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Synthesis of novel nitrogen-containing ligands for the enantioselective addition of diethylzinc to aldehydes

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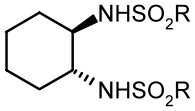
Abstract—New nitrogen-containing ligands derived from the (1*R*,2*R*)-*trans*-cyclohexanediamine chiral core unit have been synthesized and fully characterized. Their catalytic activity was tested in the asymmetric addition of diethylzinc to aldehydes leading to the respective secondary alcohols with enantioselectivities of up to 74% ee.

1. Introduction

The search for new ligands for asymmetric catalysis is a field of continuous interest. To facilitate practical applications new ligands should be easy to prepare from simple and accessible starting materials.[1] In this context the use of nitrogen-containing ligands is growing. Recent reports have shown that these compounds are suitable for many types of catalysis including heterogeneous catalysis.[2,3] High stability and good accessibility from the chiral pool are particular advantages of nitrogen-containing ligands if compared with phosphines.

Bis(sulfonamide)-based ligands derived from (1*R*,2*R*)-*trans*-cyclohexanediamine **1** have successfully been applied as catalysts for many asymmetric transformations, such as the Simmons–Smith reaction[4] and the addition of organozinc reagents to carbonyl compounds.[5,6]



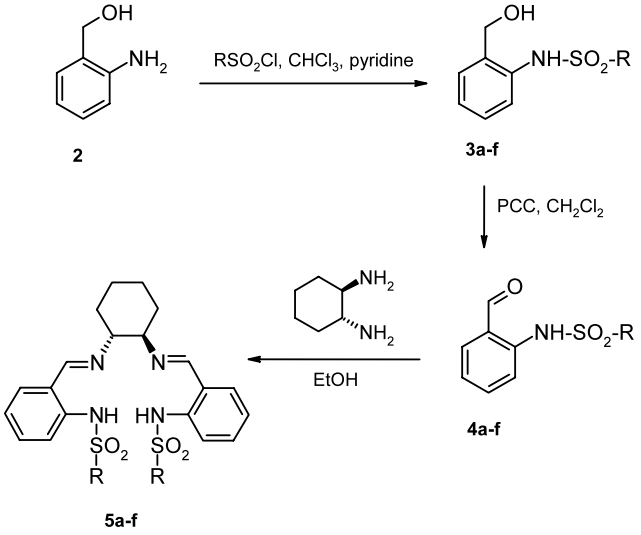
1a: R = CF_3
1b: R = *p*-MeC_6H_4
1c: R = 1-naphthyl

We report here the synthesis of novel tetradentate sulfonamide ligands, bearing the same homochiral core and additional coordination sites. The tetraza ligands were used as catalysts for the asymmetric alkylation of aldehydes with diethylzinc.

2. Results and discussion

2.1. Synthesis of ligands

The synthesis shown in Scheme 1 yields sulfonamides **4a**–**f** in three steps with yields higher than those previously reported by Katsuki et al. for the synthesis of a similar achiral Schiff bases.[7] The commercially available *o*-aminobenzyl alcohol **2** is used as starting material.[8] It is reacted with different sulfonyl chlorides in the presence of pyridine to give the corresponding *N*-pro-



R = a: *p*-MeC_6H_4 , **b:** C_6H_5, **c:** *p*-$MeOC_6H_4$, **d:***p*-$NO_2C_6H_4$, **e:** *p*-ClC_6H_4, **f:** 2,4,6-$Cl_3C_6H_2$

Scheme 1.

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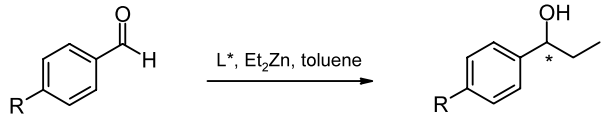
tected alcohols **3a**–**f** in almost quantitative yields (Table 1). In the ^{1}H NMR spectra of the six derivatives a broad singlet at about $\delta = 8$ is observed, corresponding to the sulfonamide proton, which confirms the successful substitution. By use of PCC[9] the alcohols are oxidized to the corresponding aldehydes **4a**–**f** in very good yields (Table 1). The Schiff bases **5a**–**f** were obtained in good yields from the condensation of chiral (1*R*,2*R*)-*trans*-cyclohexanediamine and the respective aldehydes in ethanol in a ratio of 1:2 (Table 1).

Table 1. Yields of substituted benzylalcohols **3**, aldehydes **4** and Schiff bases **5**

R	**3** (%)	**4** (%)	**5** (%)
a: *p*-MeC_6H_4	98	74	85
b: C_6H_5	95	61	74
c: *p*-$MeOC_6H_4$	100	90	78
d: *p*-$NO_2C_6H_4$	100	95	91
e: *p*-ClC_6H_4	100	99	69
f: 2,4,6-$Cl_3C_6H_2$	100	90	71

2.2. Catalysis

The sulfonamide derivatives **5a**–**f** (Scheme 1) were screened in the asymmetric alkylation of benzaldehyde **6a** with diethylzinc (Scheme 2).



6a: R = H
6b: R = Cl
6c: R = MeO

7a: R = H
7b: R = Cl
7c: R = MeO

Scheme 2.

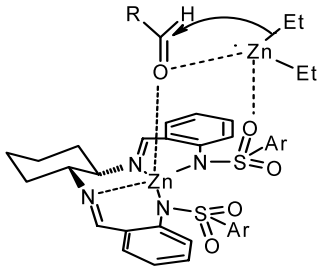
Table 2 summarizes the yields and enantioselectivities of (*R*)-1-phenylpropanol **7a** reached with the sulfonamides (5 mol%) by addition of 2.5 equiv. of diethylzinc and reaction in toluene at room temperature over 24 h. Quantitative yields of the secondary alcohol and good asymmetric induction (70 and 74% ee, respectively) were obtained with ligands **5a** and **5b**. A lower yield, but still good enantioselectivity was obtained with the *p*-methoxybenzene sulfonamide substituted ligand **5c**. Ligands **5d**–**f** gave less satisfactory results.

Table 2. Results obtained using the diimine-sulfonamide ligands **5a**–**f** in the asymmetric diethylzinc addition to benzaldehyde **6a**

Entry	Catalyst	Yield (%)	ee (%)
1	**5a**	100	70 (*R*)
2	**5b**	100	74 (*R*)
3	**5c**	74	70 (*R*)
4	**5d**	43	38 (*R*)
5	**5e**	47	55 (*R*)
6	**5f**	34[a]	21 (*R*)

[a] Yield determined by GC.

Dangel and Polt have proposed a mechanism for the asymmetric addition of diethylzinc with tetraaza-ligands, in which it was assumed that two Zn atoms are involved in the alkyl transfer: the 'inner' Zn atom and the 'outer' Zn atom.[10] This mechanism could explain the catalytic activity of our ligands. When diethylzinc was added to the ligand a tetracoordinate sulfonamido zinc complex is formed (Scheme 3). By coordination to the Lewis acidic Zn atom the aldehyde is activated and its electrophilicity is enhanced towards attack by the diethylzinc.[11] On the other hand, the 'outer' zinc atom is coordinated ('solvated') by exchangeable oxygens. This increases its nucleophilicity and favors the alkyl transfer.

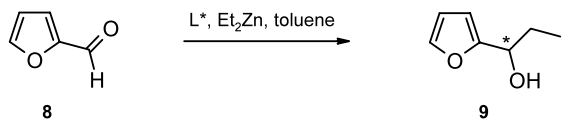


Scheme 3.

Screening the synthesized ligands revealed that only the sulfonamide-derivatives **5a** and **5b** promote the asymmetric alkylation of benzaldehyde with diethylzinc in high yields and significant enantioselectivities.

In order to determine the optimal amount of the ligand needed for the addition of diethylzinc to benzaldehyde **6a**, experiments with variable quantities of ligand **5a** were carried out. Low yields and low enantiomeric excesses of **7a** were observed using 1 or 2.5 mol% of the catalyst (48 h reaction time). However, quantitative yield and good enantioselectivity were achieved when 5 mol% were used. Further increases to 7 or 10 mol% of the catalyst did not improve the progress of the catalysis. Thus, for all subsequent reactions 5 mol% of catalyst were used.

Encouraged by the results obtained with the sulfonamide derivatives **5a** and **5b** in the addition of diethylzinc to benzaldehyde **6a** the asymmetric alkylation was extended to other aldehydes: *p*-chlorobenzaldehyde **6b**, *p*-methoxybenzaldehyde **6c** (Scheme 2) and furfural **8** (Scheme 4) were selected as substrates. The reactions were run under the same conditions described above but at two different temperatures (0 and 25°C). The results are summarized in Table 3. As expected, the



8 **9**

Scheme 4.

Table 3. Addition of diethylzinc to *p*-substituted benzaldehydes **6b** and **6c** and heteroaromatic aldehyde **8** using the diimine-sulfonamides **5a** and **5b**[12]

Entry	Aldehyde R	Ligand	Temp (°C)	Yield (%)	ee (%)
1	H	**5a**	0	89	71 (*R*)
2	H	**5a**	25	100	70 (*R*)
3	H	**5b**	0	93	75 (*R*)
4	H	**5b**	25	100	74 (*R*)
5	Cl	**5a**	0	21	64 (*R*)
6	Cl	**5a**	25	60	71 (*R*)
7	Cl	**5b**	0	23	69 (*R*)
8	Cl	**5b**	25	65	74 (*R*)
9	OMe	**5a**	0	53	45 (*R*)
10	OMe	**5a**	25	70	62 (*R*)
11	OMe	**5b**	0	51	57 (*R*)
12	OMe	**5b**	25	76	56 (*R*)
13	Furfural	**5a**	0	49	70 (*R*)
14	Furfural	**5a**	25	61	28 (*R*)
15	Furfural	**5b**	0	21	69 (*R*)
16	Furfural	**5b**	25	44	37 (*R*)

yields obtained with both ligands and for all aldehydes used were higher at room temperature (entries 6, 8, 10, 12, 14, and 16) than at 0°C (entries 5, 7, 9, 11, 13, 15), but they were much lower than those obtained with benzaldehyde (entries 1–4). The presence of an electron-donor substituent (OMe) at the *para*-position of aldehyde **6c** contributes to an increase in the yield of the secondary alcohol **7c**, while the electron-acceptor substituent (Cl, aldehyde **6b**) in the same position causes the opposite effect.

Unexpectedly, the enantioselectivities achieved for both *para*-substituted aromatic secondary alcohols **7b** and **7c** were higher when the reactions were carried out at room temperature (entries 6, 8, and 10). For the heteroaromatic aldehyde furfural **8** the opposite effect was observed, i.e. at 0°C a better enantioselectivity (70 and 69% ee, entries 13 and 15) than at room temperature.

The attempts to alkylate heptanal with diethylzinc in the presence of the chiral sulfonamides **5a** and **5b** were unsuccessful. No conversion could be detected after 4 days, neither at 0°C nor at room temperature.

To investigate the surprising increase in enantioselectivity with temperature in the reactions of **5a** and **5b** and *para*-substituted benzaldehydes an additional set of reactions was performed with both ligands[13] at 50°C. Using benzaldehyde **6a** as substrate, quantitative yields of 1-phenylpropanol **7a** were achieved after 5 h. Enantioselectivities decrease only slightly (by approx. 8%) in comparison with the reaction at room temperature (Table 4).

2.2.1. Asymmetric alkylation using $Ti(O^iPr)_4$ as Lewis acid. Ohno and Kobayashi reported that the asymmetric alkylation using bidentate sulfonamide ligands **1** as catalysts is rather slow even at room temperature and yields chiral secondary alcohols in moderate yields and enantioselectivities.[5a] But when this reaction was carried out in the presence of $Ti(O^iPr)_4$, very good yields and enantioselectivities were obtained.[5b]

Table 4. Catalyzed addition of diethylzinc to benzaldehyde at increased temperatures.

Entry	Ligand	Temp (°C)	Yield (%)	ee (%)
1	**5a**	50	100	62
2	**5a**	25	100	70
3	**5b**	50	100	67
4	**5b**	25	100	74

Therefore the effect of $Ti(O^iPr)_4$ on the activity of ligand **5a** in the addition of diethylzinc to benzaldehyde was investigated. A mixture of ligand (5 mol%) and $Ti(O^iPr)_4$ (0.6 or 1.2 equiv.) dissolved in toluene was stirred for 1 h under reflux to form the titanium complex. After cooling to −30°C, diethylzinc (2.5 equiv.) and benzaldehyde were added. The yield (36 and 48% yield, respectively) and enantioselectivities (6 and 3% ee, respectively, versus 70% ee without Lewis acid) of 1-phenylpropanol **7a** decrease drastically under these conditions. A likely rationale for this observation is the formation of a complex of titanium and the chiral sulfonamide **5a**, analogous to the structurally characterized complex by Walsh.[14] With the addition of $Ti(O^iPr)_4$, sulfonamides are deprotonated and titanium is coordinated by sulfonamido nitrogens and two sulfonyl oxygens. This may lead to a less favorable catalyst geometry.

3. Conclusions

We have prepared six new tetradentate sulfonamide ligands with (1*R*,2*R*)-*trans*-cyclohexane diamine as the homochiral core. The ligands are available in three simple synthetic steps in very good yields and large amounts. All ligands were tested in the asymmetric alkylation of benzaldehyde **6a** with diethylzinc. Sulfonamides **5a**–**f** showed catalytic activity in the asymmetric reaction, reaching in case of **5a** and **5b** quantitative yields of the chiral alcohol **7a** in satisfying enantioselec-

tivities 70 and 74% ee. A likely mechanism for the catalysis with these ligands is suggested on the basis of reported structures of tetraaza-complexes.

4. Experimental

4.1. General remarks

The catalytic reactions were carried out in Schlenk flasks under a nitrogen atmosphere and using dry toluene. The enantioselectivity of the products was determined by GC. To test the reproducibility of the results obtained, each catalysis was performed at least twice under exactly the same conditions.

(1*R*,2*R*)-*trans*-Cyclohexanediamine[15] was synthesized according to the literature procedure. The optical purity measured $[\alpha]_D^{25}=-25$ for the chiral diamine matches the reported literature value[16] $[\alpha]_D^{25}=-25.5$ (*c* 5, HCl 1 M).

4.2. General procedure (GP1) for the synthesis of substituted amino alcohols 3

A solution of *o*-aminobenzyl alcohol **2** and pyridine in dry $CHCl_3$ was treated dropwise with a solution of the appropriate sulfonyl chloride in $CHCl_3$ at room temperature. The reaction mixture was stirred for 3 h, evaporated to dryness, the resulting residue was taken up in ethyl acetate and saturated aqueous ammonium chloride. The organic phase was separated, dried over Na_2SO_4, filtered and evaporated to give the *N*-sulfonamides.

4.2.1. *N*-(2-Hydroxymethylphenyl)-4-methylbenzenesulfonamide 3a. Obtained from *o*-aminobenzyl alcohol **2** (2 g, 16.2 mmol) in 60 ml of $CHCl_3$, pyridine (1.6 ml) and 4-toluenesulfonyl chloride (3.4 g, 18 mmol) in 17 ml of $CHCl_3$ as a white solid (4.4 g, 15.9 mmol, 98%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=2.38$ (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.06–7.09 (m, 2H), 7.19–7.28 (m, 3H), 7.42 (d, 1H, $J=7.9$ Hz), 7.64 (dd, 2H, $J=4.7$, 1.8 Hz).

4.2.2. *N*-(2-Hydroxymethylphenyl)benzenesulfonamide 3b. Obtained from *o*-aminobenzyl alcohol **2** (4 g, 33 mmol) benzenesulfonyl chloride (4.6 ml, 36 mmol) and pyridine (3.12 ml) in $CHCl_3$ (120+35 ml) as a white solid (8.2 g, 31 mmol, 95%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=4.3$ (s, 2H, CH_2), 7.06 (dd, 2H, $J=5.4$ Hz), 7.18–7.24 (m, 1H), 7.35–7.44 (m, 3H), 7.48–7.52 (m, 1H), 7.71–7.75 (m, 2H), 8.34 (bs, 1H, NH).

4.2.3. *N*-(2-Hydroxymethylphenyl)-4-methoxybenzenesulfonamide 3c. Obtained from *o*-aminobenzyl alcohol **2** (4 g, 33 mmol), 4-methoxybenzenesulfonyl chloride (7.44 g, 36 mmol), pyridine (3.1 ml), and $CHCl_3$ (120+34 ml) as a light yellow solid (8.6 g, 31 mmol, 100%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=3.82$ (s, 3H, OCH_3), 4.40 (d, 2H, $J=4.1$ Hz, CH_2), 6.86–6.89 (m, 2H), 7.07–7.1 (m, 2H), 7.19–7.28 (m, 1H), 7.41 (d, 1H, $J=7.9$ Hz), 7.66–7.70 (m, 2H), 7.88 (bs, 1H, NH).

4.2.4. *N*-(2-Hydroxymethylphenyl)-4-nitrobenzenesulfonamide 3d. Obtained from *o*-aminobenzyl alcohol **2** (1 g, 8.1 mmol in 30 ml of $CHCl_3$), pyridine (0.8 ml) and 4-nitrobenzenesulfonyl chloride (1.96 g, 8.8 mmol, in 9 ml of $CHCl_3$) as a yellow solid (2.5 g, 8.1 mmol, 100%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=2.48$ (bs, OH), 4.31 (s, 2H, CH_2), 7.09 (m, 2H), 7.19–7.24 (m, 1H), 7.37 (d, 1H, $J=7.9$ Hz), 7.89–7.94 (m, 2H), 8.21–8.26 (m, 2H), 8.8 (bs, 1H, NH).

4.2.5. *N*-(2-Hydroxymethylphenyl)-4-chlorobenzenesulfonamide 3e. Obtained from *o*-aminobenzyl alcohol **2** (1 g, 8.1 mmol in 30 ml of $CHCl_3$), pyridine (0.8 ml) and 4-chlorobenzenesulfonyl chloride (1.87 g, 8.8 mmol in 9 ml of $CHCl_3$) as a white solid (2.4 g, 8.1 mmol, 100%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=2.12$ (s, OH), 4.34 (s, 2H, CH_2), 7.06–7.1 (m, 2H), 7.18–7.25 (m, 1H), 7.35–7.4 (m, 3H), 7.64–7.7 (m, 2H), 8.44 (bs, 1H, NH).

4.2.6. *N*-(2-Hydroxymethylphenyl)-2,4,6-trichlorobenzenesulfonamide 3f. Obtained from *o*-aminobenzyl alcohol **2** (180 mg, 1.46 mmol in 8 ml of $CHCl_3$), pyridine (0.14 ml) and 2,4,6-trichlorobenzenesulfonyl chloride (450 mg, 1.6 mmol in 8 ml of $CHCl_3$). During the reaction the color of the mixture changes from yellow to red. Product **3f** was obtained in quantitative yield (536 mg, 1.46 mmol, 100%) and was directly used for oxidation.

4.3. General procedure (GP2) for the oxidation of substituted amino alcohols to aldehydes 4

To a stirred suspension of PCC in CH_2Cl_2 was added dropwise a solution of the *N*-substituted amino alcohol **3** in the same solvent. The mixture was stirred for 3 h at room temperature. The liquid was decanted from the solid which was washed several times with Et_2O. The combined organic layer was passed through a short pad of silica gel and evaporated to give the product. The product was recrystallized from the specified solvent.

4.3.1. *N*-(2-Formylphenyl)-4-methylbenzenesulfonamide 4a. A suspension of PCC (5.13 g, 24 mmol) in CH_2Cl_2 (80 ml) and alcohol **3a** (4.4 g, 15.9 mmol) in the same solvent (160 ml) was reacted as described above. The raw product was crystallized from $CHCl_3$/EtOH (1:5, 24 ml) to yield **4a** as white solid (3.2 g, 11.7 mmol, 74%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=2.37$ (s, 3H), 7.13–7.25 (m, 3H), 7.47–7.79 (m, 5H), 9.83 (s, 1H, CHO), 10.79 (bs, 1H, NH).

4.3.2. *N*-(2-Formylphenyl)benzenesulfonamide 4b. A suspension of PCC (5 g, 23.3 mmol) in CH_2Cl_2 (75 ml) and the protected alcohol **3b** (4.1 g, 15.5 mmol) in CH_2Cl_2 (155 ml) was reacted according to the GP2. After crystallization from $CHCl_3$/EtOH (1:5, 12 ml) a white solid (2.5 g, 9.5 mmol, 61%) was obtained; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.17$ (ddd, 1H, $J=7.5$, 6.7, 0.77 Hz), 7.42–7.59 (m, 5H), 7.66 (dd, 1H, $J=1.6$ Hz), 7.89 (dd, 2H, $J=6.7$, 1.6 Hz), 9.83 (s, 1H, CHO), 10.82 (bs, 1H, NH).

4.3.3. *N*-(2-Formylphenyl)-4-methoxybenzenesulfonamide 4c. The alcohol **3c** (8.6 g, 29 mmol) in 320 ml of CH_2Cl_2, PCC (10 g, 46.57 mmol) in 160 ml of CH_2Cl_2 gave aldehyde **4c** as a white solid (7.7 g, 26.4 mmol, 90%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H), 6.88–6.91 (m, 2H), 7.16–7.19 (m, 1H), 7.47–7.85 (m, 5H), 9.82 (s, 1H, CHO), 10.75 (bs, 1H, NH).

4.3.4. *N*-(2-Formylphenyl)-4-nitrobenzenesulfonamide 4d. To a suspension of PCC (2.8 g, 13 mmol) in 40 ml of CH_2Cl_2 was added a solution of the protected alcohol **3d** (2.7 g, 8.7 mmol in 80 ml of CH_2Cl_2) according to GP2. After crystallization from $CHCl_3$/EtOH (1:7, 16 ml) **4d** as yellow solid (2.5 g, 8.3 mmol, 95%) was obtained; ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 7.08$ (d, 1H, $J = 7.96$ Hz), 7.39 (t, 1H, $J = 7.5$ Hz), 7.58 (ddd, 1H, $J = 7.5$, 1.6 Hz), 7.81 (dd, 1H, $J = 7.5$, 1.6 Hz), 7.94 (ddd, 2H, $J = 6.9$, 4.4, 2.4 Hz), 8.36 (ddd, 2H, $J = 6.9$, 4.4, 2.4 Hz), 10.06 (s, 1H, CHO), 10.84 (bs, 1H, NH).

4.3.5. *N*-(2-Formylphenyl)-4-chlorobenzenesulfonamide 4e. To a stirred suspension of PCC (2.8 g, 12.9 mmol) in 40 ml of CH_2Cl_2 was added a solution of alcohol **3e** (2.6 g, 8.6 mmol) in 80 ml of CH_2Cl_2 following the described procedure. After work-up aldehyde **4e** (2.5 g, 8.5 mmol, 99%) was obtained; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.17$–7.24 (m, 1H), 7.42 (dt, 2H, $J = 6.7$, 4.4 Hz), 7.50–7.70 (m, 3H), 7.82 (dt, 2H, $J = 6.7$, 4.4 Hz), 9.83 (s, 1H, CHO), 10.82 (bs, 1H, NH).

4.3.6. *N*-(2-Formylphenyl)-2,4,6-trichlorobenzenesulfonamide 4f. Alcohol **3f** (536 mg, 1.5 mmol in CH_2Cl_2 (70 ml) was added to a suspension of PCC (472 mg, 2.2 mmol) in 50 ml of CH_2Cl_2 according to GP2. After work-up the product was obtained as a yellow solid (480 mg, 1.3 mmol, 90%); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.20$ (ddd, 1H, $J = 7.5$, 6.4 Hz), 7.44 (s, 2H), 7.55 (ddd, 1H, $J = 7.5$, 6.4, 1.5 Hz), 7.64–7.69 (m, 2H), 9.89 (s, 1H, CHO), 11.56 (bs, 1H, NH).

4.4. General procedure (GP3) for the synthesis of imines 5

(1*R*,2*R*)-*trans*-Cyclohexane diamine and the corresponding aldehyde **4** were dissolved in dry EtOH in a molar ratio of 1:2, respectively. The resulting mixture was refluxed under nitrogen atmosphere for the time stated and the solvent was evaporated in vacuum. The crude Schiff base was recrystallized in the indicated solvent.

4.4.1. *N*,*N*′-Bis-(4-methylbenzenesulfonamidphenyl-2-ylmethylene)cyclohexane-1*R*,2*R*-diamine 5a. Aldehyde **4a** (1.6 g (5.7 mmol) and (1*R*,2*R*)-*trans*-cyclohexanediamine (326 mg, 2.86 mmol) were solved in 15 ml of dry EtOH. The reaction mixture was refluxed for 1 h. Yellow crystals of the Schiff base **5a** (1.54 g, 2.45 mmol, 85%) were obtained after recrystallization from EtOH (10 ml); mp = 273–274°C; IR (KBr): $\nu = 3649$, 3443, 2925, 2860, 2361, 1630, 1599, 1578, 1497, 1449, 1411, 1338, 1288, 1157, 1089, 928, 811, 757 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.48$–1.59 (m, 2H), 1.72–1.96 (m, 6H), 2.06 (s, 6H), 3.54–3.58 (m, 2H), 6.62 (d, 4H, $J = 8.2$ Hz), 6.91 (ddd, 2H, $J = 7.7$, 0.91 Hz), 7.16–7.27 (m, 4H), 7.43 (d, 4H, $J = 8.2$ Hz), 7.48 (d, 2H, $J = 7.7$ Hz), 8.46 (s, 2H, N=CH), 13.20 (s, 2H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 21.25$, 24.29, 33.58, 73.44, 116.93, 120.39, 122.29, 127.08, 129.27, 131.27, 133.71, 136.45, 139.38, 143.1, 164.1; MS (ESI), m/z (%): 629.1 (100) [MH$^+$]. Anal. calcd for $C_{34}H_{36}N_4O_4S_2$: C, 64.95; H, 5.78; N, 8.92. Found: C, 64.65; H, 5.79; N, 8.86.

4.4.2. *N*,*N*′-Bis-(benzenesulfonamidphenyl-2-ylmethylene)cyclohexane-1*R*,2*R*-diamine 5b. The aldehyde **4b** (997 mg, 3.8 mmol) and (1*R*,2*R*)-*trans*-cyclohexanediamine (218 mg, 1.9 mmol) were solved in dry EtOH (7 ml), and the reaction mixture was refluxed for 1 h under nitrogen. After work-up and recrystallization from EtOH (5 ml), yellow crystals (850 mg, 1.41 mmol, 74%) were obtained; mp = 185–186°C; IR (KBr): $\nu = 3441$, 3060, 2933, 2858, 1634, 1579, 1500, 1444, 1421, 1199, 1157, 1089, 931, 862, 752, 713 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.51$–1.59 (m, 2H), 1.78–1.93 (m, 6H), 3.51–3.55 (m, 2H), 6.88–7.05 (m, 6H), 7.16–7.29 (m, 6H), 7.45 (d, 2H, $J = 8.0$ Hz), 7.62 (dd, 4H, $J = 8.0$ Hz), 8.44 (s, 2H, N=CH), 13.3 (s, 2H, NH–SO_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 24.25$, 33.46, 73.33, 116.99, 120.35, 122.43, 127.01, 128.75, 131.41, 132.52, 133.65, 139.24, 139.56, 164.12; MS (ESI), m/z (%): 601.2 (100) [MH$^+$]. Anal. calcd for $C_{32}H_{32}N_4O_4S_2$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.19; H, 5.65; N, 9.53; S, 10.66.

4.4.3. *N*,*N*′-Bis-(4-methoxybenzenesulfonamidphenyl-2-ylmethylene)cyclohexane-(1*R*,2*R*)-diamine 5c. Aldehyde **4c** (2 g, 6.87 mmol) and (1*R*,2*R*)-*trans*-cyclohexanediamine (0.39 g, 3.43 mmol) in EtOH (25 ml) reacted for 1 h as described by GP3. A yellow powder (3.5 g, 5.4 mmol, 78%) was obtained after crystallization from EtOH (16 ml); mp = 200–202°C; IR (KBr): $\nu = 3574$, 2929, 2856, 2360, 2341, 1627, 1595, 1577, 1497, 1338, 1261, 1154, 1093, 925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.53$–1.64 (m, 2H), 1.78–1.96 (m, 6H), 3.48 (s, 6H), 3.62–3.64 (m, 2H), 6.19 (dd, 4H, $J = 7.0$, 2.0 Hz), 6.97 (dd, 2H, $J = 7.5$, 6.7 Hz), 7.22–7.3 (m, 2H), 7.33 (dd, 2H, $J = 7.5$ Hz), 7.43 (dd, 4H, $J = 6.7$, 2.0 Hz), 7.52 (d, 2H, $J = 8.2$ Hz), 8.55 (s, 2H, N=CH), 13.22 (s, 2H, NH–SO_2); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.26$, 33.67, 55.24, 73.43, 113.68, 116.75, 120.3, 122.2, 129.22, 130.61, 131.22, 133.7, 139.4, 162.48, 163.92; MS (ESI), m/z (%): 661.2 (100) [MH$^+$]. Anal. calcd for $C_{34}H_{36}N_4O_6S_2$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.73; H, 5.45; N, 8.43.

4.4.4. *N*,*N*′-Bis-(4-nitrobenzenesulfonamidphenyl-2-ylmethylene)cyclohexane-(1*R*,2*R*)-diamine 5d. (1*R*,2*R*)-*trans*-Cyclohexanediamine (415 mg, 3.64 mmol) and the aldehyde **4d** (2.23 g, 7.28 mmol) in dry EtOH (20 ml) were refluxed for 3 h following GP3. The product was obtained as a yellow solid (2.3 g, 3.3 mmol, 91%); mp = 118–120°C; IR (KBr): $\nu = 3576$, 3448, 3103, 2933, 2861, 1630, 1606, 1578, 1531, 1499, 1347, 1311, 1088, 1043, 760, 733 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.53$–1.98 (m, 8H), 3.57–3.61 (m, 2H), 7.01 (dt, 2H, $J = 8.0$, 1.1 Hz), 7.29–7.34 (m, 4H), 7.50 (d, 2H, $J = 8.0$ Hz), 7.72 (s, 8H), 8.5 (s, 2H, N=CH), 13.62 (s, 2H,

NH–SO_2); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.17$, 33.58, 73.15, 116.96, 120.21, 123.22, 123.88, 128.17, 132.07, 133.82, 138.75, 145.22, 149.68, 164.33; MS (ESI), m/z (%): 691.2 (100) [MH^+].

4.4.5. *N,N′*-Bis-(4-chlorobenzenesulfonamidphenyl-2-ylmethylene)cyclohexane-(1*R*,2*R*)-diamine 5e. A mixture of (1*R*,2*R*)-*trans*-cyclohexanediamine (260 mg, 2.28 mmol) and the aldehyde **4e** (1.35 g, 4.57 mmol) in EtOH (14 ml) was stirred at reflux for 1 h. A yellow powder (1 g, 1.6 mmol, 69%) was obtained after recrystallization from EtOH (12 ml); mp = 177–178°C; IR (KBr): $v = 3466$, 2939, 2860, 1630, 1579, 1500, 1475, 1427, 1394, 1337, 1282, 1201, 1157, 1089, 933, 831, 767, 613 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.55$–1.60 (m, 2H), 1.76–1.94 (m, 6H), 3.55–3.59 (m, 2H), 6.77 (dt, 4H, $J = 6.6$, 4.4 Hz), 6.97 (ddd, 2H, $J = 7.5$, 6.6, 0.9 Hz), 7.23–7.31 (m, 4H), 7.41–7.5 (m, 6H), 8.48 (s, 2H, N=CH), 13.33 (s, 2H, NH–SO_2–); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.21$, 33.56, 73.29, 116.84, 120.25, 122.7, 128.37, 128.92, 131.61, 133.72, 137.76, 138.94, 138.97, 164.11; MS (ESI, -pESI), m/z (%): 667.3 (100) [$M-H^+$]$^-$. Anal. calcd for $C_{32}H_{30}Cl_2N_4O_4S_2$: C, 57.40; H, 4.52; N, 8.37. Found: C, 57.45; H, 4.41; N, 8.35.

4.4.6. *N,N′*-Bis-(2,4,6-trichlorobenzenesulfonamidphenyl-2-ylmethylene)cyclohexane-(1*R*,2*R*)-diamine 5f. According to GP3 a mixture of (1*R*,2*R*)-*trans*-cyclohexanediamine (29 mg, 0.25 mmol) and aldehyde **4f** (186 mg, 0.51 mmol) in EtOH (5 ml) was refluxed for 1 h. Yellow crystals of **5f** (147 mg, 0.18 mmol, 71%) were obtained after recrystallization from EtOH (4 ml); mp = 132–134°C; IR (KBr): $v = 3446$, 3067, 2931, 2858, 1633, 1562, 1537, 1498, 1412, 1367, 1290, 1177, 1140, 1040, 934, 864, 834, 797, 756, 661, 617, 574 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.43$–1.97 (m, 8H), 3.41–3.48 (m, 2H), 6.96–7.02 (dt, 2H, $J = 7.6$ Hz), 7.19–7.25 (dt, 2H, $J = 7.6$ Hz), 7.33–7.40 (m, 8H), 8.42 (s, 2H, N=CH), 14.15 (s, 2H, NH–SO_2); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 24.17$, 33.05, 73.16, 115.55, 119.71, 122.29, 131.27, 131.83, 133.88, 133.93, 136.32, 138.3, 139.04, 164.18; MS (ESI), m/z (%): 807.1 (100) [MH]$^+$. Anal. calcd for $C_{32}H_{26}Cl_6N_4O_4S_2$: C, 47.60; H, 3.25; N, 6.94. Found: C, 47.32; H, 3.41; N, 6.78.

4.5. General procedure for the addition of diethylzinc to aldehydes

The ligand (5 mol%) was dissolved in dry toluene (6 ml) under nitrogen, diethylzinc (1.1 M solution in toluene, 0.1 ml, 0.11 mmol) was added, and the mixture was allowed to stir for 1 h at room temperature, then cooled to 0°C or maintained at room temperature. Additional diethylzinc (2.17 ml, 2.39 mmol) was added slowly and after five minutes the aldehyde (1 mmol) was added. The reaction was stirred until TLC showed complete conversion of the aldehyde, quenched with 2 M HCl (6 ml), the phases were separated and the aqueous phase was extracted with Et_2O (3×10 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by short path distillation or by flash chromatography to give the alcohol as colorless oil. The enantiomeric excess was determined by chiral GC (Column Restek Rt βDEX). The absolute configuration was determined by polarometric measurements and compared with the literature values.[17–19]

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12. 5 mol% of the chiral ligands **4a** and **4b** were used in the catalytic reactions. The reaction time was 48 h in all cases.
13. The procedure of the reaction was as described before. After complexation of the ligand with diethylzinc the temperature of the mixture was increased to 50°C, subsequently the remaining amount of diethylzinc and the benzaldehyde were added and the reaction was stirred for 5 h.
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