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Titanium-promoted enantioselective diethylzinc addition to benzaldehyde in the presence of C_2-symmetrical bis(camphorsulfonamide) ligands

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Abstract—The synthesis of several C_2-symmetric bissulfonamides is described, starting from camphorsulfonyl chloride and various aromatic as well as aliphatic diamines. These compounds have been used as ligands for titanium tetraisopropoxide promoted diethylzinc addition to benzaldehyde. The best enantiomeric excess obtained in this study was 67%. The stereochemical outcome of the reaction is highly influenced both by the structure of ligand and the reaction parameters.

1. Introduction

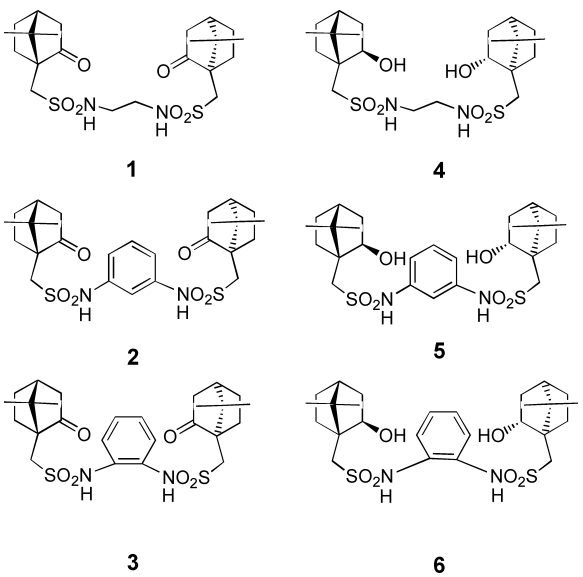
The formation of optically active secondary alcohols by the enantioselective addition of organometallic reagents to carbonyl compounds is one of the most promising methodologies in organic synthesis. Due to excellent chemoselectivity, the mostly used organometallic reagent is diethylzinc. Several efficient ligands have been introduced in recent years e.g. hydroxysulfonamides[1] and α-hydroxy acids.[2] These new ligands are very efficient under modified reaction conditions, when the process is performed in the presence of titanium alkoxide.

C_2-Symmetrical ligands, due to reduced number of possible transition states should exhibit enhanced enantioselectivity. To this class of compounds belong bissulfonamides used by Uang[3] and Walsh.[4] Chirality of their ligands originates from a chiral diamine. Recent papers by Yus,[5] presenting C_2-symmetrical bis(hydroxysulfonamide) ligands prompted us to reveal our results. Independently, we took similar approach, combining achiral diamines with chiral sulfonic acids and the obtained compounds were used as chiral ligands.

2. Results and discussion

2.1. Synthesis of chiral ligands

Bissulfonamide ligands **1**–**3** were synthesized from the commercially available diamines and (+)-camphorsulfonic chloride (2 equiv., prepared from the (+)-camphorsulfonic acid by the reaction with thionyl chloride). Hydroxy derivatives **4**–**6** were obtained by the *exo*-selective reduction of the carbonyl group in **1**–**3** with L-Selectride,[6] followed by flash chromatography and/or crystallisation (Scheme 1).



Scheme 1. Camphorsulphonic acid derived ligands.

2.2. Asymmetric addition of diethylzinc to benzaldehyde

With ligands **1**–**6** in hand, we studied the reaction of benzaldehyde with diethylzinc in the presence of titanium tetraisopropoxide (Scheme 2).

Keywords: camphorsulfonamides; diethylzinc; titanium tetrapropoxide; enantioselectivity.
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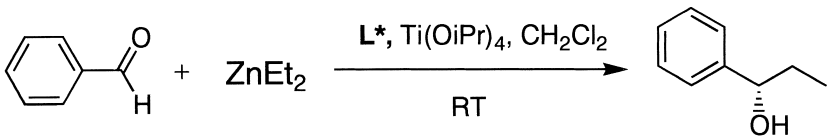

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Scheme 2. Diethylzinc addition to benzaldehyde.

Table 1.

Entry	Ligand	Ratio $Ti(OiPr)_4/ZnEt_2$ [equiv.]	Addition order	Temperature [°C]	Time [h]	Yield [%]	E.e.[a] [%]	Configuration
1	**1**	7:3	Zn/Ti	20	14	90	1.9	*R*
2	**2**	7:3	Zn/Ti	20	14	85	25	*R*
3	**2**	7:3	Ti/Zn	20	20	96	20	*R*
4	**4**	7:3	Zn/Ti	−20	26	66	2.8	*S*
5	**4**	7:3	Zn/Ti	20	24	90	55	*S*
6	**4**	7:3[b]	Zn/Ti	20	4.5	85	40	*S*
7	**4**	7:3	Ti/Zn	20	20	96	12	*R*
8	**5**	7:3	Zn/Ti	20	3	78	67	*S*
9	**5**	2.4:3	Zn/Ti	0	48	65	66	*S*
10	**5**	2.4:3	Zn/Ti	20	4.5	95	58	*S*
11	**5**	2.4:3	Ti/Zn	20	3	95	52	*S*
12	**6**	7:3	Zn/Ti	−20	26	60	18	*S*
13	**6**	7:3	Zn/Ti	20	24	80	40	*S*
14	**6**	7:3	Ti/Zn	20	24	80	7.7	*R*

[a] Determined by HPLC analysis using a Daicel Chiracel OD column.
[b] Reaction in toluene.

First, we started with reactions catalysed by ligands **1** and **2**. Due to lack of other strongly binding sites, we could expect that only sulfonamide nitrogen atoms will chelate the metal centre, and the asymmetric induction, if any, will arise from the chiral environment provided by camphorsulfonic moiety. The ligands were dissolved in methylene chloride, then Et_2Zn was added followed by $Ti(OiPr)_4$. Finally, freshly distilled benzaldehyde was added and the mixture was stirred for the time indicated in Table 1 until TLC showed full consumption of aldehyde.

After workup, the enantiomeric excess was determined by HPLC on Chiracel OD column. Not surprisingly, almost racemic product for ligand **1** was obtained, while ligand **2** gave very modest enantioselectivity (Table 1, entries 1 and 2). For the very similar compound derived from *ortho*-xylylenediamine, Yus et al. obtained 40% ee.[5c]

Then we turned our attention to ligands **4**–**6**, which have the ability to co-ordinate to the central metal atom by the hydroxy group located in the camphor ring. Best results were obtained for bis(hydroxysulfonamide) **5** obtained from 1,3-benzenediamine. Its more conformationally labile aliphatic analogue **4** gave lower enantiomeric excess, while ligand **6** derived from 1,2-benzenediamine was the worst one. The magnitude of the asymmetric induction obtained for our ligands matches that obtained by Yus et al. for C_1-symmetric ligands, which suggests similar transition states for both systems.[5a]

The results obtained for bis(hydroxycamphorsulfonamides) **4**–**6** clearly show that the enantioselectivity observed for this catalytic system is highly depended not only on the ligand used, but also on the reaction conditions. All reactions were performed in methylene chloride, except one case when we tested toluene. In this solvent the reaction was much faster, but proceeded with lower selectivity (40 vs 55% ee, entries 5 and 6, respectively). The smaller amount of titanium tetraisopropoxide has significant influence on the asymmetric induction. Very interesting information come from experiments, in which reagents were added in reverse order. For ligands **4** and **6** complexation first with titanium then with zinc gave not only much lower enantiomeric excess, but also lead to the opposite configuration (Table 1, entries 7 and 14 vs entries 5 and 13). Similarly, such direction of the asymmetric induction was observed for ligands **1** and **2**, irrespective of the addition order. It suggests that both nitrogen atoms are bound to the same titanium atom and the camphorsulfonyl moiety is not involved. In ligand **5** distance between nitrogen atoms seems to preclude such complexation. Comparison of our results (e.g. entry 8) with results obtained for phenyl hydroxycamphorsulfonamide by Yus et al.[5a] suggest that, at least in this case, ligand **5** is not working in a multidentate manner and both sides behave independently.

3. Conclusions

In summary, we have presented here synthesis of C_2-symmetrical ligands derived from achiral 1,2- and 1,3-diamines and (+)-camphorsulphonic acid. Investigation of the enantioselective addition of diethylzinc to benzaldehyde in the presence of these ligands clearly shows that C_2-symmetry is not always advantageous. In our case both sides of C_2-symmetric molecule can behave independently.

4. Experimental

4.1. General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer PE-241 polarimeter with a thermally jacketed 10 cm cell at 19°C. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian 200 Unity Plus and Varian 500 Unity Plus spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hz. Mass spectra were recorded on an AMD-604 Intectra instrument using the EI (electron impact) technique. Infrared spectra were recorded using a Beckmann IR-240 spectrometer. Reactions were carried under argon using Schlenk technique when necessary. Flash column chromatography was made on silica gel (Kieselgel-60, Merck, 230–400 mesh).

4.2. Preparation of disulfonamides 1–3

4.2.1. *N*,*N*′-Bis[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl]methanesulfonyl-ethane-1,2-diamine (1). The solution of (1*S*)-camphorsulfonyl chloride (320 mg, 1.3 mmol) in DMF (2 mL) was cooled to 0°C and 1,2-ethylenediamine (0.043 mL, 0.65 mmol), Et_3N (0.195 mL, 1.4 mmol) and catalytical amount of DMAP were added. The reaction mixture was allowed to warm up to room temperature. After 30 min reaction mixture was diluted with diethyl ether, washed with water, brine and dried over anhydrous $MgSO_4$. The drying agent was filtered off, solvent was evaporated in vacuo and the oily residue was purified by crystallisation (ether–hexane) to give 227 mg of ligand **1** (73% yield). Mp 130°C. $[\alpha]_D$=+33.5 (c=1.45, $CHCl_3$). ^{1}H NMR (500 MHz): 5.69 (bs, 2H, 2×N*H*), 3.46, 2.95 (2d, 2×2H, J=14.5 Hz, 2×CH_2S), 3.40 (m, 4H, 2×CH_2N), 2.42–1.39 (m, 14H, 2×$CH_2CH_2CHCH_2$), 1.03, 0.91 (2s, 2×6H, 2×CH_3). ^{13}C NMR (125 MHz): 216.9, 59.0, 49.7, 48.8, 43.7, 42.9, 42.7, 27.0, 26.2, 19.9, 19.5. ν_{max} (KBr): 3434, 3280, 3246, 2958, 2888, 1727, 1441, 1332, 1147, 1070, 776. Anal. calcd for $C_{22}H_{36}N_2O_6S_2$: C, 54.07; H, 7.43; N, 5.73; S, 13.12. Found: C, 53.98; H, 7.51; N, 5.71; S, 13.12. MS LR: 977 (2M+H), 511 (M+Na), 489 (M+H), 471, 275, 215, 154, 137, 109.

4.2.2. *N*,*N*′-Bis[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl]methanesulfonyl-benzene-1,3-diamine (2). The solution of (1*S*)-camphorsulfonyl chloride (250 mg, 1.0 mmol) in of DMF (2 mL) was cooled to 0°C and 1, 3-diaminobenzene (0.54 mg, 0.5 mmol), *i*PrEt$_2$N (0.21 mL, 1.2 mmol) and catalytical amount of DMAP were added. The reaction mixture was allowed to warm up to room temperature. After 1 h, reaction mixture was diluted with diethyl ether, washed with water, brine and dried over anhydrous $MgSO_4$. The drying agent was filtered off, solvent was evaporated in vacuo and the residue was purified by flash chromatography (hexane–ethyl acetate 6:4) to give 107 mg (40% yield) of **3**. Mp 206–207°C. $[\alpha]_D$=+53.0 (c=1.32, acetone). ^{1}H NMR (200 MHz): 7.96 (s, 2H, 2×N*H*), 7.39–7.11 (m, 4H, Ar*H*), 3.42, 2.90 (2d, 2×2H, J=15 Hz, 2×CH_2S), 2.53–1.26 (m, 14H, 2×$CH_2CH_2CHCH_2$), 0.97, 0.89 (2s, 2×6H, 2×CH_3). ^{13}C NMR (50 MHz, $(CD_3)_2CO$): 215.3, 206.2, 140.5, 131.1, 116.3, 112.1, 59.3, 48.9, 48.8, 43.6, 43.0, 27.4, 26.4, 20.0, 19.9. ν_{max} (KBr): 3254, 2963, 1748, 1608, 1388, 1318, 1148, 997. Anal. calcd for $C_{26}H_{36}N_2O_6S_2$: C, 58.18; H, 6.76; N, 5.22; S, 11.95. Found: C, 58.22; H, 6.76; N, 5.12; S, 12.09. MS LR: 536, 322, 215, 151, 123, 109, 81, 67, 41.

4.2.3. *N*,*N*′-Bis[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]-hept-1-yl]methanesulfonyl-benzene-1,2-diamine (3). To the solution of 1,2-diaminobenzene (64 mg, 0.6 mmol) and catalytical amount of DMAP in dry pyridine (2 mL), (1*S*)-camphorsulfonyl chloride (300 mg, 1.2 mmol) in pyridine (2 mL) was added dropwise. After TLC showed completion of the reaction, pyridine was distilled off under reduced pressure. The residue was washed three times with ethyl ether, combined etheral washings were treated with $CuSO_4$ solution, dried over anhydrous $MgSO_4$. The drying agent was filtered off, solvent was evaporated in vacuo and the oily residue was purified by flash chromatography (CH_2Cl_2–MeOH 50:1) to give 80 mg (30% yield) of bissulfonamide **2**. $[\alpha]_D$=+61.5 (c=2.83, $CHCl_3$). ^{1}H NMR (200 MHz): 7.94 (s, 2H, 2×N*H*), 7.59–7.48 (m, 2H, Ar*H*), 7.30–7.19 (m, 2H, Ar*H*), 3.55, 2.98 (2d, 2×2H, J=15 Hz, CH_2S), 2.51–1.37 (m, 14H, 2×$CH_2CH_2CHCH_2$), 1.04, 0.93 (2s, 2×6H, 2×CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 217.0, 131.0, 127.2, 125.2, 59.6, 49.7, 48.8, 42.9, 27.0, 26.8, 19.9, 19.6. ν_{max} (liquid film): 3266, 2961, 2890, 1745, 1500, 1415, 1339, 1150, 927, 756. Anal. calcd for $C_{26}H_{36}N_2O_6S_2$: C, 58.18; H, 6.76; N, 5.22; S, 11.95. Found: C, 58.14; H, 6.38; N, 4.93; S, 11.72. MS LR: 1095 (2M+Na), 559 (M+Na).

4.3. Preparation of bis(hydroxysulfonamides) 4–6

The solution of corresponding diketone **1**–**3** (1.5 mmol) in THF (10 mL) was cooled to −78°C under argon atmosphere. L-Selectride (12 mmol, 1 M solution in THF) was then slowly added. Reaction was stirred at this temperature for 1 h, allowed to warm to RT and stirred for 48 h. Then reaction 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 phases were washed with water, brine and dried over anhydrous $MgSO_4$. The drying agent was filtered off, solvent was evaporated in vacuo and the residue was purified by flash chromatography.

4.3.1. *N*,*N*′-Bis[(1*S*,4*R*)-2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl]methanesulfonyl-ethane-1,2-diamine (4). Flash chromatography (hexane–ethyl acetate 8:2) led to obtain 610 mg of ligand **4** (82% yield). Mp 185–187°C. $[\alpha]_D$=−51.6 (c=1.20, $CHCl_3$). ^{1}H NMR (200 MHz): 5.56 (bs, 2H, 2×N*H*), 4.07 (m, 2H, 2×C*H*OH) 3.50, 2.94 (2d, 2×2H, J=13.8 Hz, 2×CH_2S), 3.35 (m, 4H, 2×CH_2N), 1.90–1.30 (m, 14H, 2×$CH_2CH_2CHCH_2$), 1.06, 0.83 (2s, 2×6H, 2×CH_3). ^{13}C NMR (50 MHz): 76.2, 52.2, 50.3, 48.8, 44.3, 43.5, 39.2, 30.3, 27.3, 20.5, 19.8. ν_{max} (KBr): 3534, 3293, 2956, 2881, 1455, 1320, 1140, 1075, 879, 790, 573. Anal. calcd for $C_{22}H_{40}N_2O_6S_2$: C, 53.65; H, 8.12; N, 5.69; S, 13.03. Found: C, 53.50; H, 8.24; N, 5.52; S, 13.05. MS LR: 1007 (2M+Na), 515 (M+Na).

4.3.2. *N*,*N*′-Bis[(1*S*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl]methanesulfonyl-benzene-1,3-diamine (5). Flash chromatography (CH_2Cl_2–MeOH 190:2) led to obtain 640 mg of ligand **6** (79% yield). Mp 201–203°C. $[\alpha]_D=-52.4$ ($c=1.05$, acetone). ^{1}H NMR (500 MHz): 7.31 (t, 2H, $J=8$ Hz, Ar*H*), 7.23 (s, 1H, Ar*H*), 7.16 (s, 2H, 2×N*H*), 6.96 (d, 2H, $J=7.5$ Hz, Ar*H*), 4.15 (m, 2H, C*H*OH), 3.61, 3.01 (2d, 2×2H, $J=14$ Hz, 2×CH_2S), 2.41 (s, 2H, O*H*), 1.90–1.06 (m, 14H, 2×$CH_2CH_2CHCH_2$), 1.01, 0.78 (2s, 2×6H, 2×CH_3). ^{13}C NMR (50 MHz, $(CD_3)_2CO$): 206.2, 140.5, 131.3, 115.4, 110.5, 76.6, 51.3, 50.9, 49.4, 45.3, 40.5, 30.8, 27.9, 20.8, 20.3. ν_{max} (KBr): 3544, 3263, 2956, 2882, 1609, 1499, 1316, 1140, 1074, 757, 570. Anal. calcd for $C_{26}H_{40}N_2O_6S_2$: C, 57.77; H, 7.40; N, 5.18; S, 11.87. Found: C, 57.93; H, 7.44; N, 5.37; S, 11.74. MS LR: 1103 (2M+Na), 563 (M+Na).

4.3.3. *N*,*N*′-Bis[(1*S*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl]methanesulfonyl-benzene-1,2-diamine (6). Flash chromatography (chloroform) led to obtain 650 mg of ligand **5** (80% yield). $[\alpha]_D=-27.2$ ($c=2.61$, $CHCl_3$). ^{1}H NMR (500 MHz): 7.54–7.44 (m, 2H, Ar*H*), 7.45 (s, 2H, 2×N*H*), 7.32–7.27 (m, 2H, Ar*H*), 4.16–4.10 (m, 2H, 2×C*H*OH), 3.60, 3.04 (2d, 2×2H, $J=14$ Hz, CH_2S), 2.69 (s, 2H, O*H*) 1.89–1.08 (m, 14H, 2×$CH_2CH_2CHCH_2$), 1.03, 0.79 (2s, 2×6H, 2×CH_3). ^{13}C NMR (50 MHz): 130.6, 127.7, 125.3, 52.1, 50.5, 48.9, 44.4, 39.3, 30.4, 27.3, 20.5, 19.9. ν_{max} (liquid film): 3547, 3270, 2956, 2882, 1601, 1499, 1392, 1327, 1147, 1074, 930, 731, 569. MS HR calcd for $C_{26}H_{36}N_2O_6S_2Na$: 563.2226. Found: 563.2245. MS LR: 1103 (2M+Na), 563 (M+Na).

4.4. Enantioselective diethylzinc addition to benzaldehyde. Typical procedure

To the ligand **5** (43.5 mg, 0.2 mmol) dissolved in methylene chloride (5 mL) titanium tetraisopropoxide (0.42 mL, 1.4 mmol) was added. The mixture was stirred for 1 h at room temperature, cooled to −78°C, and diethylzinc (0.27 mL of 1.1 M toluene solution, 3 mmol) was added. Stirring was continued at this temperature, and freshly distilled benzaldehyde (0.1 mL, 1 mmol) was added. The mixture was allowed to warm up to the room temperature and stirred for the time indicated in Table 1. The reaction was quenched with 1 M HCl (10 mL), and insolubles were filtered off. 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 flash chromatography (hexane–ethyl acetate 5:1 v/v) to give (*S*)-1-phenylpropanol. Yield mg; 78%. This product was subjected to HPLC analysis using a Chiracel OD column (3% 2-propanol in hexane).

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