12**)

Colorless solid (97.5%), mp 149–150 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 3.64 (t, $J$ = 6.2 Hz, 4H, 2 × $CH_2$), 3.32–3.21 (m, 4H, 2 × $CH_2$), 3.35, 2.70 (2d, $J$ = 13.8 Hz, $J$ = 11.1 Hz, 2H, $CH_2S$), 3.45–3.38 (m, 1H, CHS), 2.53 (d, $J$ = 7.5 Hz, 1H, SH), 2.46–2.32, 2.12–1.90, 1.68–1.57, 1.46–1.37 (4m, 2, 3, 1, 1H, $CH_2CH(CH_2)_2$), 1.10, 0.83 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 66.43 (2 × $CH_2$), 58.01 (C), 47.82 (C), 45.68 (2 × $CH_2$), 44.39 ($CH_2$), 43.70 (CH), 42.71 (CH), 42.50 ($CH_2$), 26.83 ($CH_2$), 25.06 ($CH_2$), 19.90 ($CH_3$), 19.69 ($CH_3$). IR(KBr): 2561 (SH), 1319, 1146 ($SO_2N$) cm$^{-1}$. Anal. Calcd (%) for $C_{14}H_{25}N_1O_3S_2$: C, 52.63; H, 7.89; N, 4.38. Found (%): C, 52.50; H, 7.81; N, 4.45.

### 2.4. Preparation of hydroxysulfonamides **13**–**20**

The general procedure of reduction of **1**–**8** to obtain **13**–**20** is as follows. The solution of ketosulfonamide (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 re-crystallized from methanol (**13**, **14**, **16**–**20**) or ethanol (**15**).

#### 2.4.1. (1S,2R,4S)-(N-benzyl)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**13**)

Colorless solid (92.4%), mp 98–101 °C, $[\alpha]_D^{20}$ = −40.00 [$c$ = 0.1 ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.42–7.29 (m, 5H, 5 × CH), 4.78 (t, $J$ = 5.7 Hz, 1H, NH), 4.33 (d, $J$ = 5.1 Hz, 2H, $CH_2$), 4.07 (dt, $J$ = 6.9 Hz, $J$ = 3.3 Hz, 1H, CHOH), 3.17 (d, $J$ = 3.3 Hz, 1H, OH), 3.31, 2.72 (2d, $J$ = 13.8 Hz, 2H, $CH_2S$), 1.79–1.56, 1.53–1.40, 1.15–1.05 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 0.98, 0.72 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 136.64 (C), 128.92 (2 × CH), 128.19 (2 × CH), 128.10 (CH), 76.37 (CHOH), 53.18 ($CH_2$), 50.35 (C), 48.66 (C), 47.39 ($CH_2$), 44.32 (CH), 38.95 ($CH_2$); 30.43 ($CH_2$); 27.33 ($CH_2$); 20.44 ($CH_3$), 19.77 ($CH_3$). IR(Nujol): 3529 (OH), 3303 (NH), 1453 (HC=C), 1308, 1132 ($SO_2N$), 1086 (CO) cm$^{-1}$. Anal. Calcd (%) for $C_{17}H_{25}N_1O_3S_1$: C, 63.13; H, 7.79; N, 4.33. Found (%): C, 63.15; H, 7.84; N, 4.39.

*2.4.2. (1S,2R,4S)-N-(4-methylphenyl)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**14**)*

Colorless solid (95.8%), mp 102–104 °C, $[\alpha]_D^{20} = -44.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.18–7.10 (m, 4H, 4 × CH), 6.9–6.8 (bs, 1H, NH), 4.17–4.07 (bs, 1H, CHOH), 3.23–3.14 (bs, 1H, OH), 3.60, 2.94 (2d, $J$ = 13.8, 2H, $CH_2S$), 2.33 (s, 3H, $CH_3$), 1.83–1.63, 1.60–1.47, 1.16–1.04 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.00, 0.75 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C, NMR, $CDCl_3$, $\delta$ (ppm): 135.36 (C), 133.98 (C), 130.24 (2 × CH), 121.23 (2 × CH), 76.42 (CHOH), 51.23 ($CH_2$), 50.34 (C), 48.82 (C), 44.37 (CH), 39.09 ($CH_2$), 30.47 ($CH_2$), 27.29 ($CH_2$), 20.81 ($CH_3$), 20.47 ($CH_3$), 19.83 ($CH_3$). IR(Nujol): 3562 (OH), 3277 (NH), 1511 (HC=C), 1332, 1140 ($SO_2N$), 1087 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{25}N_1O_3S_1$: C, 63.13; H, 7.79; N, 4.33. Found (%): C, 63.18; H, 7.86; N, 4.45.

*2.4.3. (1S,2R,4S)-N-(2-methylphenyl)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**15**)*

Colorless solid (87.5%), mp 88–90 °C, $[\alpha]_D^{20} = -43.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.47–7.40 (m, 1H, CH), 7.29–7.21 (m, 2H, 2 × CH), 7.18–7.10 (m, 1H, CH), 6.35 (s, 1H, NH), 4.12 (dt, $J$ = 7.8 Hz, $J$ = 3.9 Hz, 1H, CHOH), 3.13 (d, $J$ = 3.9 Hz, 1H, OH), 3.55, 3.00 (2d, $J$ = 13.5 Hz, 2H, $CH_2S$), 2.34 (s, 3H, $CH_3$), 1.81–1.63, 1.60–1.50, 1.18–1.10 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.03, 0.78 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 134.75 (C), 131.24 (CH), 129.93 (C), 127.40 (CH), 125.89 (CH), 122.06 (CH), 76.38 (CHOH), 52.23 ($CH_2$), 50.48 (C), 48.80 (C), 44.35 (CH), 39.04 ($CH_2$), 30.42 ($CH_2$), 27.30 ($CH_2$), 20.52 ($CH_3$), 19.85 ($CH_3$), 18.05 ($CH_3$). IR (Nujol): 3542 (OH), 3275 (NH), 1497 (HC=C), 1325, 1139 ($SO_2N$), 1086 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{25}N_1O_3S_1$: C, 63.13; H, 7.79; N, 4.33. Found (%): C, 63.19; H, 7.82; N, 4.48.

*2.4.4. (1S,2R,4S)-N-(2,4-dimethylphenyl)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**16**)*

Colorless solid (94.9%), mp 120–123 °C, $[\alpha]_D^{20} = -24.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.31–7.23 (m, 1H, CH), 7.08–7.00 (m, 2H, 2 × CH), 6.19 (s, 1H, NH), 4.11 (dt, $J$ = 7.8 Hz, $J$ = 3.9 Hz, 1H, CHOH), 3.12 (d, $J$ = 3.9 Hz, 1H, OH), 3.51, 2.97 (2d, $J$ = 13.5 Hz, 2H, $CH_2S$), 2.31 (s, 3H, $CH_3$), 1.85–1.62, 1.60–1.48, 1.17–1.07 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.02, 0.78 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 136.23 (C), 131.93 (CH), 131.89 (C), 131.04 (C), 127.90 (CH), 123.41 (CH), 76.38 (CHOH), 52.10 ($CH_2$), 50.46 (C), 48.77 (C), 44.37 (CH), 39.00 ($CH_2$), 30.43 ($CH_2$), 27.30 ($CH_2$), 20.87 ($CH_3$), 20.54 ($CH_3$), 19.86 ($CH_3$), 18.07 ($CH_3$). IR(Nujol): 3616 (OH), 3247 (NH), 1498 (HC=C), 1334, 1158 ($SO_2N$), 1084 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{27}N_1O_3S_1$: C, 64.06; H, 8.06; N, 4.15. Found (%): C, 64.02; H, 8.10; N, 4.21.

*2.4.5. (1S,2R,4S)-N-(3,4-dimethylphenyl)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methanesulfonamide (**17**)*

Colorless solid (94.1%), mp 135–138 °C, $[\alpha]_D^{20} = -45.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.12–7.07 (m, 1H, CH), 7.05–6.91 (m, 2H, 2 × CH), 6.51 (s, 1H, NH), 4.13 (dt, $J$ = 7.5 Hz, $J$ = 4.2 Hz, 1H, CHOH), 3.14 (d, $J$ = 4.2 Hz, 1H, OH), 3.49, 2.95 (2d, $J$ = 13.8 Hz, 2H, $CH_2S$), 2.24 (d, $J$ = 5.7 Hz, 6H, 2 × $CH_3$), 1.87–1.61, 1.59–1.47, 1.18–1.08 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.01, 0.76 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 138.19 (C), 134.16 (C), 134.10 (C), 130.67 (CH), 122.58 (CH), 118.54 (CH), 76.41 (CHOH), 51.27 ($CH_2$), 50.39 (C), 48.83 (C), 44.37 (CH), 39.05 ($CH_2$), 30.49 ($CH_2$), 27.31 ($CH_2$), 20.51 ($CH_3$), 19.91 ($CH_3$), 19.84 ($CH_3$), 19.16 ($CH_3$). IR(Nujol): 3464 (OH), 3126 (NH), 1499 (HC=C), 1323, 1137 ($SO_2N$), 1086 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{27}N_1O_3S_1$: C, 64.06; H, 8.06; N, 4.15. Found (%): C, 64.04; H, 8.11; N, 4.19.

*2.4.6. (1S,2R,4S)-N-methyl-N-phenyl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**18**)*

Colorless solid (88.2%), mp 105–108 °C, $[\alpha]_D^{20} = -33.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.44–7.39 (m, 4H, 4 × CH), 7.37–7.28 (m, 1H, CH), 4.08 (dt, $J$ = 7.8 Hz, $J$ = 3.9 Hz, 1H, CHOH), 3.36 (s, 3H, $CH_3$), 3.07 (d, $J$ = 3.9 Hz, 1H, OH), 3.37, 2.79 (2d, $J$ = 13.2 Hz, 2H, $CH_2S$), 1.82–1.61, 1.59–1.46, 1.19–1.05 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.03, 0.77 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 141.33 (C), 129.37 (2 × CH), 127.42 (CH), 126.28 (2 × CH), 76.38 (CHOH), 50.04 (C), 48.76 (C), 47.29 ($CH_2$), 44.44 (CH), 38.91 ($CH_2$), 38.37 ($CH_3$), 30.56 ($CH_2$), 27.28 ($CH_2$), 20.57 ($CH_3$), 19.89 ($CH_3$). IR (Nujol): 3516 (OH), 1454 (HC=C), 1330, 1142 ($SO_2N$), 1087 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{17}H_{25}N_1O_3S_1$: C, 63.13; H, 7.79; N, 4.33. Found (%): C, 63.21; H, 7.84; N, 4.50.

*2.4.7. (1S,2R,4S)-N,N-di-iso-butyl-(2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl) methanesulfonamide (**19**)*

Colorless solid (86.5%), mp 82–85 °C, $[\alpha]_D^{20} = -36.00$ [$c = 0.1$ ($CHCl_3$)]. $^1$H, NMR, $CDCl_3$, $\delta$ (ppm): 7.44–7.39 (m, 4H, 4 × CH), 7.37–7.28 (m, 1H, CH), 4.08 (dt, $J$ = 7.8 Hz, $J$ = 3.9 Hz, 1H, CHOH), 3.36 (s, 3H, $CH_3$), 3.07 (d, $J$ = 3.9 Hz, 1H, OH), 3.37, 2.79 (2d, $J$ = 13.2 Hz, 2H, $CH_2S$), 1.82–1.61, 1.59–1.46, 1.19–1.05 (3m, 5, 1, 1H, $CH_2CH(CH_2)_2$), 1.03, 0.77 (2s, 2 × 3H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 76.49 (CHOH), 56.46 (2 × $CH_2$), 50.23 (C), 49.36 ($CH_2$), 48.63 (C), 44.46 (CH), 38.87 ($CH_2$), 30.78 ($CH_2$), 27.31 ($CH_2$), 27.26 (2 × CH), 20.58 ($CH_3$), 20.12 (4 × $CH_3$), 19.92 ($CH_3$). IR(Nujol): 3521 (OH), 1326, 1139 ($SO_2N$), 1087 (CO) $cm^{-1}$. Anal. Calcd (%) for $C_{18}H_{35}N_1O_3S_1$: C, 62.57; H, 10.21; N, 4.05. Found (%): C, 62.60; H, 10.32; N, 4.41.

*2.4.8. (1S,2R,4S)-(2-hydroxy-7,7-dimethylbicyclo[2.2.1] hept-1-yl) morpholinesulfonmethane (**20**)*

Colorless solid (90.4%), mp 174–176 °C, $[\alpha]_D^{20} = -39.00$ [$c = 0.1$ ($CH_3Ph$)]. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 4.09 (q, $J$ = 4.2, 1H, CHOH), 3.82–3.76 (m, 4H, 2 × $CH_2$), 3.31–3.25 (m, 4H, 2 × $CH_2$), 3.24, 2.66 (2d, $J$ = 14.1 Hz, $J$ = 13.2 Hz, 2H, $CH_2S$), 3.17 (d, $J$ = 3.9 Hz, 1H, OH), 1.87–1.48, 1.17–1.09 (2m, 6, 1H, $CH_2CH(CH_2)_2$), 1.07, 0.83 (2s, 6H, 2 × $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 76.39 (CHOH), 66.45 (2 × $CH_2$), 49.97 (C), 48.81 (C), 46.41 ($CH_2$), 45.86 (2 × $CH_2$), 44.43 (CH), 38.94 ($CH_2$), 30.73 ($CH_2$), 27.31 ($CH_2$), 20.57 ($CH_3$), 19.90 ($CH_3$). IR(Nujol): 3520 (OH), 1334, 1128 ($SO_2N$) 1072(CO) $cm^{-1}$. Anal. Calcd (%) for $C_{14}H_{25}N_1O_4S_1$: C, 55.42; H, 8.30; N, 4.62. Found (%): C, 55.40; H, 8.22; N, 4.58.

### *2.5. Enantioselective addition of diethylzinc to benzaldehyde*

The reaction of $Et_2Zn$ addition was performed according to Scheme 1, under dry argon. Titanium tetraisopropoxide (0.42 ml, 1.4 mmol) was added to the appropriate ligand (**1**–**20**) (0.2 mmol) dissolved in methylene chloride (5 ml). The mixture was stirred for 1 h at room temperature, cooled to −50 °C, and diethylzinc was added (3 ml of 1 M hexane solution, 3 mmol). 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), then precipitate was 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 enan-

**Table 1**
Addition of $Et_2Zn$ to benzaldehyde in a presence of sulfonamides **1**–**20**.

| | $R^3$ | $R^1$ | $R^2$ | Sequence of additives | Field [%] | ee% (configuration)[a] |
|---|---|---|---|---|---|---|
| **1** | =O | H | Bn | Ti/Zn | 87 | 16(*R*) |
| **2** | =O | H | 4-$C_6H_4Me$ | Ti/Zn | 64 | 12(*R*) |
| **3** | =O | H | 2-$C_6H_4Me$ | Ti/Zn | 64 | 7.6(*R*) |
| **4** | =O | H | 2,4-$C_6H_3Me_2$ | Ti/Zn | 48 | 5.5(*R*) |
| **5** | =O | H | 3,4-$C_6H_3Me_2$ | Ti/Zn | 52 | 5.9(*R*) |
| **6** | =O | Me | Ph | Ti/Zn | 51 | 5.6(*R*) |
| **7** | =O | $^i$Bu | $^i$Bu | Ti/Zn | 50 | 1.9(*R*) |
| **8** | =O | | Morpholine | Ti/Zn | 53 | 1.1(*R*) |
| **13** | –OH | H | Bn | Ti/Zn | 98 | 53(*S*) |
| **14** | –OH | H | 4-$C_6H_4Me$ | Ti/Zn | 95 | 36(*S*) |
| **15** | –OH | H | 2-$C_6H_4Me$ | Ti/Zn | 92 | 38(*S*) |
| **16** | –OH | H | 2,4-$C_6H_3Me_2$ | Ti/Zn | 92 | 35(*S*) |
| **17** | –OH | H | 3,4-$C_6H_3Me_2$ | Ti/Zn | 92 | 51(*S*) |
| **18** | –OH | Me | Ph | Ti/Zn | 50 | 1.3(*S*) |
| **19** | –OH | $^i$Bu | $^i$Bu | Ti/Zn | 52 | 0.6(*S*) |
| **20** | –OH | | Morpholine | Ti/Zn | 45 | 1.1(*S*) |
| **13** | –OH | H | Bn | Ti/Zn | 97 | 69(*S*)[b,c] |
| **14** | –OH | H | 4-$C_6H_4Me$ | Ti/Zn | 96 | 65(*S*)[b,d] |
| **15** | –OH | H | 2-$C_6H_4Me$ | Ti/Zn | 94 | 65(*S*)[b,d] |
| **16** | –OH | H | 2,4-$C_6H_3Me_2$ | Ti/Zn | 95 | 36(*S*)[b] |
| **17** | –OH | H | 3,4-$C_6H_3Me_2$ | Ti/Zn | 97 | 64(*S*)[b] |
| **18** | –OH | Me | Ph | Ti/Zn | 52 | 0.2(*S*)[b] |
| **19** | –OH | $^i$Bu | $^i$Bu | Ti/Zn | 54 | 2.1(*S*)[b] |
| **20** | –OH | | Morpholine | Ti/Zn | 54 | 2.0(*S*)[b] |
| **9** | =S | H | Bn | Ti/Zn | 47 | 9.2(*R*) |
| **10** | =S | H | 2-$C_6H_4Me$ | Ti/Zn | 49 | 3.7(*R*) |
| **9** | =S | H | Bn | Zn/Ti | 59 | 5(*R*) |
| **10** | =S | H | 2-$C_6H_4Me$ | Zn/Ti | 56 | 1(*R*) |
| **9** | =S | H | Bn | Zn | 57 | 10(*R*)[e] |
| **10** | =S | H | 2-$C_6H_4Me$ | Zn | 52 | 2(*R*)[e] |
| **11** | –SH | H | Bn | Ti/Zn | 46 | 2.3(*R*) |
| **12** | –SH | | Morpholine | Ti/Zn | 44 | 1.7(*R*) |
| **11** | –SH | H | Bn | Zn/Ti | 52 | 1(*R*) |
| **12** | –SH | | Morpholine | Zn/Ti | 59 | 0.6(*R*) |

Reaction conditions:
[a] 1.4 mmol Ti($O^iPr$)$_4$ added to the appropriate ligand (**1** to **20**) (0.2 mmol) dissolved in $CH_2Cl_2$.
[b] 1.4 mmol Ti($O^iPr$)$_4$ added to the appropriate ligand (**1** to **20**) (0.2 mmol) dissolved in toluene. The mixture stirred for 1 h at room temperature, cooled to −50 °C, then diethylzinc (3 mmol) and benzaldehyde (1 mmol) were added. The reaction quenched with 1 M HCl (10 ml). The enantiomeric excess determined by GC using a β-Dex column.
[c] Literature data previously published for **13** by Ramón et al. [8]: 71% ee of (*S*)-1-phenylpropanol by Hui et al. [9]: 71% ee of (*S*)-1-phenylpropanol.
[d] Literature data previously published for **14** and **15** by Hui et al. [9]: 48% ee of (*S*)-1-phenylpropanol.
[e] The activity of mercapto- and thioketosulfonamide auxiliaries was determined for the Ti/Zn and Zn/Ti sequence of metal compound dosage, results of addition performed with the use of **9** and **10** ligands in an absence of Ti($O^iPr$)$_4$.

tiomeric excess was determined by GC analysis using a β-Dex column.

### 2.6. Synthesis of Ti-sulfonamide complexes *21*–*24* and *26*

The Ti(IV) complexes **21**–**24** and **26** obtained from sulfonamides **1**, **7**, **13**, **19** and **25** [17] respectively, were synthesized using the following procedure. The sample of ketosulfonamide **1** (0.719 g, 2.238 mmol) was dissolved in 20 ml dry toluene, then Ti(NMe2)4 was added (0.3 ml, 1.119 mmol), and the reaction mixture was stirred under argon for 2.5 h at ambient temperature. The color change from yellow to dark red confirmed the formation of the complex **21**. The mixture was concentrated using vacuum pump. The addition of dry hexane (20 ml) resulted in the formation of red sediment, which was dried under vacuum. The IR spectra of the formed complexes were recorded. However, attempts to obtain monocrystals suitable for the structural analysis had failed. Due to the instability of the complexes, we have not been able to obtain the NMR spectra.

The IR results for the obtained complexes are as follows. Complex **21** (ligand **1**), dark red, IR (Nujol) ($cm^{-1}$): 3290 (NH), 1739 (C=O), 1323, 1144 (SO2N). Complex **22** (ligand **7**), orange, IR (Nujol) ($cm^{-1}$): 1747 (C=O), 1332, 1142 (SO2N). Complex **23** (ligand **13**), orange, IR (Nujol) ($cm^{-1}$): 1312, 1140 (SO2N), 662 (Ti–O). Complex **24** (ligand **19**), orange, IR (Nujol) ($cm^{-1}$): 1325, 1139 (SO2N), 665 (Ti–O). Complex **26** (ligand **25** [17]) orange, IR (Nujol) ($cm^{-1}$): 3501 (OH), 3256 (NH), 1315, 1142 ($SO_2N$), 665 (Ti–O).

## 3. Results and discussion

Ketosulfonamide ligands **1**–**8** were synthesized from amines and (+)-10-camphorsulfonic acid chloride. Hydroxy ligands **13**–**20** were obtained by the reduction of the carbonyl group in ligands **1**–**8** with L-Selectride (Scheme 3). Selected thioketo- or mercaptosulfonamides differing significantly by the bulk of the N-bound group have also been synthesized to explore the effect of such substituents. Thioketosulfonamides **9** and **10** were synthesized from ketosulfonamides **1** and **3** with the use of the Lawesson reagent. Reduction of respective thioketosulfonamides with $LiAlH_4$ gave mercaptosulfonamides **11**–**12** (Scheme 3). Crystal structures of the sulfonamides with the N-benzyl moiety were determined with the X-ray diffraction method. The sulfonamide ligands were applied in the asymmetric addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide (Scheme 1).

**Table 2**
Crystallographic data for sulfonamide ligands: **1**, **9**, **11** and **13**.

| | **1** | **9** | **11** | **13** |
|---|---|---|---|---|
| Formula sum | $C_{17}H_{23}N_1O_3S_1$ | $C_{17}H_{23}N_1O_2S_2$ | $C_{17}H_{25}N_1O_2S_2$ | $C_{17}H_{25}N_1O_3S_1$ |
| Formula weight | 321.42 | 337.48 | 339.50 | 323.44 |
| Color | Colorless | Orange | Colorless | Colorless |
| Crystal system | Monoclinic | Orthorhombic | Orthorhombic | Orthorhombic |
| Space group | $P2_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ |
| *Unit cell dimensions* | | | | |
| $a$ (Å) | 11.0662(9) | 6.7784(7) | 6.8777(4) | 8.391(2) |
| $b$ (Å) | 9.3451(7) | 14.822(1) | 9.7499(5) | 10.882(2) |
| $c$ (Å) | 15.913(1) | 17.305(1) | 26.297(1) | 37.009(7) |
| $\beta$ (°) | 92.639(7) | | | |
| $V$ (Å$^3$) | 1643.9(2) | 1738.7(3) | 1763.4(2) | 3379.3(12) |
| $Z$ | 4 | 4 | 4 | 8 |
| Density (calculated) (Mg/m$^3$) | 1.299 | 1.289 | 1.279 | 1.271 |
| Absorption coefficient (mm$^{-1}$) | 0.209 | 0.313 | 0.308 | 0.204 |
| $F$(000) | 688 | 720 | 728 | 1392 |
| Crystal size (mm) | 0.16 × 0.16 × 0.08 | 0.29 × 0.16 × 0.11 | 0.26 × 0.24 × 0.22 | 0.40 × 0.25 × 0.05 |
| $\theta$ range for data collection(deg) | 2.29–25.99 | 2.73–31.49 | 2.60–31.45 | 2.17–24.00 |
| Index ranges | $-13 \le h \le 13$<br>$-11 \le k \le 10$<br>$-15 \le l \le 19$ | $-9 \le h \le 7$<br>$-21 \le k \le 20$<br>$-25 \le l \le 24$ | $-8 \le h \le 10$<br>$-13 \le k \le 13$<br>$-36 \le l \le 38$ | $-7 \le h \le 9$<br>$-12 \le k \le 12$<br>$-42 \le l \le 42$ |
| Reflections collected | 12158 | 17370 | 17532 | 21119 |
| Independent reflections | 6208[$R_{int}$ = 0.1132] | 5334[$R_{int}$ = 0.1534] | 5390[$R_{int}$ = 0.0483] | 5319 [$R_{int}$ = 0.1618] |
| Transmission max/min | 0.9826/0.9669 | 0.9668/0.9158 | 0.9552/0.9241 | 0.9899/0.9230 |
| Parameters | 401 | 201 | 201 | 437 |
| Goodness-of-fit on $F^2$ | 0.988 | 1.057 | 1.035 | 1.125 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1$ = 0.0973, $wR_2$ = 0.1428 | $R_1$ = 0.0968, $wR_2$ = 0.1692 | $R_1$ = 0.0521, $wR_2$ = 0.1125 | $R_1$ = 0.1372, $wR_2$ = 0.3310 |
| $R$ indices (all data) | $R_1$ = 0.1730, $wR_2$ = 0.1730 | $R_1$ = 0.1978, $wR_2$ = 0.2144 | $R_1$ = 0.0776, $wR_2$ = 0.1248 | $R_1$ = 0.1780, $wR_2$ = 0.3662 |
| Flack ($x$) | −0.06(18) | −0.47(17) | 0.08(8) | 0.1(3) |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.238 and −0.275 | 0.357 and −0.263 | 0.327 and −0.276 | 0.429 and −0.318 |

$R_1 = \sum||F_0| - |F_c||/\sum|F_0|$, $wR_2 = [\sum w(F_0^2 - F_c^2)^2/\sum(w|F_0|^2)^2]^{1/2}$

The catalytic activity was determined for Ti(IV) complexes with four groups of ligands differing by the substituent bound to C2 atom of the bornyl moiety. The addition was performed in $CH_2Cl_2$. The lowest % ee was obtained for sulfonamides with the S atom bound to bornyl C2 (1–9% ee), while 2-hydroxysulfonamides revealed the highest activity among the investigated ligands, reaching 53% ee for **13** and the yield up to 98% (Table 1). Our data on the catalytic activity of **13**–**15** are consistent with those published previously by other authors [8,9] and are the reference data for the whole procedure. Additionally, for the group of most active ligands, the addition was also performed in toluene. For some ligands (**14**, **15**), the use of toluene increased the % ee values by the factor of 2. The best values, obtained also for ligand **13**, were 69% ee and yield 97%. Results for 13 are in good accordance with those published by Ramón et al. [8]. Data obtained for addition performed in $CH_2Cl_2$ and toluene reported here are also consistent with the suggested importance of the low dipole moment of the solvent molecule for the efficiency of addition [9].

The use of 2-hydroxysulfonamides as chiral auxiliaries in the $Et_2Zn$ addition resulted in (*S*)-1-phenylpropanol as a main product. For all other groups of investigated ligands the main product was (*R*)-1-phenylpropanol. That indicates the different spatial arrangement of the complex catalyst, in particular the position of bulky bornyl moiety as a factor responsible for the stereoselectivity.

Previous reports on the use of bis(sulfonamides) with the O atom at bornyl C2 indicated that the sequence of adding the metal compounds has no significant effect on the yield and enantiomeric excess obtained in the $Et_2Zn$ addition to benzaldehyde [17–18]. In our previous research for bis(sulfonamide) auxiliaries [17], the product of the $Et_2Zn$ addition was not detected, when the reaction was conducted in an absence of $Ti(O^iPr)_4$. For monosulfonamides with hydroxy- and keto-groups reported here, no addition product was also obtained in an absence of $Ti(O^iPr)_4$. It suggests that the formation of Ti-sulfonamide complex prior to the addition process is important for that group of ligands. In the research reported here we have investigated the effect of the sequence of metal addition (Ti/Zn or Zn/Ti) for the group of mercapto- and thioketosulfonamides, but the effect was negligible (Table 1). The use of $Et_2Zn$ alone was tested for thioketosulfonamides and gave the same results as observed with the use of $Ti(O^iPr)_4$ and subsequent addition of $Et_2Zn$ (Table 1). That clearly indicates that C2=S is involved in the interactions with Zn atom and the initial formation of Ti-sulfonamide complex is not necessary for the activity of that group of ligands.

Our data indicate that the substituent at N atom also affects the catalytic properties of the investigated sulfonamides. The highest catalytic efficacy in each group is obtained for N-benzyl sulfonamides (**1**, **9**, **11**, **13**). The replacement of benzyl moiety with the methylphenyl or dimethylphenyl group caused significant reduction in the yield and % ee (Table 1). The small effect observed for thioketo- or mercaptosulfonamides is caused by the small efficiency of these ligands (1–9% ee). The difference is even more pronounced for use of $Et_2Zn$ alone (Table 1). These results suggest the importance of the bulk of substituents on the sulfonamide N atom. The $CH_2$ group of the benzyl moiety plays a role of a spacer decreasing the steric hindrance on N and allowing the easy formation of the catalytically active species by N coordination to the metal center. The increasing bulk of substituents results in the decrease of the yield of the $Et_2Zn$ addition to benzaldehyde. The lowest yields and % ee are found for the sulfonamides derived from the secondary amines (di-*iso*-butyl, morpholine). That is consistent with data published by Ramón and Yus [8], although the authors have not formulated such conclusion.

### 3.1. Crystal structure determination

To assess the configuration of the chiral centers, conformation of molecules and intramolecular interactions, the crystal structure

**Table 3**
Hydrogen bonds and intramolecular C–H···X interactions involving heteroatoms of the sulfonamide group or substituent at C2 in crystal structures of **1**, **9**, **11** and **13**.

| | D–H···A | *d*(D–H) | *d*(H···A) | <DHA | *d*(D···A) |
|---|---|---|---|---|---|
| **1** | N2–H2B···O1[*x* + 1, *y*, *z*] | 0.900 | 2.458 | 116.37 | 2.969(8) |
| **9** | N1–H1B···O1[*x* − 1/2, −*y* + 3/2, −*z*] | 0.900 | 2.086 | 147.86 | 2.888(6) |
| **13** | O1–H1A···O3 | 0.820 | 1.776 | 149.87 | 2.519(2) |
| | O1–H1A···S1 | 0.820 | 2.642 | 127.82 | 3.211(2) |
| | O1–H1A···O2B | 0.820 | 2.563 | 145.96 | 3.275(3) |
| | N2–H2N···O3B | 1.059 | 2.000 | 162.85 | 3.028(2) |
| | N2–H2N···O2 | 1.059 | 2.325 | 149.16 | 3.280(2) |
| | O4–H4B···O5 | 0.820 | 2.091 | 148.07 | 2.820(1) |
| | O4–H4B···S2 | 0.820 | 2.923 | 128.88 | 3.497(2) |
| | C–H···X | *d*(D–H) | *d*(H···X) | <CHX | *d*(C···X) |
| **1** | C8–H8A···O3 | 0.96 | 2.48 | 140 | 3.272(10) |
| | C17–H17A···N1 | 0.93 | 2.60 | 101 | 2.925(12) |
| | C25–H25B···O6[1 − *x*, 1/2 + *y*, 1 − *z*] | 0.97 | 2.50 | 149 | 3.369(10) |
| | C30–H30B···O4 | 0.97 | 2.57 | 100 | 2.897(11) |
| **9** | C6–H6A···O1 | 0.97 | 2.59 | 129 | 3.285(7) |
| | C10–H10B···S1 | 0.97 | 2.57 | 120 | 3.171(5) |
| | C17–H17A···O2[1 + *x*, *y*, *z*] | 0.93 | 2.58 | 166 | 3.486(7) |
| **11** | C9–H9B···S1 | 0.96 | 2.66 | 131 | 3.368(3) |
| | C10–H10B···S1 | 0.97 | 2.79 | 109 | 3.236(2) |
| | C11–H11B···O2 | 0.97 | 2.57 | 105 | 2.972(4) |
| **13** | C4–H4A···O4[1 − *x*, 1/2 + *y*, 1/2 − *z*] | 0.98 | 2.56 | 152 | 3.455(18) |
| | C8–H8B···O1 | 0.96 | 2.36 | 120 | 2.962(19) |
| | C29–H29A···O4 | 0.96 | 2.30 | 136 | 3.072(22) |

was determined for sulfonamides **1**, **9**, **11**, **13** with N-benzyl moiety, that revealed the highest catalytic efficacy in four groups of ligands. The details of the data collection and structure refinement are presented in Table 2. Details of the H-bonds and intramolecular C–H···X interactions involving heteroatoms of the sulfonamide group or substituent at C2 are presented in Table 3. The valence geometry of the investigated compounds is typical for the bornyl and sulfonamide moieties. The details of the crystal structures can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

### 3.2. Crystal structure of (1S,4S)-(N-benzyl)-(2-keto-7,7-dimethylobicyclo[2.2.1]hept-1-yl)methane sulfonamide (**1**)

The asymmetric part of the structure contains two molecules of sulfonamide **1** (Fig. 1). The absolute configuration was determined using the Flack method [15] and is consistent with the chirality of (+)-camphor substrate used for the synthesis. Conformation of the sulfonamide fragments of two molecules is different, the C2–C1–C10–S1 and C1–C10–S1–N1 torsion angles being 75.3(8)/−170.0(6) and −95.4(8)/166.7(6)° for molecules I and II, respectively. Despite that difference, position of the benzyl moiety relative to the bornyl ring system is similar in both molecules. Position of the sulfonamide oxygen atoms relative to the *gem*-dimethyl moiety is also different, since they are located on the same side of the C4–S1 line in molecule I and on the opposite side in molecule II. The sulfonamide NH and the C=O group form the intermolecular H-bond N2–H2B···O1 [*x* + 1, *y*, *z*] with N2···O1 distance being 2.969(8) Å. The differences in the conformation of two molecules result in their different interactions in the crystal lattice. Molecule I forms the intramolecular interactions C8–H8A···O3 3.272 Å and C17–H17A···N1 2.925 Å. For molecule II, the spatial proximity of camphor C30 and the carbonyl oxygen results in the intramolecular contact C30–H30B···O4 of 2.897 Å. Molecule II also participates in the intermolecular interaction C25···O6[1 − *x*, 1/2 + *y*, 1 − *z*], the distance being 3.369 Å (Table 3).

### 3.3. Crystal structure of (1S,4S)-(N-benzyl)-(7,7-dimetylobicyclo[2.2.1]hept-1-yl-2-tion)methanesulfonamide (**9**)

The asymmetric part of the structure contains one molecule of sulfonamide **9** (Fig. 2). Determination of the absolute structure with the Flack method was inconclusive, since the Flack parameter was *x* = −0.47(17). Therefore the absolute structure was assigned based on the known chirality of C1 and C4 centers in the (+)-camphor substrate used for the synthesis. The sulfonamide $SO_2$

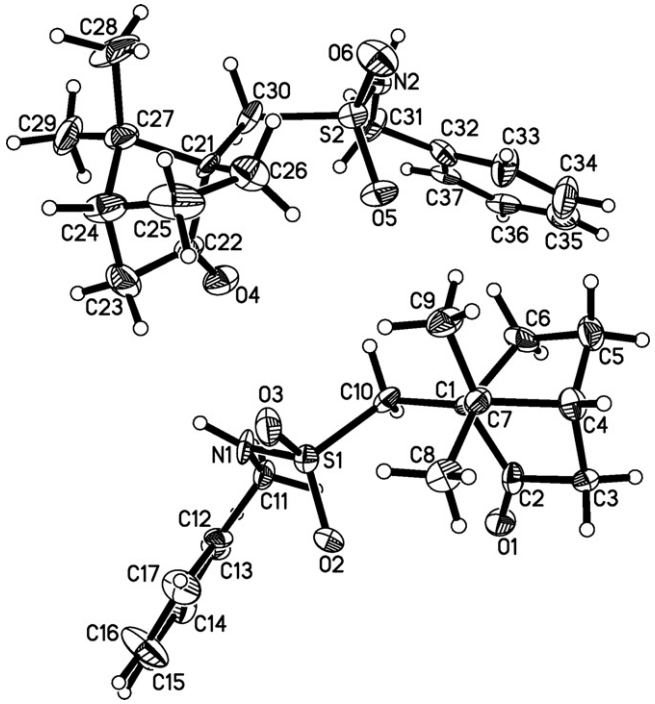



**Fig. 1.** Asymetric part of the crystal structure of **1**.

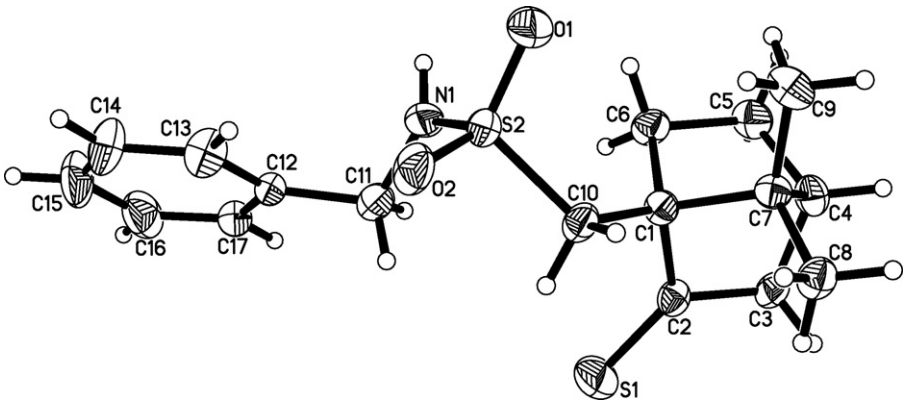



**Fig. 2.** Asymmetric part of the crystal structure of **9**.

and bornyl *gem*-dimethyl groups are positioned on the same side of the C4–C7–C1–C10–S2 axis of the molecule. Conformation of the molecule can be described as twisted with the torsion angles C2–C1–C10–S2 and C1–C10–S2–N1 of −132.8(4) and 62.7(5)°, respectively. The twist around C10–S2 bond, describing the position of C10 methylene group relative to the sulfonic oxygens, reflects the steric hindrance around C10. In that orientation, the C10 methylene is involved in the intramolecular interactions with S1 substituent of the bornyl moiety, the C10···S1 distance being 3.170 Å. Analysis of the crystal packing of **9** revealed the presence of the intermolecular hydrogen bonds N2–H1B···O1[$x-1/2$, $-y+3/2$, $-z$], the N···O distance is 2.888(6) Å. Also the sulfonamide oxygen atoms are involved in the C–H···O interactions, the intermolecular C6–H6A···O1 of 3.285 Å and intramolecular C17–H17A···O2[$1+x$, $y$, $z$] of 3.486 Å (Table 3).

### 3.4. Crystal structure of (1S,2R,4S)-(N-benzyl)-(1,7,7-dimetylobicyclo[2.2.1]hept-1-yl-2-tiol) methanesulfonamide (*11*)

Single molecule of mercaptosulfonamide **11** constitutes the asymmetric part of the crystal structure (Fig. 3). The configuration of the C2 atom was determined as *R* using the Flack method [15]. The bornyl *gem*-dimethyl and sulfonic groups are positioned anticlinal relative to each other. The respective torsion angles are C2–C1–C10–S2 −70.7(2)° and C1–C10–S2–N1 166.6(2)°. The C10 methylene hydrogen atoms and sulfonamide oxygen atoms are positioned *trans* relative to the C10–S2 axis. The C10 group participates in the intramolecular interaction with the –SH group, the C10–H10B···S1 distance being 3.236 Å. The 2*R* configuration results in the formation of the intramolecular C9···S1 interaction of 3.368 Å. The packing analysis revealed the intermolecular interactions between C8 methyl group and the aromatic ring of the adjacent molecule, the distance between C–H and the center of gravity of the aromatic ring C8–H8C···π[$-1/2+x$, $1/2-y$, $-z$] being 3.585 Å. Also the intramolecular interaction C11···O2 2.972 Å is formed between the aromatic ring and the sulfonamide group.

### 3.5. Crystal structure of (1S,2R,4S)-(N-benzyl)-(2-hydroxy-7,7-dimethylobicyclo[2.2.1]hept-1-yl) methanesulfonamide (*13*)

The asymmetric part of the unit cell contains two molecules of hydroxysulfonamide (Fig. 4). The configuration of the C2 atom was determined as *R* using the Flack method [15]. The observed anisotropy of the atomic displacement parameters indicate the rotational disorder of the bornane and sulfonamide moieties. However, it was impossible to define the discrete model of that disorder. The crystal structure reveals the conformational disorder of the sulfonamide group in molecule I with major population 60%. The C2–C1–C10–S1 torsion angle is similar for molecule I in the minor population and molecule II (−58.2(15)° and −55.6(13)°) while for molecule I in a major population it is −32.8(14)°. However, the statistically significant differences in C1–C10–S1–N1 torsion angle are found between the two molecules, the values being 163.4(9)/−153.8(12)° and −56.9(10)° for molecule I and II, respectively. That results in different relative position of benzyl groups. Analysis of crystal packing revealed that benzyl groups form the interactions C31···π1[$-1/2+x$, $1/2-y$, $-z$] being 3.752 Å and N1B···π2[$1/2+x$, $1/2-y$, $-z$] of 3.239 Å, where π1 and π2 denote for the gravity centers of the aromatic ring in molecule I and II, respectively. The relative orientation of the sulfonamide $SO_2$ and *gem*-dimethyl groups is found *trans* in molecule I, while in

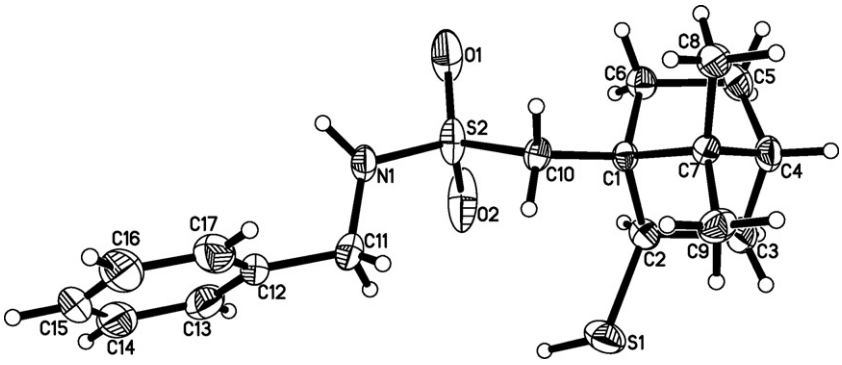



**Fig. 3.** Asymmetric part of the crystal structure of **11**.

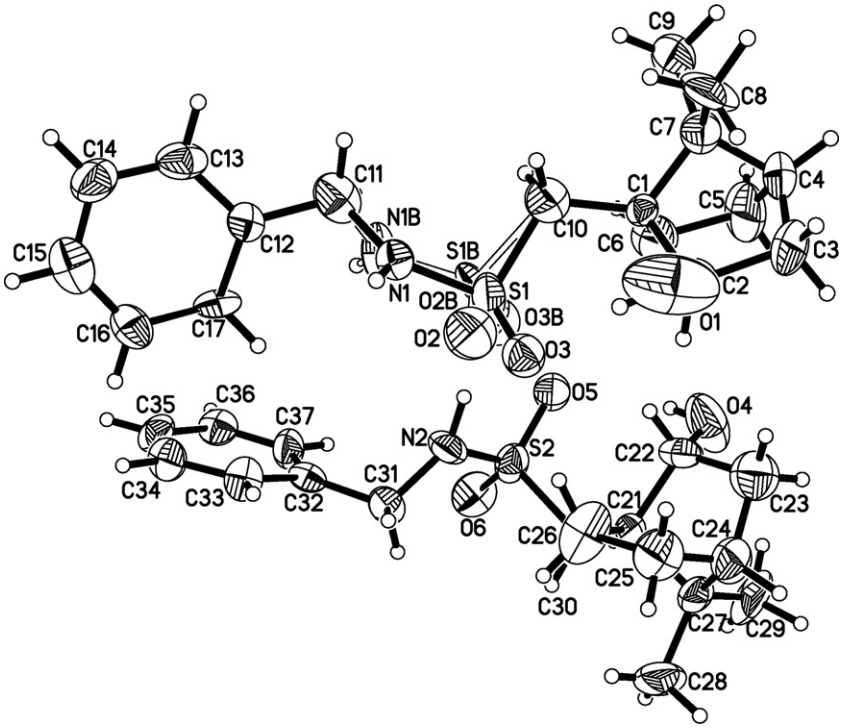



**Fig. 4.** Asymmetric part of the crystal structure of **13**.

molecule II it is *gauche* (Fig. 4). The hydrogen atoms of C10 methylene are positioned *gauche* relative to the $SO_2$ oxygens in molecule II, while in molecule I they occupy the opposite positions relative to the C10–S1 axis. The described conformation results in the intermolecular H-bonds involving atoms of the sulfonamide moieties (N2···O3, N2···O2A) and the intramolecular H-bonds involving the bornyl OH and sulfonamide O and S atoms (Table 3). The hydroxyl groups of both molecules participate in the intramolecular interactions with the methyl groups of the bornane moiety (C8–H8B···O1 2.962 Å and C29–H29A···O4 3.072 Å). Also there is an intermolecular C–H···O interaction C4–H4A···O4[$1-x$, $1/2+y$, $1/2-z$] of 3.455 Å.

### 3.6. Model of the catalyst architecture

Literature reports revealed that the most frequent mode of sulfonamide coordination to Ti(IV) is $\eta^2$ –NO or $\eta^2$ –OO *via* the sulfonamide group [10,19–21]. The sulfonamides reported here are derived from camphor and have an additional substituent at bornyl C2, which also might participate in the ligand binding to the metal center [11–13]. So far, there are no structural reports on the Ti(IV) complexes of such sulfonamides. However, their ability to adopt the conformation required for the bidentate coordination involving C2-bound group might be estimated based the known structures of sulfonamides. Analysis of camphor-derived sulfonamide structures in the CSD database revealed the presence of the intramolecular N···O(C2) hydrogen bonds, the N···O distance ranging from 2.774 to 3.052 Å. The structures of sulfonamides **1**, **9**, **11**, **13** reported here do not have such interaction. Analysis revealed that the reported hydroxysulfonamide **13** or similar molecules deposited with CCDC can form the intramolecular H-bond (C2)O···$O_{sulfo}$, with the distance ranging from 2.813 to 2.980 Å, resembling the distance between the donor groups in the Ti coordination sphere. Also, analysis of the intramolecular interactions indicates lack of steric factors restricting the conformation of the investigated molecules. Therefore, we might conclude that molecules belonging to the reported groups of ligands could coordinate bidentately to Ti(IV) center *via* the sulfonamide group and the substituent at C2, forming the 7-membered chelate ring.

The experimental confirmation of the coordination mode for complexes was difficult due to their instability in a presence of water traces. However, some information can be obtained from the IR spectra by analysis of frequencies for Ti-ligand bands or those characteristic for the sulfonamide ligands. The IR spectra for the obtained Ti-sulfonamide complexes **21**–**24** and **26** have been compared with those for the respective sulfonamides **1**, **7**, **13**, **19** and **25** (Table 4; Fig. 5a and b).

For the ketosulfonamide **1** derived from the primary amine, the changes in the frequencies of bands attributed to the stretching N–H vibrations 3241 $cm^{-1}$ (**1**) to 3290 $cm^{-1}$ (**21**) and C=O from 1724 $cm^{-1}$ (**1**) to 1739 $cm^{-1}$ (**21**) suggest that these groups are involved in the Ti(IV) binding. The lack of shifts for the bands attributed to the stretching vibrations of $SO_2N$ group (Table 4) suggests that its O atoms are not involved in the metal coordination. However, no shifts have been detected between IR spectra of sulfonamide **7** and its Ti complex **22**. That might suggest that either

**Table 4**
Selected bands in the IR spectra of complexes **21–24**, **26** and sulfonamide ligands **1**, **7**, **13**, **19** and **25** [$cm^{-1}$].

| | ν(NH) | ν(OH) | ν(C=O) | ν($SO_2N$) | ν(Ti–O) | |
|---|---|---|---|---|---|---|
| **1** | 3241 | – | 1724 | 1325 | 1145 | – |
| **21** | 3290 | – | 1739 | 1323 | 1144 | – |
| **7** | – | – | 1747 | 1331 | 1140 | – |
| **22** | – | – | 1747 | 1332 | 1142 | – |
| **13** | 3529 | 3302 | – | 1308 | 1132 | – |
| **23** | –[a] | –[a] | – | 1312 | 1140 | 662 |
| **19** | 3521 | – | – | 1326 | 1139 | – |
| **24** | –[a] | – | – | 1325 | 1139 | 665 |
| **25** [15] | 3245 | 3516 | – | 1309 | 1130 | – |
| **26** | 3256 | 3501 | – | 1315 | 1142 | 665 |

[a] Bands masked by the stretching vibrations attributed to water molecule.

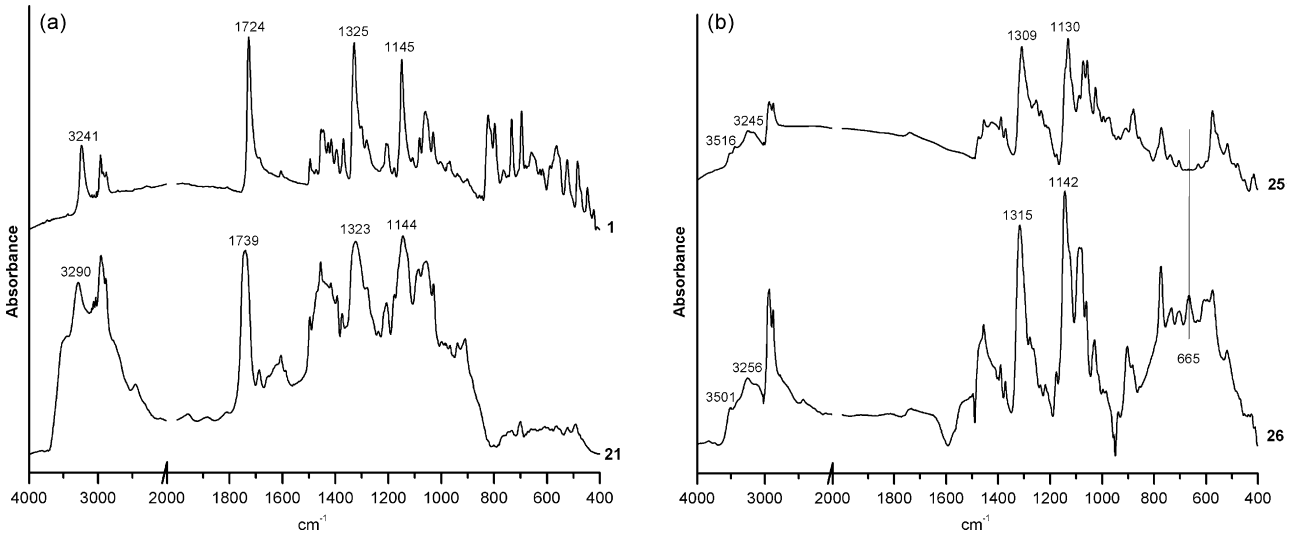



**Fig. 5.** Comparison of the IR spectra for (a) ketosulfonamide **1** and its complex **21**. (b) hydroxysulfonamide **25** and its complex **26**.

complex was not formed, unstable or too labile to be detected. In the IR spectra for that group of complexes, the bands for Ti–O or Ti–N cannot be assigned with no doubt, since the vibrations of the ligand groups occur in the same range as those for the Ti–$NMe_2$ moieties originated from substrate.

For complexes **23** and **24** the broad bands from water had masked any bands that could be attributed to the ligand NH or OH bands. Therefore, no direct conclusions could be derived for these complexes. However, comparison of the IR spectra for the synthesized Ti complex **26** and for previously reported bis(hydroxysulfonamide) **25** [15] revealed shifts for the NH and OH bands (Table 4), what confirms an involvement of these groups in the coordination to Ti. In the IR spectrum of complex **23** the shift of the bands related to stretching of the sulfonamide group were detected relative to the spectrum of the pure ligand **13**, also indicating that the sulfonamide group is coordinated to Ti. No such shift was found between the spectra of complex **24** and the respective ligand **19**. That difference suggests that sulfonamides derived from the secondary amines (e.g. **19**) do not bind to the metal center *via* their sulfonamide group, contrary to those derived from the primary amines, such as **13**. The additional bands at 664 $cm^{-1}$ observed in the IR spectra of **23**, **24** and **26** can be attributed to the stretching Ti–O vibrations [22]. The lack of shifts observed for the bands of sulfonamide group for **24** and the presence of identical band at 664 $cm^{-1}$ suggests the involvement of the ligand hydroxyl group in coordination.

The structural data and IR spectra allow to conclude that the hydroxy- and ketosulfonamides derived from primary amines coordinate bidentately *via* the sulfonamide group and the substituent at C2 of the bornyl moiety. The ketosulfonamides obtained from the secondary amines coordinate to Ti only *via* the sulfonamide group ($\eta^2$ –NO or $\eta^2$ –OO). The IR data reveal that hydroxysulfonamides obtained from the secondary amines coordinate to Ti *via* the hydroxyl group, but do not reveal their bidentate coordination involving the sulfonamide group. Such difference in the coordination mode between hydroxysulfonamides derived from primary and secondary amines is consistent with the observed differences in their catalytic activity (Table 1).

The possible architecture of the Ti-sulfonamide complexes, in particular the position of groups that might determine the orientation of substrate in the complex, was analyzed using program Mercury [23]. The obtained models were optimized with Molecular Mechanics method as implemented in Arguslab program [24] using UFF forcefield.

The model obtained for the catalysts formed with the ketosulfonamide auxiliaries **1**–**5** with the –NHR group (Fig. 6) is consistent with the results of the catalytic $Et_2Zn$ addition to benzaldehyde (Table 1). The observed enantiomeric excess for the (*R*)-1-phenylpropanol product was small (5–16% ee). The model reveals that, despite the coordination *via* the carbonyl oxygen, the *gem*-dimethyl group is distant from the catalytic center and causes only small steric hindrance, which is not a discriminating factor for the substrate positioning. Therefore, the addition to *Re* and *Si* sides of the aldehyde is almost equally probable. The obtained yields vary from 48% to 87% (Table 1). Such difference might result from the difficulties in forming a Ti–N coordination bond by ligands with bulky substituents on the sulfonamide N atom.

Ketosulfonamides **6**–**8** derived from the secondary amines bind to Ti(IV) *via* atoms of the sulfonamide group. The model of such architecture was proposed in our previous paper [17]. Such architecture of the active complex explains the observed enantiomeric excesses and yields (Table 1). Low yields (50–53%) obtained with auxiliaries **6**–**8** might result from the presence of two substituents at N atom, which restrict the access to the free electron pair of nitrogen. The coordination *via* the keto group results in a relatively

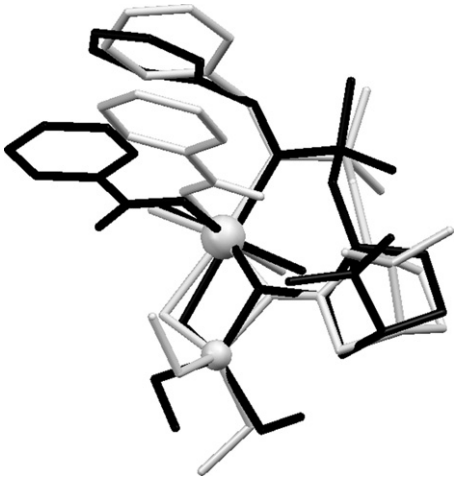


**Fig. 6.** Model of the active complex formed with **1** keto- (gray) and **13** hydroxysulfonamide (black) with the preferred orientation of the substrate as obtained with Arguslab MM calculations [24]. The preferred *Si* and *Re* faces are exposed for $Et_2Zn$ addition for hydroxy- and keto-auxiliaries, respectively.

large distance of the terpene group compared to that calculated for hydroxysulfonamide, what decreases significantly the steric control of the substrate positioning. That conclusion derived from the model is consistent with the observed low % ee of 1.1–5.6% (Table 1).

Hydroxysulfonamides **13**–**17** coordinate to Ti *via* the hydroxyl O and one of the atoms of the sulfonamide group. The presence of *exo* hydroxyl group results in a position of *gem*-dimethyl group close to the reaction center. Such arrangement causes the steric restrictions for the substrate on one side of the coordination plane and consequently the increased control of enantioselectivity of addition. That explains the observed increase of enatioselectivity with the use of hydroxysulfonamides comparing to the effect of ketosulfonamide auxiliaries. The change from the keto- to hydroxysulfonamides also causes the reversion of the configuration of the newly formed chiral center in the dominant product from *R* to *S*. The MM calculation for the model with hydroxysulfonamides clearly indicated the preferred orientation of the substrate corresponding to the addition to the *Si* face, consistent with the activity data presented in Table 1.

The crystal structure analysis for **1**, **9**, **11** and **13** revealed the importance of the intramolecular interactions of C10–H or bornane CH groups with the sulfonamide moiety or substituent at C2 for the conformation of the sulfonamide molecule (Table 3). For the sulfonamide coordination *via* the substituent at C2, the *gem*-dimethyl group should be a major steric factor influencing the orientation of the substrate molecule in the reaction center.

Differences in the position of *gem*-dimethyl group in keto- and hydroxysulfonamides relative to the reaction center are displayed on Fig. 6. For ligands with the $sp^2$ character of bornyl C2 (C=O), the substituent at C2 is positioned in the plane defined by C1, C2, C3 and C4 atoms, while for (2*R*)-hydroxysulfonamides that group is positioned above the plane. Therefore, in all hydroxysulfonamides of the known structure, the *gem*-dimethyl group C8–C7–C9 is significantly closer to substituent at C2 than in ketosulfonamides (Fig. 6), with the average distance between the center of mass of the *gem*-dimethyl and C2-bound oxygen being 3.512(11) Å for hydroxy- and 3.904(10) Å for keto-compounds.

The obtained models for the auxiliaries with the benzyl group suggest the explanation for their highest activity among the investigated compounds. The $CH_2$ group of benzyl allows the aromatic ring positioning approximately 3.7 Å from the plane of the ring of benzaldehyde substrate (Fig. 6). That indicates the importance of the stacking interactions between the substrate and the ligand. The lack of the $CH_2$ group in the aniline derivatives does not permit such positioning of both rings and would decrease the stabilizing effect in the active complex.

The ligands with the sulfur atom bound to C2 gave the lowest yields and % ee among four investigated groups. These results suggest that the formation of catalytically active complex involves the substituent containing an oxygen atom, while the presence of S atom prevents the coordination. One might assume that lack of coordination *via* the sulfur atom results in an increased distance between the bulky bornyl moiety and the center of reaction, what decreases the steric control of the enantioselectivity of the addition. The observation made during the procedure of assessing the activity was that the addition of thioketo- or mercaptosulfonamides to the $Ti(O^iPr)_4$ solution had caused no color change. That is an indicator for the lack of coordination of these ligands to Ti. However, the presence of S=C or HS–C donors could result in the formation of a complex between the ligand and $Et_2Zn$. Such a process competes with a formation of the Ti-ligand complex. The experiments performed with $Et_2Zn$ added to the reaction mixture containing these ligands prior to the addition of $Ti(O^iPr)_4$ resulted in the increase of the yield but decrease in the enantiomeric excess, when compared to the $Et_2Zn$ addition performed with hypothetical formation of the Ti-sulfonamide catalyst before injection of $Et_2Zn$. That seems to confirm that in a presence of the sulfur-containing ligands the direct non-stereospecific addition of $Et_2Zn$ to benzaldehyde is a significant process in the system.

The structural analysis revealed that sulfonamides **9**–**12**, with sulfur-containing substituent at C2, might bidentately coordinate to Ti(IV) either *via* two atoms of the sulfonamide group or *via* substituent at the bornyl C2 and the sulfonamide group. The active complex with such ligands might have an architecture analogous to that of the corresponding oxygen ligands. Data in Table 1 revealed that the difference in activity of thioketo- and mercaptosulfonamides are much smaller than those found for keto- and hydroxy-compounds. That does not exclude the possibility of coordination of the sulfur compounds *via* substituent at C2. The presence of S atom bound to C2 causes much larger distance between S and the center of mass of the *gem*-dimethyl [4.320(25) Å for C2=S and 3.903(10) Å for C2–SH], compared to the oxygen ligands. In both cases the *gem*-dimethyl is distant from the reaction center due to the distance of S to C2 much longer than that to oxygen. The assumed bidentate coordination $\eta^2$ –NO or $\eta^2$ –NS(C2) is in good agreement with the low % ee (1.7–9.2%) observed for (*R*)-1-phenylpropanol. The research revealed that the formation of Ti-sulfonamide complex with auxiliaries containing the C2-oxygen group is necessary for the $Et_2Zn$ addition to benzaldehyde. However, the addition performed with the sulfur-containing ligands resulted in the formation of 1-phenylpropanol (Table 1) even without addition of $Ti(O^iPr)_4$. That leads to the conclusion, that mercapto- and thioketosulfonamides can form a homodimeric catalyst with the Zn-sulfonamide moiety, what is consistent with the paper by Kitamura et al. [25].

## 4. Conclusions

The structural data and IR spectra allow to conclude that the hydroxy- and ketosulfonamides derived from primary amines coordinate bidentately *via* the sulfonamide group and the substituent at C2 of the bornyl moiety. The ketosulfonamides obtained from the secondary amines coordinate to Ti only *via* the sulfonamide group ($\eta^2$ –NO or $\eta^2$ –OO). The hydroxysulfonamides obtained from the secondary amines coordinate monodentately to Ti *via* the hydroxyl group, but there is no IR data indicating if they coordinate bidentately *via* other group. The crystal structure analysis for **1**, **9**, **11** and **13** revealed the importance of the intramolecular interactions of C10–H or bornane $CH_n$ groups with the sulfonamide moiety of substituent at C2 for the conformation of the sulfonamide molecule. Both the structural data and molecular modeling indicate that for sulfonamides coordinating *via* the substituent at C2, the *gem*-dimethyl group is a major steric factor determining the orientation of the substrate molecule in the reaction center and consequently the chirality of the product. Data for the sulfur-containing auxiliaries indicate that the non-stereospecific addition conducted with the $Et_2Zn$-sulfonamide active complex is a significant process in the investigated system. In all groups of the investigated auxiliaries the presence of bulky substituents on the sulfonamide N results in a decrease of the catalytic efficacy, while the best results are obtained for N-benzyl sulfonamides. That is consistent with the modeling results suggesting the importance of the $\pi$–$\pi$ interactions between the benzyl ring and the substrate.

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