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Asymmetric addition of diethylzinc to benzaldehyde catalyzed by novel chiral C_2-symmetric tetrakis(sulfonamide)–titanium(IV) complexes

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ABSTRACT

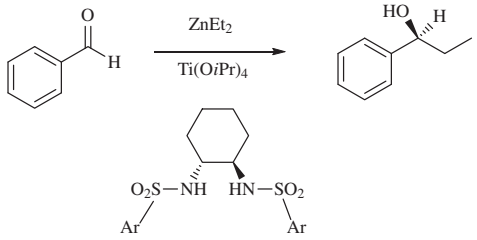
A series of chiral C_2-symmetric tetrakis(sulfonamides) **3a–f**, **4a–f** were prepared and employed as ligands for titanium(IV) complexes in the asymmetric addition of diethylzinc to benzaldehyde. The chiral secondary alcohols were obtained in high yields and in moderate enantioselectivities.

1. Introduction

The catalytic asymmetric addition of organozinc to various aldehydes is an important method for the preparation of optically active secondary alcohols, and this has attracted a great deal of interest since the first report in 1984 by Oguni, who used (*S*)-leucinol, a β-amino alcohol as the base catalyst.[1,2] Subsequent work by Noyori et al. with DAIB amino alcohol contributed a great deal to the understanding of the mechanism of the catalyzed diethylzinc addition to the aldehydes to obtain amino alcohols.[3] It is well established that enantioselectivity can be accomplished either by Lewis base or by Lewis acid catalysis. Consequently, there are now a series of chiral functionalities that have been successfully used, either as a base catalyst or as ligands for transition metal complexes. These include the well known β, γ, δ-amino alcohols,[4] β-imino alcohols,[5] piperazines,[6] oxazaborolidines,[7] aminothiolates,[8] aminothiols,[9] aminoesters,[10] diols,[11] disulfonamides,[2c,12] diphosphoramides,[13] amino acid derivatives,[14] ferrocene-based amino alcohols,[15] and oxazolines.[16]

The use of a chiral bis(sulfonamide) with titanium(IV) *iso*-propoxide [Ti(O*i*Pr)$_4$] as a catalyst to add diethylzinc to benzaldehyde was first reported by Ohno et al. (Scheme 1).[12a,b]

The synthesis of a variety of C_2-symmetric bis(sulfonamides) and the extensive mechanistic studies reported by Walsh et al. have greatly contributed to our understanding of the mechanism of this reaction.[2c,17] Nonetheless, the identification of new catalytic systems for this transformation remains an important challenge. In this context, to the best of our knowledge no C_2-symmetric tetrakis(sulfonamide)–Ti(IV) complexes have been employed as a catalyst in the asymmetric addition of organozinc to benzaldehyde.



Scheme 1. A chiral bis(sulfonamide) with Ti(O*i*Pr)$_4$ as the catalyst of the asymmetric addition of organozinc to benzaldehyde.

2. Results and discussion

We recently reported on the use of C_2-symmetric bis(sulfonamide) ligands **1** and **2**, which with Ru(II) and Rh(III) catalyzed the asymmetric transfer hydrogenation of aromatic ketones to secondary alcohols in excellent yields and enantioselectivities.[18] Inspired by these results, we further explored the possibility of transforming bis(sulfonamides) **1** and **2** into tetrakis(sulfonamides) ligands **3** and **4**, using various sulfonyl chlorides, as shown in Scheme 2. Our intention with ligand **3** was to surround the Lewis acid titanium metal center with four chiral nitrogen atoms in a *cisoid* conformation, hoping that the additional chirality would enhance the enantioselectivity in the diethylzinc addition to benzaldehyde.

The tetrakis(sulfonamides) **3a–f** and **4a–f** coordinated to Ti(IV) were tested as catalysts in the alkylation of benzaldehyde. The results are summarized in Table 1.

The results from the catalytic use of tetrakis(sulfonamide)–Ti(IV) complexes show the same trend that was previously observed by Walsh et al. with the bis(sulfonamide) ligands,[2c] but with moderate enantioselectivities (57–81%). Ligands **3a–f** and **4a–f** gave good yields (82–98%). These results also show that electron withdrawing and donating groups on the sulfonamide

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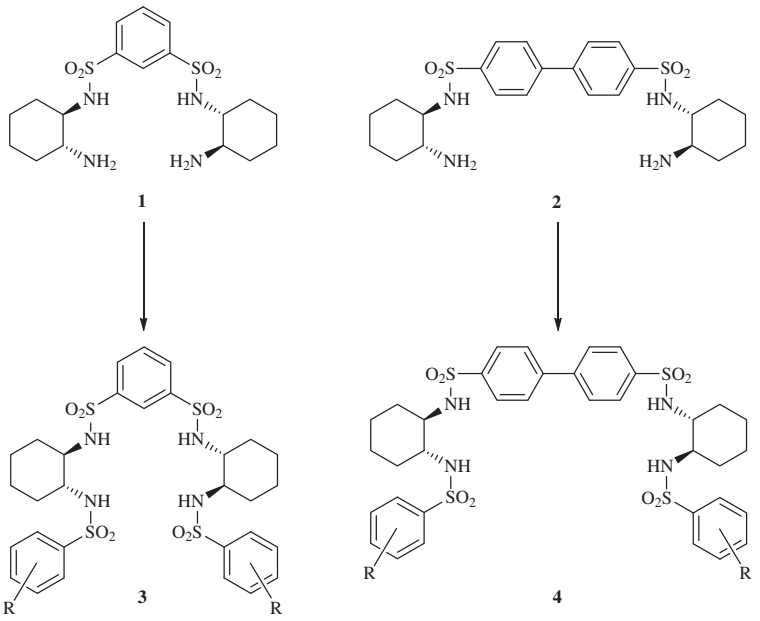
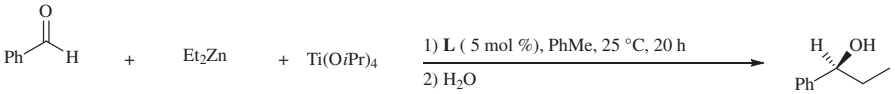


R: **a** = H, **b** = *p*-CH_3, **c** = *p*-CF_3, **d** = *p*-NO_2, **e** = 2,4,6-trimethyl, **f** = 2,4,6-tri*iso*propyl

Scheme 2. Bis(sulfonamides) **1** and **2** and tetrakis(sulfonamides) **3a–f** and **4a–f**.

Table 1
Diethylzinc addition of benzaldehyde with Ti(O*i*Pr)$_4$ complexes[a]



1 eq 1.6 eq 2.4 eq

Ligand	**3**		**4**	
R	Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
a = H	98	78	90	68
b = *p*-CH_3	98	81	97	64
c = *p*-CF_3	97	57	98	68
d = *p*-NO_2	97	64	98	65
e = 2,4,6-trimethyl	82	70	96	71
f = 2,4,6-triisopropyl	95	68	90	68

[a] Absolute configuration of the alcohols is (*S*), assigned by comparing the specific rotation with literature values.[8] Reaction conditions: 20 °C. S/C = 20.
[b] Yields were measured after column chromatography on silica gel (Et_3N/SiO_2 = 2.5% v/v, hexanes/EtOAc 15:1 as eluent).
[c] The enantiomeric excesses were determined by HPLC with a Chiracel OD column.[21]

benzene ring have a modest effect on the enantioselectivity. The use of complexes formed with ligands **3c,d** (*p*-CF_3 and *p*-NO_2 substitution, respectively) resulted in lower enantioselectivity compared with either **3a** or **3b** (H and *p*-CH_3 substitution, respectively), while steric bulk appears to play a major role with ligands **3e** (2,4,6-trimethyl substitution) and **3f** (2,4,6-triisopropyl substitution), which is again in agreement with Walsh et al.'s observations that 2,6-substitution on the sulfonamide ring leads to lower enantioselectivity.[2c]

Based on our earlier studies on the conformation of ligand **1**, these results indicate that the ligand prefers a *transoid* conformation by ~3 kcal/mol over the *cisoid* conformer.[19] Further experimental data showed that increasing the titanium(IV) *iso*propoxide from 1 to 2 equiv increases the enantioselectivity by 10%, suggesting the two coordinating sites act independently and are more likely in a *transoid* conformation. This is further supported by the similar results obtained with ligands **3** and **4**.

Results with tetrakis(sulfonamide)–Ti(IV) complexes **4a–f** showed lower enantioselectivities than with **3a–f**, probably due to the fact that the two bis(sulfonamides) were farther apart from each other, and thus did not result in enough steric interaction when the Ti(IV) is complexed to the ligand. Better yields and enantioselectivities were achieved when 2.4 equiv of metal was used, suggesting the formation of binuclear complexes.

Finally, the lower activities of the tetrakis(sulfonamides) **3a–f** and **4a–f** compared to the bis(sulfonamides) may be attributed to the partial solubility of the former when using toluene as the reaction solvent.

3. Conclusion

In conclusion, a series of novel chiral C_2-symmetric tetrakis (sulfonamide) ligands **3a–f** and **4a–f**, have been prepared from bis(sulfonamide) ligands **1** and **2** and employed as ligands for tita-

nium(IV) complexes in the asymmetric addition of diethylzinc to benzaldehyde. High yields (82–98%) and moderate enantioselectivities (64–81%) have been obtained for the chiral secondary alcohol.

4. Experimental

4.1. Instrument and measurements

Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin–Elmer FT-IR 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded either on a Varian Nova 600 or 500 MHz spectrometer. Rotation was measured with a Perkin–Elmer 343 Polarimeter. Elemental analyses were conducted by NuMega San Diego.

4.2. General procedure for synthesis of monosulfonamides

Monosulfonamides were obtained as reported in the literature from the corresponding commercially available benzenesulfonyl chloride with chiral (1*R*,2*R*)-1,2-cyclohexanediamine and were characterized by comparison of the spectroscopic data with literature values.[20]

4.2.1. *N*-[(1*R*,2*R*)-2-Aminocyclohexyl]-2,4,6-triisopropylbenzenesulfonamide f

Grey solid 1.9 g (87% yield). $[\alpha]_D^{25} = -26$ (*c* 0.5, $CHCl_3$). IR (KBr): 3347, 3286, 1602, 1448, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.10 (s, 2H), 4.20 (sept, *J* = 6.8 Hz, 2H), 3.56 (dt, *J* = 11.0, 3.5 Hz, 1H), 3.54 (dt, *J* = 11.0, 3.8 Hz, 1H), 2.87 (m, sept, *J* = 6.8 Hz, 1H), 2.54 (d, *J* = 5.5 Hz, 1H), 1.65 (m, 2H), 1.49 (m, 1H), 1.35 (m, 2H) 1.23 (d, *J* = 6.8 Hz, 6H), 1.20 (d, 6.8 Hz, 12H), 1.06 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.4, 149.8, 135.3, 123.9, 55.5, 53.5, 34.1, 31.8, 30.4, 29.5, 24.9, 24.5, 23.7, 23.6.

4.3. General procedure for synthesis of ligands 3a–f

To a stirred solution of the corresponding monosulfonamide (1.6 mmol) in CH_2Cl_2 (32 mL) was added triethylamine (0.8 mL, 15.2 mmol). The mixture was cooled to 0 °C and a solution of benzene-1,3-disulfonyl chloride (0.8 mmol) in dichloromethane (30 mL) was added over 30 min. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 12 h. The resulting reaction mixture was washed with aqueous HCl (2 mol L^{-1}, 3 × 50 mL), a saturated solution of $NaHCO_3$ (1 × 30 mL) and water (2 × 30 mL). The dichloromethane layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to obtain the tetrakis(sulfonamide) ligands **3a–f**.

4.3.1. N^1,N^3-Bis[(1*R*,2*R*)-2-(phenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3a

White solid 0.5 g (82% yield). Mp 129–131 °C. $[\alpha]_D^{25} = -16$ (*c* 1.28, CH_2Cl_2). IR (KBr): 3282, 2938, 2861, 1448, 1328, 1157 cm^{-1}.[1] ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.47 (t, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.80 (m, 5H), 7.57 (tt, *J* = 8.0, 1.8 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 4H), 5.57 (d, *J* = 5.3 Hz, 2NH), 5.50 (d, *J* = 8.3 Hz, 2NH), 3.00 (m, 2H), 2.80 (m, 2H), 2.20 (m, 2H), 1.58 (m, 2H), 1.46 (m, 4H), 1.29 (m, 2H), 1.12 (m, 4H), 1.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 141.6, 140.3, 133.0, 131.8, 130.6, 129.3, 126.9, 125.3, 57.7, 56.3, 34.3, 32.3, 24.5. Anal. Calcd for $C_{30}H_{38}N_4O_8S_4$: C, 50.68; H, 5.39. Found: C, 50.66; H, 5.36.

4.3.2. N^1,N^3-Bis[(1*R*,2*R*)-2-(4-methylphenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3b

White solid 0.5 g (86% yield). Mp 144–145 °C. $[\alpha]_D^{25} = -10$ (*c* 1.0, CH_2Cl_2). IR (KBr): 3280, 2937, 2862, 1598, 1451, 1329, 1158 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.46 (t, *J* = 1.5 Hz, 1H), 8.15 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 4H), 7.29 (d, *J* = 7.9 Hz, 4H), 5.49 (d, *J* = 8.8 Hz, 2NH), 5.41 (d, *J* = 8.5 Hz, 2NH), 2.98 (m, 2H), 2.76 (m, 2H), 2.41 (s, 6H), 2.24 (m, 2H), 1.59 (m, 2H), 1.47 (m, 4H), 1.30 (m, 2H), 1.02 (m, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.9, 141.6, 137.3, 131.4, 130.5, 130.0, 126.9, 125.3, 57.8, 56.1, 34.5, 32.3, 24.5, 24.0, 21.6. Anal. Calcd for $C_{32}H_{42}N_4O_8S_4$: C, 52.01; H, 5.73. Found: C, 52.05; H, 5.76.

4.3.3. N^1,N^3-Bis[(1*R*,2*R*)-2-(4-trifluoromethylphenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3c

White solid 0.5 g (86% yield). Mp 237–238 °C. $[\alpha]_D^{25} = +15$ (*c* 0.2, CH_2Cl_2). IR (KBr): 3257, 2942, 2865, 1475, 1440, 1324, 1167 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6 600 MHz) δ 8.39 (t, *J* = 1.7 Hz, 1H), 8.06 (dd, *J* = 8.0, 2.0 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 4H), 7.78 (d, *J* = 8.5 Hz, 4H), 7.70 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.10 (d, *J* = 6.8 Hz, 2NH), 7.02 (d, *J* = 6.3 Hz, 2NH), 3.00–2.70 (m, 4H), 1.75 (m, 2H), 1.60 (m, 2H), 1.51 (m, 4H), 1.20 (m, 4H), 1.06 (m, 4H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 150 MHz) δ 144.8, 142.4, 133.5 (J_{CF} = 32.5 Hz), 130.4, 130.2, 127.6 (br), 126.0 (br), 125.5, 123.4 (J_{CF} = 271.4 Hz), 56.8, 56.4, 32.6, 32.4, 23.9, 23.8. Calcd for $C_{32}H_{36}F_2N_4O_8S_4$: C, 45.38; H, 4.28. Found: C, 45.33; H, 4.25.

4.3.4. N^1,N^3-Bis[(1*R*,2*R*)-2-(4-nitrophenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3d

Yellow solid 0.5 g (80% yield). Mp 150–152 °C. $[\alpha]_D^{25} = +36$ (*c* 0.32, CH_2Cl_2). IR (KBr): 3286, 3105, 2938, 2862, 1605, 1503, 1450, 1350, 1162 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 600 MHz) δ 8.38 (d, *J* = 8.8 Hz, 4H), 8.05 (d, *J* = 8.8 Hz, 4H), 8.16 (s, 1H), 7.97 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 2NH), 7.75 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 2NH), 2.87 (m, 4H), 2.32 (m, 2H), 1.43 (m, 2H), 1.33 (m, 2H), 1.23 (m, 2H), 1.03 (m, 8H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 125 MHz) δ 149.7, 147.0, 142.5, 130.3, 130.1, 128.4, 125.4, 124.2, 57.0, 56.3, 32.9, 32.2, 24.0, 23.9. Calcd for $C_{30}H_{36}N_6O_{12}S_4$: C, 44.99; H, 4.53. Found: C, 45.02; H, 4.58.

4.3.5. N^1,N^3-Bis[(1*R*,2*R*)-2-(2,4,6-trimethylphenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3e

White solid 0.5 g (76% yield). Mp 138–140 °C. $[\alpha]_D^{25} = -30$ (*c* 0.12, CH_2Cl_2). IR (KBr): 3381, 2937, 2859, 1629, 1597, 1312, 1154 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.49 (t, *J* = 2.0 Hz, 1H), 8.19 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.97 (t, *J* = 8.0 Hz, 1H), 6.95 (s, 4H), 5.89 (d, *J* = 5.6 Hz, 2NH), 5.20 (d, *J* = 8.5 Hz, 2NH), 2.99 (m, 2H), 2.65 (m, 2H), 2.54 (m, 2H), 2.24 (m, 2H), 2.17 (s, 6H), 2.15 (s, 12H), 1.59 (m, 2H), 1.49 (m, 2H), 1.44 (m, 4H), 1.38 (m, 2H), 1.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 142.5, 141.5, 138.7, 134.0, 132.1, 131.2, 130.7, 126.2, 57.6, 55.1, 34.5, 31.9, 24.6, 23.9, 22.9, 20.9. Calcd for $C_{36}H_{50}N_4O_8S_4$: C, 54.38; H, 6.34. Found: C, 54.34; H, 6.32.

4.3.6. N^1,N^3-Bis[(1*R*,2*R*)-2-(2,4,6-triisopropylphenylsulfonamido]cyclohexyl)benzene-1,3-disulfonamide 3f

Pale white solid 0.6 g (75% yield). Mp 131–133 °C. $[\alpha]_D^{25} = -30$ (*c* 0.12, CH_2Cl_2). IR (KBr): 3286, 2958, 2868, 1600, 1462, 1331, 1154 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.52 (t, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 7.9 Hz, 1.8 Hz, 2H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.10 (s, 4H), 5.98 (d, *J* = 5.3 Hz, 2NH), 4.80 (d, *J* = 7.3 Hz, 2NH), 3.96 (sept, *J* = 6.8 Hz, 4H), 2.98 (m, 4H), 2.88 (sept, *J* = 7.0 Hz, 2H), 2.20 (m, 2H), 1.61 (m, 2H), 1.52 (m, 4H), 1.41 (m, 8H), 1.24 (d, *J* = 7.0 Hz, 12H), 1.22 (d, *J* = 6.8 Hz, 12H) 1.18 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.0, 149.9, 141.7, 133.3, 131.2, 130.7,

125.9, 124.0, 57.4, 55.9, 34.3, 34.1, 32.4, 29.7, 25.0, 24.7, 24.6, 24.0, 23.6, 23.5. Calcd for $C_{48}H_{74}N_4O_8S_4$: C, 59.84; H, 7.64. Found: C, 59.84; H, 7.74.

4.4. General procedure for the synthesis of ligands 4a–f

Ligands **4a–f** were obtained as described for ligands **3a–f**, but using the corresponding monosulfonamide (1.6 mmol) and biphenyl-4,4′-disulfonyl chloride (0.8 mmol).

4.4.1. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(phenylsulfonamido)cyclohexyl] biphenyl-4,4′-disulfonamide 4a

White solid 0.6 g (75% yield). Mp 141–142 °C. $[\alpha]_D^{25} = +15$ (*c* 0.6, CH_2Cl_2). IR (KBr): 3279, 2937, 2860, 1595, 1448, 1327, 1159 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.98 (d, *J* = 8.3 Hz, 4H), 7.86 (dd, *J* = 7.0, 3.2 Hz, 4H), 7.74 (d, *J* = 8.3 Hz, 4H), 7.57 (td, *J* = 7.3, 1.2 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 4H), 5.37 (d, *J* = 5.9 Hz, 2NH), 5.07 (d, *J* = 6.8 Hz, 2NH), 2.81 (m, 4H), 1.99 (m, 2H), 1.66 (m, 2H), 1.54 (m, 4H), 1.41 (m, 8H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.6, 140.2, 139.8, 132.9, 129.3, 128.2, 128.0, 127.1, 57.1, 56.6, 33.6, 32.9, 24.4, 24.1. Calcd for $C_{36}H_{42}N_4O_8S_4$: C, 54.94; H, 5.38. Found: C, 54.98; H, 5.43.

4.4.2. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(4-methylphenylsulfonamido) cyclohexyl]biphenyl-4,4′-disulfonamide 4b

White solid 0.5 g (79% yield). Mp 139–140 °C. $[\alpha]_D^{25} = -19$ (*c* 1.0, CH_2Cl_2). IR (KBr): 3278, 2936, 2860, 1596, 1450, 1328, 1159, 1109 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.99 (d, *J* = 8.2 Hz, 4H), 7.75 (d, *J* = 8.3 Hz, 4H), 7.73 (d, *J* = 8.2 Hz, 4H), 7.28 (d, *J* = 8.3 Hz, 4H), 5.53 (d, *J* = 5.6 Hz, 2NH), 5.08 (d, *J* = 6.8 Hz, 2NH), 2.81 (m, 4H), 2.40 (s, 6H), 2.03 (m, 2H), 1.63 (m, 2H), 1.53 (m, 4H), 1.50 (m, 8H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.7, 143.5, 139.8, 137.3, 129.8, 128.1, 128.0, 127.1, 57.2, 56.4, 33.6, 32.8, 24.4, 24.1, 21.6. Calcd for $C_{38}H_{46}N_4O_8S_4$: C, 56.00; H, 5.69. Found: C, 56.04; H, 5.72.

4.4.3. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(4-trifluoromethylphenylsulfonamido)cyclohexyl]biphenyl-4,4′-disulfonamide 4c

White solid 0.5 g (79% yield). Mp 253–254 °C. $[\alpha]_D^{25} = +25$ (*c* 0.3, CH_2Cl_2). IR (KBr): 3282, 2938, 2863, 1595, 1440, 1405, 1325, 1162, 1163 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 600 MHz) δ 8.07 (d, *J* = 8.3 Hz, 4H), 7.98 (d, *J* = 8.3 Hz, 4H), 7.79 (d, *J* = 8.3 Hz, 4H), 7.77 (d, *J* = 8.3 Hz, 4H), 7.13 (d, *J* = 5.4 Hz, 2NH), 7.09 (d, *J* = 6.4 Hz, 2NH), 2.87 (m, 4H), 1.78 (m, 2H), 1.68 (m, 2H), 1.33 (m, 4H), 1.21 (m, 4H), 1.08 (m, 4H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 150 MHz) δ 144.3, 142.2, 140.3, 132.7 (J_{CF} = 32.5 Hz), 126.9 (br), 125.2 (br), 122.7 (J_{CF} = 271.0 Hz), 56.0, 55.5, 31.8, 31.4, 23.2, 23.1. Calcd for $C_{38}H_{40}F_6N_4O_8S_4$: C, 49.45; H, 4.37. Found: C, 49.40; H, 4.35.

4.4.4. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(4-nitrophenylsulfonamido)cyclohexyl]biphenyl-4,4′-disulfonamide 4d

Yellow solid 0.6 g (80% yield). Mp 164–167 °C. $[\alpha]_D^{25} = +15$ (*c* 0.5, MeOH). IR (KBr): 3287, 2937, 2862, 1596, 1530, 1349, 1161, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.34 (d, *J* = 8.6 Hz, 4H), 8.12 (d, *J* = 8.6 Hz, 4H), 7.95 (d, *J* = 8.4 Hz, 4H), 7.75 (d, *J* = 8.4 Hz, 4H), 7.18 (d, *J* = 6.1 Hz, 2NH), 7.05 (d, *J* = 7.0 Hz, 2NH), 2.88 (m, 4H), 1.88 (m, 2H), 1.72–1.45 (m, 6H), 1.30–1.04 (m, 8H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 149.0, 146.5, 142.3, 140.5, 127.8, 127.1, 126. 9, 123.5, 56.4, 55.5, 32.3, 31.4, 23.4, 23.2. Calcd for $C_{36}H_{40}N_6O_{12}S_4$: C, 49.30; H, 4.60. Found: C, 49.34; H, 4.64.

4.4.5. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(2,4,6-trimethylphenylsulfonamido) cyclohexyl]biphenyl-4,4′-disulfonamide 4e

White solid 0.5 g (75% yield). Mp 140–143 °C. $[\alpha]_D^{25} = -5$ (*c* 4.8, CH_2Cl_2). IR (KBr): 3286, 2937, 2860, 1602, 1452, 1328, 1158 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.01 (d, *J* = 8.8 Hz, 4H), 7.75 (d, *J* = 8.8 Hz, 4H), 6.95 (s, 4H), 5.56 (d, *J* = 5.6 Hz, 2NH), 4.71 (d, *J* = 7.3 Hz, 2NH), 2.84 (m, 2H), 2.76 (m, 2H), 2.58 (s, 12H), 2.29 (s, 6H), 1.65 (m, 2H), 1.57 (m, 4H), 1.22 (m, 8H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.5, 142.5, 139.9, 138.9, 134.1, 132.1, 128.1, 128.0, 57.2, 56.0, 33.8, 32.6, 24.4, 24.1. 23.1, 21.0. Calcd for $C_{42}H_{54}N_4O_8S_4$: C, 57.91; H, 6.25. Found: C, 57.91; H, 6.24.

4.4.6. N^4,$N^{4'}$-Bis[(1*R*,2*R*)-2-(2,4,6-triisopropylphenylsulfonamido)cyclohexyl] biphenyl-4,4′-disulfonamide 4f

White solid 0.6 g (74% yield). Mp 138–139 °C. $[\alpha]_D^{25} = +20$ (*c* 0.32, CH_2Cl_2). IR (KBr): 3285, 1599, 1460, 1328, 1161 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.05 (d, *J* = 8.5 Hz, 4H), 7.79 (d, *J* = 8.5 Hz, 4H), 7.15 (s, 4H), 5.79 (d, *J* = 6.2 Hz, 2NH), 4.67 (d, *J* = 7.0 Hz, 2NH), 4.06 (sept, *J* = 7.0 Hz, 4H), 3.28 (m, 2H), 3.08 (m, 2H), 2.90, (sept, *J* = 7.0 Hz, 2H), 2.05 (m, 2H), 1.62 (m, 2H), 1.59 (m, 2H), 1.52 (m, 2H), 1.45 (m, 2H), 1.25 (d, *J* = 7.0 Hz, 12H), 1.24 (d, *J* = 7.0 Hz, 24H), 1.19–1.10 (m, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.0, 150.0, 143.5, 140.3, 133.3, 128.1, 128.0, 123.9, 57.2, 56.0, 34.1, 33.8, 33.1, 29.8, 25.0, 24.8, 24.5, 24.2, 23.5. Calcd for $C_{54}H_{78}N_4O_8S_4$: C, 62.39; H, 7.56. Found: C, 62.34; H, 7.52.

4.5. General procedure for the asymmetric diethylzinc addition to benzaldehyde

Ligands **3a–f** and **4a–f** (5 mol %) were weighed into the reaction vessel and diethylzinc (1.0 M in hexane, 1.6 equiv, 1.5 mL) and titanium(IV) isopropoxide (2.4 equiv, 0.76 mL) were then added at rt. After 10 min, benzaldehyde (1.0 equiv, 0.94 mmol) was added. The homogeneous reaction mixture was stirred at rt. After 20 h the reaction was quenched with water (5 mL), extracted with EtOAc (2 × 40 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2 = 2.5% v/v, hexanes/EtOAc 95:5) to afford 1-phenyl-1-propanol.

4.6. Conditions for the determination of enantiomeric excess

Chiral HPLC: Chiracel OD column, 254 nm UV detector, 95:5 hexanes/IPA, flow rate 0.5 mL/min, retention time (*R*) 15 min, retention time (*S*): 18 min.[21]

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