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Synthesis of C_2-symmetrical bis(1,2-hydroxy sulfonamide) ligands and application in the enantioselective addition of dialkylzinc to aldehydes

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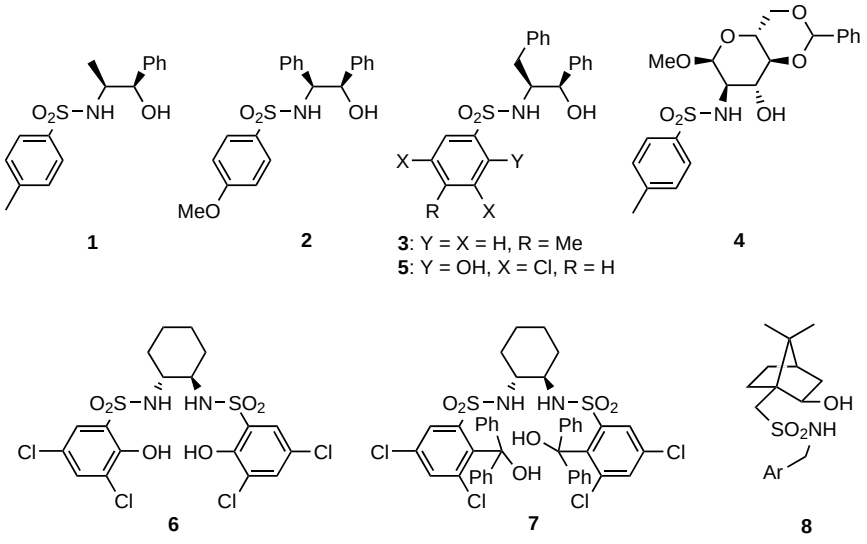
Abstract—The preparation of several C_2-symmetric disulfonamides derived from 1,2-amino alcohols and disulfonyl derivatives, as well as their use in the titanium tetraisopropoxide-promoted enantioselective additions of dialkylzinc to aldehydes are described. The enantiomeric ratio is up to 96:4, the best results being obtained for aromatic aldehydes with electron-donating groups in the *para*-position. There are some differences in the enantioselectivity depending on the relative positioning of the amino alcohol moieties in the chiral ligand, the 1,3-disulfonyl derivative being the best system. In the case of *para*-substituted benzaldehyde derivatives, a negative relationship between the electron-withdrawing character of the *para*-substituted group and the enantioselectivity of the addition was seen, whereas the more electronic-donating character the substituent has, the higher the observed enantioselectivity.

1. Introduction

One of the major challenges in organic synthesis is the asymmetric preparation of compounds by means of forming carbon–carbon bonds.[1] Among the different strategies, the enantioselective 1,2-addition of organometallic reagents to carbonyl compounds is probably the most straightforward and useful manner of achieving this goal.[2] Among these approaches, the enantioselective addition of dialkylzinc reagents to aldehydes is the most widely used methodology.[3–6] An interesting modification involves the use of titanium tetralkoxides as Lewis acids,[7] which usually allows the same enantioselectivity irrespective of the nature of both the aldehyde or the organozinc reagent used.



1 2 **3**: Y = X = H, R = Me **5**: Y = OH, X = Cl, R = H 4 6 7 8

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After the pioneering work of Reetz's group using β-hydroxy sulfonamide **1**,[8] a new class of ligands for the aforementioned reaction is emerging. Concerning the enantioselectivity, this new type of ligand has proved to be equal or superior to other types of ligands[6] having the advantage that a huge number of different building blocks may be used because of its modular synthesis. Thus, other β-hydroxy sulfonamides, such as ligands **2**,[9] **3**[10] and **4**,[11] as well as tridentate ligand **5**,[12] have been introduced for the enantioselective alkylation of aldehydes. In addition, γ-hydroxy sulfonamide **6**[13,14] and the corresponding δ-derivatives **7**[15] and **8**[16] have proved to be excellent ligands in the aforementioned reaction. It must be pointed out that system **8** is the only chiral ligand able to induce the catalytic enantioselective addition of dialkylzinc reagents to ketones.[17,18]

On the other hand, recent investigations in the field of Lewis acid catalysis have focused on the use of dinuclear metal complexes.[19–25] These complexes show unique catalytic properties as a result of distinct synergistic effects occurring at the proximal metal centers. One metal center acts usually behaves as a Lewis acid, activating the carbonyl derivative, while the other metal center acts as an activating metal for the nucleophile,[26] although the possibility of forming a double coordination complex of the carbonyl compound with both Lewis acidic metal centers can not be ruled out.[22,27,28]

With these two facts in mind [(a) the possible synergistic effect in dinuclear metal complexes and the high enantioselectivities observed in the addition of dialkylzinc reagents to aldehydes in the presence of titanium alkoxides using C_1-symmetrical mononucleating hydroxy sulfonamides] we examined the synthesis of different C_2-symmetrical β-hydroxy sulfonamides and their use as ligands in the enantioselective alkylation of aldehydes. We think that these kind of ligands may be useful in the aforementioned addition process. Furthermore, the presence of a C_2-symmetry axis within a chiral ligand dramatically reduces the number of possible competing diastereomeric transition states[29] and the distance between both metal centers may be modulated very easily by choosing the appropriate starting disulfonyl derivative, these two factors may be crucial when we try to understand the possible role of the two metal atoms in the chiral ligand. Herein, we describe the preparation and use as chiral ligands of different bis(hydroxysulfonamide) derivatives with C_2-symmetry.

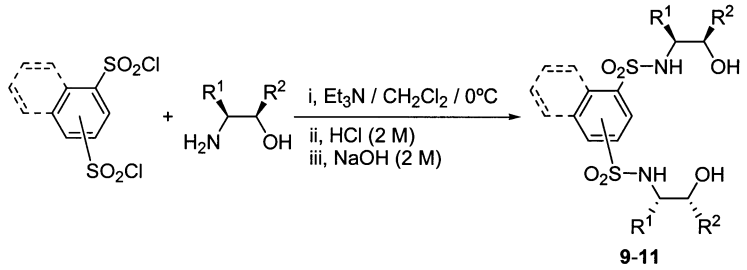
2. Results and discussion

2.1. Preparation of chiral disulfonamide ligands

Disulfonamide ligands **9** and **10** were prepared from the corresponding commercially available benzenedisulfonyl chloride by reaction with the corresponding chiral amino alcohol (2 equiv) in the presence of triethylamine at 0°C. After, subsequent quenching with HCl (2 M) for removing all amine derivatives followed by treatment with NaOH for removing the sulfonic acid derivatives, the expected pure ligands (>95% from 300 MHz ^{1}H NMR; Table 1, entries 1–7).

The naphthalene ligand derivative **11** was prepared from commercially available 1,5-naphthalenedisulfonic

Table 1.



9-11

Entry	Arenedisulfonyl chloride	C_2-ligand			
		No.	R^1	R^2	Yield (%)[a,b]
1	Benzene-1,2-disulfonyl chloride	**9**	Me	Ph	79
2	Benzene-1,3-disulfonyl chloride	**10a**	Me	H	65
3	Benzene-1,3-disulfonyl chloride	**10b**	Ph	H	80
4	Benzene-1,3-disulfonyl chloride	**10c**	H	Ph	73
5	Benzene-1,3-disulfonyl chloride	**10d**	Me	Ph	75
6	Benzene-1,3-disulfonyl chloride	**10e**		1,2-$C_6H_4(CH_2)_2$	85[c]
7	Benzene-1,3-disulfonyl chloride	**10f**	Ph	Ph	83[c]
8	Naphthalene-1,5-disulfonyl chloride	**11**	Me	Ph	45[d]

[a] Yield of isolated product.
[b] Samples for HRMS were obtained by flash chromatography.
[c] Sample for HRMS was obtained by recrystallisation from hot CH_2Cl_2.
[d] Overall yield from the corresponding 1,5-naphthalenedisulfonic acid tetrahydrate.

acid tetrahydrate by reaction with a large excess of $SOCl_2$ in refluxing benzene catalysed by DMF[30] to afford the expected 1,5-naphthalenedisulfonyl chloride which, without further purification, was reacted with (−)-norephedrine as in the previous cases to afford the pure ligand in reasonable overall yield (Table 1, entry 8).

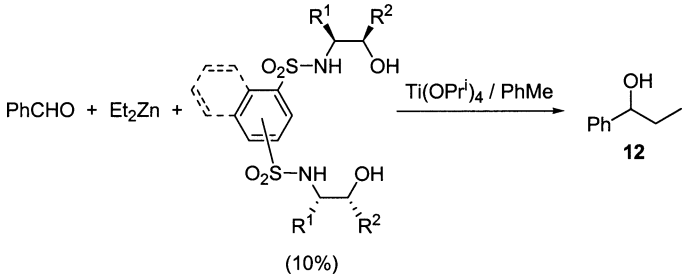
2.2. Asymmetric addition of dialkylzinc to aldehydes

Once ligands **9**–**11** were prepared, the next aim was to find the best one among them for the enantioselective addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide to give 1-phenyl-1-propanol **12**. Firstly, the influence of the sulfonyl moiety was studied using (−)-norephedrine as the amino alcohol in all cases (Table 2, entries 1, 6 and 11). The reaction using the ligand bearing the amino alcohol moieties either very close to each other (such in the case of the 1,2-benzene derivative **9**; Table 2, entry 1) or remote from each other (as in the case of 1,5-naphthalene derivative **11**; Table 2, entry 11) gave in both cases a modest chemical yield and enantiomeric ratio, after 1 day reaction time. However, in the case of the 1,3-benzene derivative **10d** (Table 2, entry 5), under the previously mentioned conditions, the chemical yield was excellent, the enantiomeric ratio being good, in a shorter reaction time. This result indicates that the length is adequate to incorporate two metal atoms only in the 1,3-system, allowing both metal centers to work in a synergistic way. In the 1,5-naphthelene derivative **11** the two metal centers are too far away from each other to work together. Conversely, in the case of the 1,2-benzene derivative **9** there is not enough space for the two metal centers, which may either force a conformation in which both centers act independently or the chiral ligand bears only one metal atom.

Having established that the 1,3-arene derivatives[31–34] were the appropriate amino alcohol-linking system, the influence of temperature was studied.[35,36] It was found that the best enantiomeric ratios were obtained at 0°C with these 1,3-arene derivatives (Table 2, entries 5–7).

The influence of different substitution of the amino alcohol was also studied. The addition of diethylzinc to benzaldehyde using the aminopropanol derivative **10a** (Table 2, entry 2) afforded the expected alcohol **12** as a near-racemic mixture. However, when the reaction was performed with the corresponding phenylglycinol derivative **10b** (Table 2, entry 3), which presents a higher steric hindrance, the enantiomeric ratio increased to 74:26. The same result was found using the corresponding 2-amino-1-phenylethanol derivative **10c** (Table 2, entry 4), which allows us to conclude that both possible stereogenic centers of the amino alcohol play a similar role in the enantiodiscrimination step. After studying amino alcohol derivatives **10a**–**c** with only one stereogenic center as chiral ligands, we examined amino alcohol derivatives with two stereogenic

Table 2.



Entry	Ligand	T (°C)	t (h)	Alcohol **12**		
				Yield (%)[a]	e.r.[b] R:S	e.e.
1	**9**	0	24	56[c]	75:25	50
2	**10a**	0	8	>95	52:48	4
3	**10b**	0	8	>95	74:26	48
4	**10c**	0	8	>95	74:26	48
5	**10d**	−20	16	>95	89:11	78
6	**10d**	0	8	>95	92:8	84
7	**10d**	25	8	>95	84:16	68
8	**10e**	0	8	>95	66:34	32
9	**10f**	0	8	>95	95:5	90
10[d]	**10f**	0	96	78[e]	65:35	30
11	**11**	0	24	30[f]	75:25	50

[a] Isolated yield after bulb-to-bulb distillation.
[b] Determined by GLC analysis using a β-CD column.
[c] Starting aldehyde was recovered in 40% yield.
[d] The reaction was performed in the absence of $Ti(OPr^i)_4$.
[e] Starting aldehyde and benzylic alcohol were detected in 10% yield each.
[f] Starting aldehyde was recovered in 65% yield.

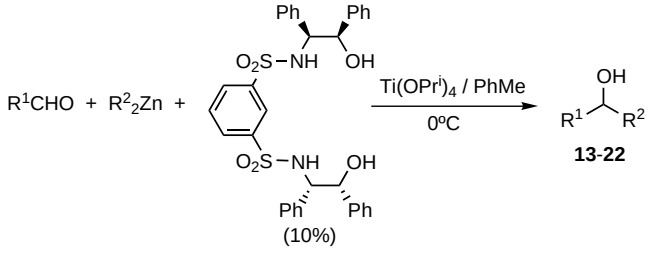
centers (Table 2, entries 6, 8 and 9). The presence of a methyl and a phenyl group in the starting amino alcohol [(−)-norephedrine derivative **10d**; Table 2, entry 6] led to an increase in the enantiomeric ratio to 92:8. When the same reaction was performed with the bicyclic ligand **10e**, derived from *cis*-1-amino-2-indanol, the enantiomeric ratio in the secondary alcohol **15** fell dramatically to 66:34 (Table 2, entry 8). However, when the 1,2-diphenyl derivative **10f** was used as chiral ligand, the observed enantiomeric ratio was the highest of all of the ligands examined here (Table 2, entry 9). Finally, it must be pointed out that the enantioselective addition of diethylzinc to benzaldehyde performed using chiral ligand **10f** in absence of titanium alcohoxide, (as has been reported for related hydroxy[37,38] as well as different functionalised[39–42] sulfonamides), induced poor enantioselectivity (Table 2, entry 10).

Once the optimal ligand **10f** was found, different aldehydes were tested as substrates in the enantioselective addition of dialkylzinc under the same conditions described in Table 2, entry 9 (Table 3). The first remark is that the enantioselectivity of the reaction using dimethylzinc instead of diethylzinc as source of nucleophile is slightly lower (compare Table 2, entry 9 with Table 3, entry 1).

The influence of different *para*-substituted benzaldehyde derivatives on the enantioselectivity of the reaction was also studied in order to establish whether there is any relationship between the Hammet constants[43] and the enantiomeric ratio of the secondary alcohol derivatives obtained. It is believed that the rate-determining step in this reaction is the transfer of the alkyl group from the metal to the carbonyl moiety, independently of the positive[44] or negative[45] sign of the aforementioned relationship. There are other possibilities, such as unchanging enantioselectivity[46] irrespective of the *para*-substituted group, which has been interpreted considering that the rate-determining step of the reaction is the removal of the alkoxide-product from the catalytic species: Finally, it is also possible to find a negative relationship between the basicity of the *para*-functional group (instead of their electronic properties) and the enantioselectivity of the reaction,[16] which could indicate that the rate-determining step of the reaction is the complexation between the acidic catalytic species and the carbonyl compound. In our case, we found that electron-donating groups (methoxy; Table 3, entry 2), neutral (hydrogen; Table 2, entry 9) or lightly electron-withdrawing groups (chlorine; Table 3, entry 3) have a slight influence on the enantioselectivity, while, strong electron-withdrawing groups such as trifluoromethyl or cyano substituents gave much lower enantiomeric ratios (Table 3, entries 4 and 5). It must be pointed out that the trend followed by *para*-substituted benzaldehydes (with the exception of benzaldehyde) is that the more electronic donating character of group the higher the enantioselectivity of the addition reaction.

The enantiomeric excess found in the case of using aliphatic aldehydes was lower than for aromatic ones

Table 3.



Entry	R^1CHO	Alcohol[a]			
		No.	R^2	e.r.[b] *R*:*S*	e.e.
1	PhCHO	**13**	Me	89:11	78
2	4-$CH_3OC_6H_4CHO$	**14**	Et	96:4	92
3	4-ClC_6H_4CHO	**15**	Et	94:6	88
4	4-$CF_3C_6H_4CHO$	**16**	Et	89:11[c]	78
5	4-NCC_6H_4CHO	**17**	Et	87:13	74
6	*n*-$C_6H_{13}CHO$	**18**	Et	80:20[d]	60
7	*c*-$C_6H_{11}CHO$	**19**	Et	77:23[d]	54
8	$PhCH_2CH_2CHO$	**20**[e]	Et	74:26[c,d]	48
9	(*E*)-PhCH=CHCHO	**21**	Et	87:13[c,d,f]	74
10	PhC≡CCHO	**22**	Et	86:14[c,d,f]	72

[a] >95% isolated yield after bulb-to-bulb distillation.
[b] Determined by GLC analysis using a β-CD column.
[c] Determined by GLC analysis using a γ-CD column.
[d] Determined as trifluoroacetate derivative.
[e] >95% isolated yield after 48 h.
[f] Determined after transformation into compound **20** by standard hydrogenolysis using Pd/C.

(Table 3, entries 6–8), the reaction time being longer for the first ones. The reaction with aldehydes conjugated with alkenes or alkynes gave enantioselectivities similar to slightly electron-deficient aromatic aldehydes (Table 3, entries 9 and 10). Finally, it must be pointed out that the addition of diethylzinc to acetophenone[17,18] under the same reaction conditions failed after 8 days, the unchanged starting ketone being recovered.

3. Conclusion

In conclusion, we have described new chiral C_2-symmetry disulfonamide ligands, which can be easily prepared from chiral amino alcohols and disulfonyl derivatives and have been successfully tested in the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of titanium isopropoxide. The enantioselectivity is higher for aromatic aldehydes than either aliphatic or α,β-unsaturated ones. In the case of *para*-substituted benzaldehyde derivatives, the method seems to show a very slight negative relationship between the electron-withdrawing character of the *para*-substituted group and the observed enantioselectivity of the addition reaction, whereas the more electronic-donating character the substituent has, the higher the observed enantioselectivity.

4. Experimental

4.1. General

Full general statements were described elsewhere.[36] All reactions using dialkylzinc reagents were carried out under argon atmosphere using standard techniques.

4.2. Preparation of ligands

To a solution of the corresponding amino alcohol (26.5 mmol) and triethylamine (53 mmol, 7.5 mL) in CH_2Cl_2 (25 mL) at 0°C was slowly added (ca. 10 min) a solution of corresponding arenedisulfonyl chloride (10 mmol) in CH_2Cl_2 (15 mL). The temperature was allowed to rise to 25°C overnight. The mixture was extracted with HCl (2×50 mL, 2 M) and the resulting organic layer was extracted again with NaOH (2×25 mL, 2 M) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr), obtaining the pure title compounds **9**–**11** in yields indicated in Table 1. Naphthalene-1,5-disulfonyl chloride was prepared by reaction of commercially available 1,5-naphthalenedisulfonic acid tetrahydrate (25 mmol, 9 g) with $SOCl_2$ (250 mmol, 18.5 mL) in refluxing benzene (175 mL) catalysed by DMF (0.5 mL), according to the literature method[30] and was used without further purification. Spectroscopic, physical and analytical data follow.

4.2.1. *N*,*N*′-Di[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-benzenedisulfonamide 9. White solid, R_f 0.69 (hexane/ethyl acetate: 1/1); mp 111–113°C (ethyl acetate/hexane); $[\alpha]_D = -63.3$ (*c* 3.0, EtOH); *ν* (melted) 3306, 3280 (OH, NH), 3091, 1610 (C=CH), 1329 (SO_2), 1120 cm^{-1} (CO); δ_H ($CDCl_3$) 0.74 (6H, d, $J=6.7$, 2×CH_3), 2.88 (2H, s, 2×OH), 3.55–3.65 (2H, m, 2×CHN), 4.75–4.80 (2H, m, CHO), 6.38 (2H, d, $J=7.9$, 2×NH), 7.20–7.30 (10H, m, 2×Ph), 7.70–7.75, 8.20–8.25 (2 and 2H, respectively, 2m, $C_6H_4S_2$; δ_C ($CDCl_3$) 13.9 (2C), 55.8 (2C), 75.6 (2C), 126.0 (4C), 127.5 (2C), 128.2 (4C), 131.35 (2C), 133.1 (2C), 138.15 (2C), 140.0 (2C); *m*/*z* (DIP) 504 (M^+, <1%), 398 (11), 397 (30), 381 (19), 380 (21), 379 (53), 338 (68), 337 (41), 336 (43), 318 (11), 272 (20), 247 (37), 246 (40), 220 (22), 205 (15), 189 (10), 183 (13), 169 (12), 168 (29), 166 (14), 150 (10), 141 (18), 135 (17), 134 (59), 133 (35), 132 (49), 131 (18), 130 (20), 118 (47), 117 (30), 115 (11), 109 (13), 108 (43), 107 (22), 106 (41), 105 (20), 104 (11), 97 (19), 96 (11), 93 (19), 92 (70), 91 (53), 90 (12), 79 (88), 78 (67), 77 (100), 76 (31), 74 (11), 65 (20), 64 (12), 57 (16), 51 (13). HRMS calcd for $C_{24}H_{28}N_2O_6S_2$: 504.1388. Found: 504.1394.

4.3. *N*,*N*′-Di[(1*S*)-2-hydroxy-1-methylethyl]-1,3-benzenedisulfonamide 10a

White solid, R_f 0.34 (ethyl acetate); mp 76–78°C (ethyl acetate/hexane); $[\alpha]_D = -5.1$ (*c* 3.4, EtOH); *ν* (melted) 3513, 3256 (OH, NH), 3052, 1631 (C=CH), 1356 (SO_2), 1153 cm^{-1} (CO); δ_H (CD_3OD) 0.93 (6H, d, $J=6.1$, 2×CH_3), 3.26 (4H, d, $J=7.3$, 2×CH_2O), 3.30–3.40 (2H, m, 2×CHN), 7.70, 8.03, 8.29 (1, 2 and 1H, respectively, t, d and s, respectively, $J=7.3$, $C_6H_4S_2$); δ_C (CD_3OD) 18.0 (2C), 52.6 (2C), 66.75 (2C), 126.0, 131.3 (2C), 131.4 (2C), 144.5; *m*/*z* (DIP) 352 (M^+, <1%), 335 (26), 324 (15), 323 (90), 322 (64), 321 (29), 305 (21), 304 (26), 303 (36), 289 (18), 265 (30), 264 (37), 263 (13), 262 (10), 260 (11), 248 (18), 247 (18), 246 (100), 232 (15), 222 (18), 221 (18), 220 (43), 215 (32), 214 (49), 196 (19), 185 (27), 184 (66), 183 (36), 182 (87), 157 (20), 156 (85), 145 (45), 141 (43), 140 (50), 124 (35), 123 (13), 119 (73), 118 (49), 117 (33), 109 (10), 108 (20), 107 (61), 96 (11), 92 (17), 91 (41), 89 (16), 77 (75), 76 (27), 75 (65), 74 (12), 65 (15), 59 (19), 58 (34). HRMS calcd for $C_{12}H_{20}N_2O_6S_2 \cdot H_2O$: 334.0657. Found: 334.0673.

4.3.1. *N*,*N*′-Di[(1*S*)-2-hydroxy-1-phenylethyl]-1,3-benzenedisulfonamide 10b. White solid, R_f 0.28 (hexane/ethyl acetate: 3/7); mp 142–144°C (ethyl acetate/hexane); $[\alpha]_D = +56.4$ (*c* 3.7, EtOH); *ν* (melted) 3513 (OH), 3283, 3280 (NH), 3060, 1647 (C=CH), 1318 (SO_2), 1159 cm^{-1} (CO); δ_H (CD_3OD) 3.69 (4H, d, $J=6.1$, 2×CH_2O), 4.47 (2H, t, $J=6.1$, 2×CHN), 7.16 (10H, s, 2×Ph), 7.29, 7.73, 8.14 (1, 2 and 1H, respectively, t, d and s, respectively, $J=7.3$, $C_6H_4S_2$); δ_C (CD_3OD) 61.1 (2C), 66.4 (2C), 126.3, 128.0 (4C), 128.4 (2C), 129.2 (4C), 130.35 (2C), 131.0 (2C), 139.3 (2C), 143.2; *m*/*z* (DIP) 476 (M^+, <1%), 446 (11), 445 (65), 379 (15), 367 (43), 327 (18), 326 (70), 325 (18), 287 (13), 246 (14), 245 (42), 220 (11), 208 (11), 207 (22), 181 (25), 180 (16), 165 (15), 157 (23), 156 (46), 154 (10), 153 (25), 149 (50), 148 (65), 134 (14), 133 (56), 132 (29), 131 (40), 130 (63), 121 (35), 120 (13), 119 (35), 118 (10), 117 (23), 116 (64), 115 (15), 107 (14), 106 (57), 105 823), 104 (42), 93 (13), 92 (23), 91 (48), 89 (10), 79 (53), 78 (25), 77 (46), 76 (30), 75 (17), 65 (15), 64 (78), 51 (13). HRMS calcd for $C_{22}H_{24}N_2O_6S_2$: 476.1075. Found: 476.1075.

4.3.2. *N,N′*-Di[(2*R*)-2-hydroxy-2-phenylethyl]-1,3-benzenedisulfonamide 10c. White solid, R_f 0.33 (hexane/ethyl acetate: 2/3); mp 116–118°C (ethyl acetate/hexane); $[\alpha]_D=-54.7$ (*c* 2.8, EtOH); *v* (melted) 3507, 3291 (OH, NH), 3070, 1632 (C=CH), 1330 (SO_2), 1152 cm^{-1} (CO); δ_H ($CDCl_3$) 2.95–3.00, 3.15–3.20 (2 and 2H, respectively, 2m, 2×CH_2N), 3.80 (2H, s, 2× OH), 4.60–4.65 (2H, m, 2×CHO), 6.22 (2H, s, 2×NH), 7.05–7.15 (10H, s, 2×Ph), 7.53, 7.94, 8.50 (1, 2 and 1H, respectively, t, d and s, respectively, $J=7.3$, $C_6H_4S_2$); δ_C ($CDCl_3$) 50.1 (2C), 72.4 (2C), 125.5, 125.75 (4C), 128.05 (2C), 128.45 (4C), 130.0 (2C), 130.9 (2C), 140.3 (2C), 141.35; *m/z* (DIP) 476 (M^+, <1%), 352 (14), 351 (48), 341 (17), 325 (20), 324 (27), 323 (24), 306 (17), 277 (56), 261 (54), 260 (17), 259 (60), 196 (28), 194 (35), 169 (19), 167 (16), 166 (13), 165 (11), 141 (35), 140 (16), 120 (40), 119 (19), 118 (34), 117 (10), 108 (52), 106 (11), 105 (19), 104 (33), 91 (50), 79 (51), 78 (35), 77 (55), 76 (41), 64 (100), 51 (19). HRMS calcd for $C_{22}H_{24}N_2O_6S_2\cdot 2H_2O$: 440.0864. Found: 440.0859.

4.3.3. *N,N′*-Di[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-1,3-benzenedisulfonamide 10d. White solid, R_f 0.58 (ethyl acetate); mp 82–84°C (ethyl acetate/hexane); $[\alpha]_D=-8.9$ (*c* 2.05, EtOH); *v* (melted) 3515 (OH), 3279, 3211 (NH), 3022, 1605 (C=CH), 1328 (SO_2), 1129 cm^{-1} (CO); δ_H ($CDCl_3$) 0.78 (6H, d, $J=6.7$, 2×CH_3), 3.33 (2H, s, 2×OH), 3.60–3.65 (2H, m, 2×CHN), 4.75–4.80 (2H, m, 2×CHO), 5.81 (2H, s, 2×NH), 7.15–7.25 (10H, s, 2×Ph), 7.60, 8.03, 8.58 (1, 2 and 1H, respectively, t, d and s, respectively, $J=7.9$, $C_6H_4S_2$); δ_C ($CDCl_3$) 14.35 (2C), 55.25 (2C), 75.65 (2C), 125.45, 125.55 (4C), 127.65 (2C), 128.27 (4C), 130.05 (2C), 130.49 (2C), 139.85 (2C), 142.55; *m/z* (DIP) 504 (M^+, <1%), 382 (29), 381 822), 380 (76), 379 (12), 355 (34), 339 (16), 338 (33), 337 (25), 334 (40), 292 (17), 291 (74), 289 (44), 275 (30), 274 (100), 273 (76), 263 (24), 248 (28), 246 (24), 210 (37), 209 (61), 208 (21), 205 (27), 193 (13), 185 (22), 184 (56), 183 (45), 182 (86), 168 (14), 167 (58), 166 (11), 165 (30), 156 (13), 155 (18), 154 (10), 153 (14), 152 (11), 142 (13), 141 (68), 140 (57), 135 (11), 134 (73), 133 (66), 124 (21), 123 (16), 120 (11), 119 (70), 118 (57), 117 (86), 108 (70), 107 (33), 106 (27), 105 (39), 104 (13), 92 (19), 91 (85), 80 (20), 79 (26), 78 (36), 76 (31), 75 (16), 64 (66), 51 (21). HRMS calcd for $C_{24}H_{28}N_2S_2O_6$: 504.1388. Found: 504.1398.

4.3.4. *N,N′*-Di[(1*R*,2*S*)-1-hydroxy-2,3-dihydro-1*H*-2-indenyl]-1,3-benzenedisulfonamide 10. White solid, R_f 0.34 (hexane/ethyl acetate: 3/7); mp 150–152°C (CH_2Cl_2); $[\alpha]_D=+9.8$ (*c* 2.85, DMSO); *v* (melted) 3469, 3267 (OH, NH), 3060, 1444 (C=CH), 1330 (SO_2), 1150 cm^{-1} (CO); δ_H (CD_3OD) 2.64, 2.83 (2 and 2H, respectively, d and dd, respectively, $J=15.8$, 4.2, 2×CH_2), 4.05–4.10 (2H, m, 2×CHO), 4.60–4.65 (2H, m, 2× CHN), 6.75–6.80, 6.95–7.00, 7.05–7.15 (2, 2 and 4H, respectively, 3m, 2×$C_6H_4C_2$), 7.78, 8.14, 8.39 (1, 2 and 1H, respectively, t, d and s, respectively, $J=7.3$, $C_6H_4S_2$), 8.02 (2H, s, 2×NH); δ_C (CD_3OD) 55.2 (2C), 70.65 (2C), 81.8 (2C), 133.55 (2C), 134.15, 134.55 (2C), 135.8 (2C), 137.1 (2C), 139.8 (2C), 140.05, 149.9 (2C), 150.4 (2C), 152.6 (2C); *m/z* (DIP) 500 (M^+, <1%), 379 (100), 273 (15), 148 (97), 132 (18), 130 (10), 105 (13), 91 (11), 64 (69), 63 (10). HRMS calcd for $C_{24}H_{24}N_2O_6S_2$: 500.1075. Found: 500.1089.

4.3.5. *N,N′*-Di[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]-1,3-benzenedisulfonamide 10f. White solid, R_f 0.55 (hexane/ethyl acetate: 2/3); mp 88–90°C (CH_2Cl_2); $[\alpha]_D=-60.6$ (*c* 2.9, EtOH); *v* (melted) 3510, 3284 (OH, NH), 3060, 1606 (C=CH), 1328 (SO_2), 1152 cm^{-1} (CO); δ_H (DMSO-d_6) 2.55 (2H, s, 2×OH), 4.25–4.30 (2H, m, 2×CHN), 4.55-4.65 (2H, m, 2×CHO), 5.41 (2H, d, $J=4.8$, 2× NH), 6.95-7.00, 7.10-7.15 (10 and 10H, respectively, 2m, 4×Ph), 7.23, 7.71, 8.35 (1, 1 and 2H, respectively, t, s and d, respectively, $J=9.6$, $C_6H_4S_2$); δ_C (DMSO-d_6) 63.5 (2C), 75.36 (2C), 124.25, 126.7 (2C), 126.8 (4C), 127.15 (2C), 127.2 (4C), 127.6 (4C), 128.2 (4C), 128.8 (2C), 129.15 (2C), 138.5 (2C), 141.75, 142.6 (2C); *m/z* (DIP) 628 (M^+, <1%), 504 (17), 503 (50), 458 (10), 325 (40), 245 (15), 167 (14), 141 (20), 105 (35), 79 (45), 77 (38), 76 (28), 64 (100). HRMS calcd for $C_{34}H_{32}N_2O_6S_2\cdot H_2O$: 610.1596. Found: 610.1592.

4.3.6. *N,N′*-Di[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl]-1,5-naphthalenedisulfonamide 11. White solid, R_f 0.44 (hexane/ethyl acetate: 2/3); mp 208–210°C (ethyl acetate/hexane); $[\alpha]_D=-23.5$ (*c* 2.35, DMF); *v* (melted) 3382, 3298 (OH, NH), 3060, 1647 (C=CH), 1316 (SO_2), 1129 cm^{-1} (CO); δ_H (CD_3OD) 0.81 (6H, d, $J=6.1$, 2×CH_3), 3.20–3.25 (2H, m, CHO), 3.25–3.35 (2H, m, CHN), 4.39 (2H, d, $J=6.1$, 2×NH), 6.80–7.05 (10H, m, 2×Ph), 7.55, 8.15, 8.71 (2, 2 and 2H, respectively, dd, d and d respectively, $J=7.3$, 8.5, $C_{10}H_6S_2$); δ_C (CD_3OD) 16.5 (2C), 57.75 (2C), 77.6 (2C), 126.9 (2C), 127.1 (4C), 128.25 (2C), 128.6 (2C) 128.7 (4C), 130.45 (2C), 131.6 (2C), 138.5 (2C), 143.15 (2C); *m/z* (DIP) 554 (M^+, <1%), 429 (47), 341 (11), 323 (72), 259 (48), 233 (12), 195 (48), 163 (12), 127 (16), 126 (51), 119 (15), 118 (22), 108 (12), 107 (100), 106 (86), 105 (56), 104 (28), 77 (61). HRMS calcd for $C_{28}H_{30}N_2O_6S_2$: 554.1545. Found: 554.1588.

4.4. Enantioselective addition of dialkylzinc to aldehydes in the presence of ligands 9–11 and titanium tetraisopropoxide. General procedure

To a solution of the corresponding ligand **9**–**11** (0.5 mmol) in toluene (5 mL) under nitrogen atmosphere was added a solution of the appropriate dialkylzinc reagent (9 mmol, 4.5 mL, ca. 2 M) at 0°C. After 10 min, titanium tetraisopropoxide (6.5 mmol, 2 mL) was added to the above solution and after 10 additional min, the corresponding aldehyde (5 mmol) was successively added. The resulting mixture was stirred at the same temperature for 5 h. Then methanol (ca. 1 mL) and saturated NH_4Cl solution (ca. 20 mL) were successively added, the mixture was filtered through Celite, extracted with ethyl acetate (3×50 mL) and the organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure (15 torr) and the residue was distilled bulb-to-bulb to yield the expected alcohols. Yields and enantiomeric ratios (e.r.) are included in Tables 2 and 3. Compounds **12**–**15**, **17**,[16] as well as **18**–**22**,[36] were already described by us and were characterised by comparison of their physical and spec-

troscopic data with those reported in the literature. Spectroscopic and physical data, as well as literature references follow.

4.4.1. 1-(4-Trifluomethylphenyl)propan-1-ol 16.[47,48] Colourless oil, bp 140–145°C (0.1 torr), t_R 6.06; t_R (*R*) 54.17, t_R (*S*) 55.40 [Conditions: $T_{column}=90$°C (5 min) and 180°C (0.1°C/min)]; R_f 0.54 (hexane/ethyl acetate: 7/3); $[\alpha]_D=+19.45$ [*c* 3.2, MeOH; e.r. (*R*/*S*) 89.0:11.0]; *v* (film) 3361 (OH), 3027, 1618 (CH=C), 1327 (CF), 1125 cm^{-1} (CO); δ_H ($CDCl_3$) 0.93 (3H, t, $J=7.3$, CH_3), 1.65–1.80 (2H, m, CH_2), 1.84 (1H, s, OH), 4.67 (1H, t, $J=6.4$, CHO), 7.45, 7.60 (2 and 2H, respectively, 2d, $J=8.1$, C_6H_4); δ_C ($CDCl_3$) 9.35, 31.5, 74.5, 127.95 (q, $^1J_{CF}=890.8$), 120.15 (q, $^2J_{CF}=271.1$), 124.8 (2C, q, $^3J_{CF}=10.9$), 125.75 (2C), 148.05; *m*/*z* 204 (M^+, 3%), 175 (100), 145 (10), 127 (78).

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