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Highly efficient chiral polydentate sulfinyl ligands/catalysts containing prolinol moiety

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ABSTRACT

New polydentate chiral ligands, containing the hydroxyl group, stereogenic sulfinyl group and enantiomeric prolinol moieties were synthesized and proved very efficient catalysts in the asymmetric diethylzinc addition to benzaldehyde, the asymmetric aldol condensation and the asymmetric Mannich reaction. Replacement of the central hydroxyl group with the second prolinol moiety of the same absolute configuration gave new ligands in which the sulfinyl group was not a stereogenic centre anymore, but which proved almost equally efficient as catalysts for the reactions investigated. The absolute configuration of the proline moiety exerted a decisive impact on the stereochemical outcome of these reactions, deciding about the absolute configuration of the products formed.

1. Introduction

A search for new organocatalysts for the stereoselective formation of optically active compounds is one of the most important and challenging tasks of contemporary asymmetric synthesis. The main advantage of using organocatalysts in asymmetric synthesis is the ability to avoid toxic and expensive metals complexes.

Our recent works have been focused on the preparation of enantiopure heteroatom-containing compounds that could be used as chiral ligands or catalysts in the asymmetric C–C bond formation. We have succeeded in the chemoenzymatic synthesis of a variety of ligands **4**, containing a stereogenic sulfinyl moiety, an enantiomeric amine fragment and the hydroxyl group (Scheme 1).[1] The crucial step was the *Candida antarctica* lipase (CAL-B)-promoted desymmetrization of prochiral bis(2-hydroxymethylphenyl) sulfoxide **1**, which allowed us to obtain the desired precursor—monoacetate **2** in one step in a high yield (98%) and in an almost enantiomerically pure form. Simple ensuing chemical transformations, consisting of mesylation of the hydroxyl group to give **3**, followed by the reaction with a relevant amine and removal of the acetyl group, led to ligands **4**, which proved to be excellent catalysts in various reactions of asymmetric synthesis.

Thus, the ligands bearing enantiomeric primary amine moieties (**4a**–**f**) proved particularly efficient catalysts in aldol,[2] nitroaldol (Henry),[3,4] aza-Henry[5] and Mannich[6] reactions, while those bearing enantiomeric aziridine moieties (**4h**–**j**)—in the reactions involving organozinc reagents, i.e., in the asymmetric organozinc additions to aldehydes,[7,8] the Michael diethylzinc additions to enones[9] and the Simmons – Smith cyclopropanation of allyl alcohols.[10] In all cases the products were obtained in the yields up to 98% and with ee's up to 98%. It was found by us that the absolute configuration of the amine substituent exerted a decisive impact on the stereochemical outcome of the reactions and, hence, on the absolute configuration of the products, with only a small 'match–mismatch' effect caused by the chirality of the sulfinyl group. Nevertheless, the presence of all the coordinating centers, i.e., the hydroxyl, sulfinyl groups and the amine nitrogen atom, was proven to be essential for the efficiency of the catalysts and allowed us to conclude that the ligands **4** demonstrated a tridentate character.[4,6] Particularly, the presence of the stereogenic sulfinyl group proved crucial for the outcome of all the reactions since its replacement with the corresponding sulfide or sulfone moiety resulted in a substantial decrease of both the yield and enantiomeric excess of the products. Interestingly, the hydroxyl group in **4** could be replaced by the identical enantiomeric amine moiety, but in order to achieve high catalytic activity of the newly formed

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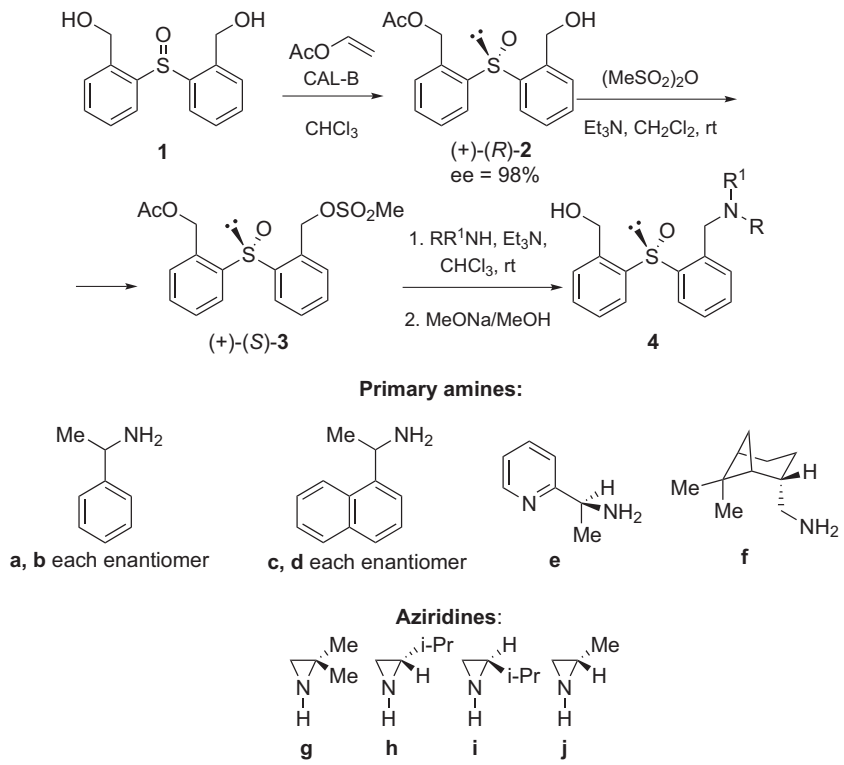


Scheme 1. Synthesis of sulfinyl ligands **4.**

ligand **5** (Fig. 1) and stereoselectivity of the reactions in which it was used as catalyst, it was necessary to retain in its molecule the sulfinyl moiety, even if the latter lost in this case its stereogenic character.[4,6]

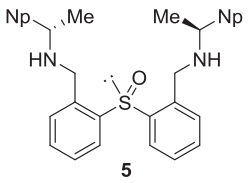


Fig. 1. The diamino analog of ligand **4d.**

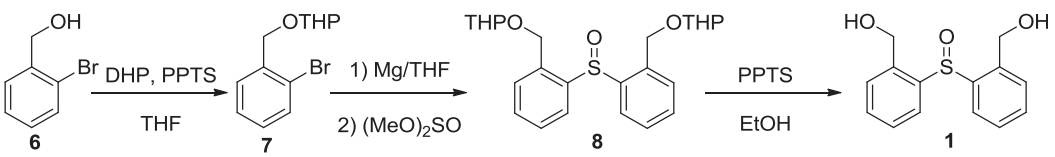
Looking for other chiral amine-type substituents that could be useful in the designing of new ligands we focused our attention on prolinol, which seemed particularly interesting due to the presence of the hydroxyl group, capable of acting as an additional coordinating centre. In this context it should be mentioned that proline and its analogs are widely used as chiral organocatalysts.[11] Particularly, prolinol and its various derivatives are commonly applied in asymmetric synthesis.[12] They proved to be valuable auxiliaries[13] and catalysts in the asymmetric formation of carbon–carbon[14] and carbon-heteroatom bonds.[15] Therefore, we decided to replace the amino groups in our original sulfinyl ligands **4** and **5** with one or two prolinol moieties, to obtain new ligands **9** and **10**, having four or five potential coordination centers, respectively (Scheme 3).

2. Results and discussion

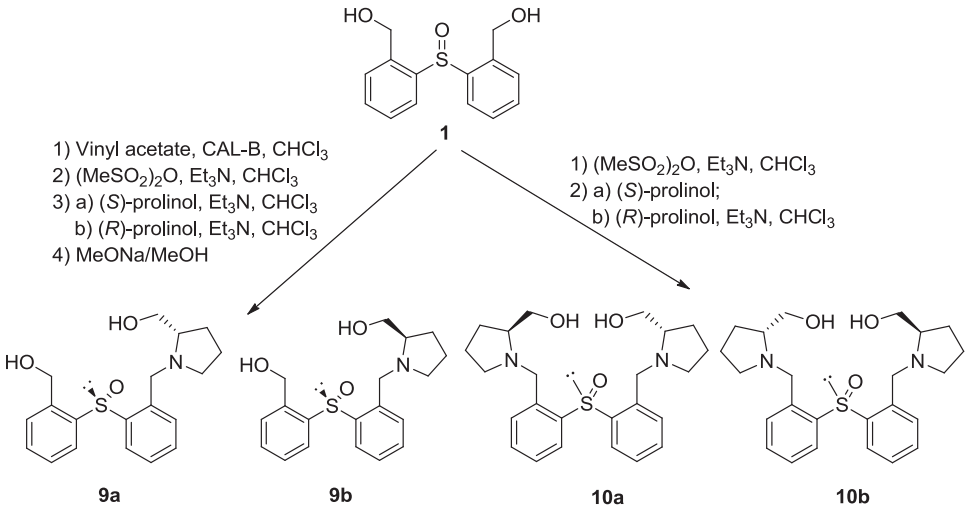
2.1. Synthesis of ligands

We attempted to synthesize the basic substrate, namely bis(2-hydroxymethylphenyl) sulfoxide **1**, in a different way than that originally described.[1] We started from *o*-bromobenzyl alcohol **6**, in which the hydroxyl group was protected with dihydropyran (DHP), according to the literature procedure,[16] to give **7** in 98% yield. In the next step the protected alcohol was transformed into a Grignard reagent and treated with dimethyl sulfite to yield **8** (83.7%), followed by the removal of the tetrahydropyranyl group (THP) with pyridinium *p*-toluenesulfonate (PPTS) to give the desired compound **1** (86.5%) (Scheme 2). The overall yield of **1** achieved using the present method was higher than using the one previously described.[1]

Synthesis of ligands/catalysts **9a** and **9b**, with a stereogenic sulfur atom, was carried out according to the procedure previously described (Scheme 1),[1] by enzymatic desymmetrization of the sulfoxide **1**, mesylation of the hydroxyl group, reaction with (*S*)-prolinol or (*R*)-prolinol, respectively, and removal of the acetyl group with sodium methoxide. In turn, the ligands/catalysts **10a**



Scheme 2. Synthesis of prochiral bis(2-hydroxymethylphenyl) sulfoxide **1.**



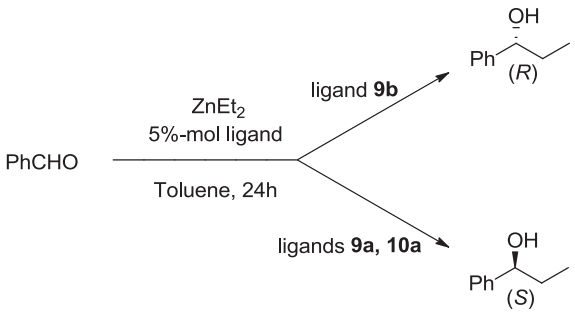
Scheme 3. Synthesis of chiral polydentate ligands **9** and **10.**

and **10b** were prepared by mesylation of both hydroxyl groups in sulfoxide **1** followed by the reaction with each enantiomer of prolinol (Scheme 3).

2.2. Screening of ligands 9 and 10

The ligands were tested as catalysts in several asymmetric reactions: diethylzinc addition to benzaldehyde (Table 1), aldol condensation (Table 2) and Mannich reaction (Table 3).

Table 1
Addition of diethylzinc to benzaldehyde in the presence of ligands **9a, 9b, 10a**



Entry	Catalyst	Product			
		Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	Abs. Conf.[c]
1	**9a**	88	−38.6	86	(*S*)
2	**9b**	83	+33.7	75	(*R*)
3	**10a**	74	−35.9	80	(*S*)

[a] In chloroform (c=1).
[b] Determined by chiral HPLC.
[c] Based on literature data.[7]

Interestingly, in case of diethylzinc addition to benzaldehyde (Table 1), the ligands containing prolinol moieties exerted a similar asymmetric induction as those containing the aziridine moieties[7] and much higher than those bearing open-chain amines.[1] Thus, the prolinol moiety must coordinate diethylzinc as efficiently as aziridines. The use of both diastereomeric ligands **9a** and **9b**, containing opposite enantiomers of prolinol, led to the formation of chiral products with opposite absolute configurations. Thus, the stereogenic centers located in the prolinol moieties exerted a decisive effect on the absolute configuration of the products. The observed differences in their ee values (Table 1, entries 1 and 2) may be explained in terms of evident 'matched' and 'mismatched' interactions with the sulfinyl stereogenic center. Following our previous results on the effect of replacement of the hydroxy group with the next identical amino moiety,[4,6] we decided to check the influence of a similar change in our new ligand and used the analog **10a**, in which the sulfinyl group is not a stereogenic centre anymore (due to the presence of two identical substituents at the sulfur atom). Table 1, entry 3 clearly indicates that the enantiomeric excess of the product was in this case only slightly lower than that obtained with ligand **9a**, which can be considered to result from the lack of the stereogenic centre at sulfur.

The same stereochemical outcome was observed for the aldol reaction (Table 2). Again the absolute configuration of the product depended on the absolute configuration of the prolinol moiety, with only a small match/mismatch effect (entries 1 and 2). Such an effect was the same as in the case of the aldol condensation performed in the presence of the catalysts **4a**–**d**, previously reported by us,[2] in spite of the fact that in the present experiments the reaction conditions were entirely different. Obviously, the catalysts **10a** and **10b** which, due to the lack of stereogenicity of the sulfinyl group, may be considered as enantiomers, led to the opposite enantiomers of the product (entries 3 and 4).

The identical relationship was noted while investigating the asymmetric Mannich reaction. Also in this case the absolute configuration of the major diastereomeric product depended on the enantiomer of prolinol used (Table 3) and the efficiency of the catalysts was very high, resembling the results obtained by us earlier.[6] Moreover, the product was obtained with very high diastereoselectivity and each enantiomer of the product was available using easily accessible enantiopure catalysts.

Since the catalysts **10** exhibited the highest efficiency in terms of chemical yield and enantiomeric excess of the chiral Mannich product, we decided to determine the scope of the activity of catalyst **10a**. It was therefore applied in the asymmetric three-component Mannich reactions involving acetone (R=H) or hydroxyacetone (R=OH) as a ketone, *p*-anisidine and a number of various aldehydes as starting materials under identical reaction conditions as in the experiments shown above. The results of these Mannich transformations are shown in Table 4.

Inspection of Table 4 makes it clear that catalyst **10a** efficiently catalyzes the title reaction leading to the appropriate Mannich adducts. Only in the case of entry 4, where an aliphatic aldehyde was applied, the corresponding optically active product was

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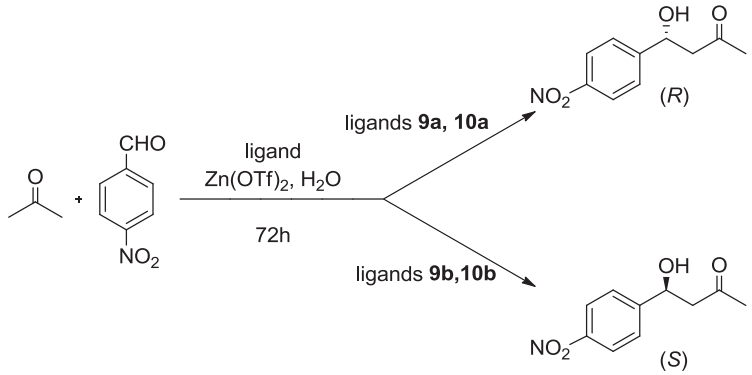
Table 2
Aldol condensation in the presence of ligands **9a**, **9b**, **10a**, **10b**



Entry	Catalyst	Product			
		Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	Abs. conf.[c]
1	**9a**	43	+57.6	87	(*R*)
2	**9b**	41	−53.6	81	(*S*)
3	**10a**	40	+55.6	84	(*R*)
4	**10b**	44	−53.5	80	(*S*)

[a] In chloroform (*c*=1).
[b] Determined by chiral HPLC.
[c] Based on literature data.[2]

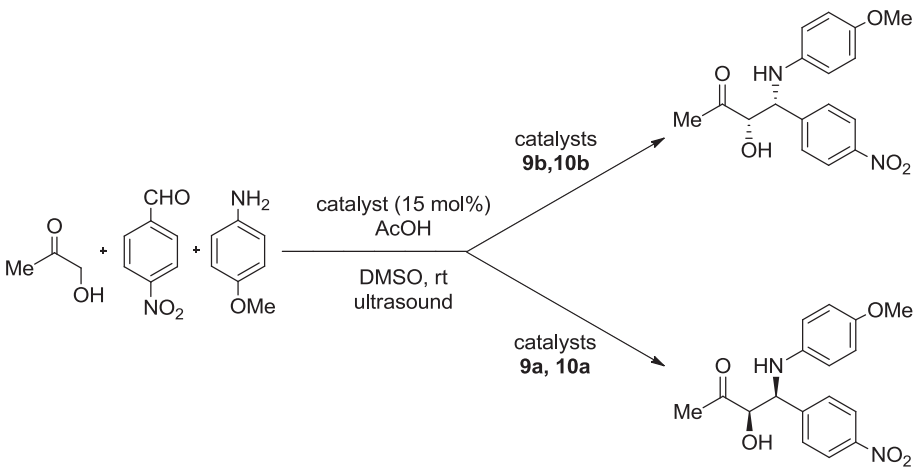
obtained in lower chemical yield and with lower enantioselectivity (62 and 73%, respectively). In the reaction of hydroxyacetone and *p*-methoxybenzaldehyde (entry 9), the product was formed in good chemical yield, but unexpectedly with a lower *ee* value. In the other entries, the enantiopure Mannich adducts were formed in high chemical yields (80–94%), excellent enantioselectivities (87–96% *ee*) and in some cases high diastereoselectivities.

Although the detailed mechanism of the above reaction cannot be presented at this stage, it seems reasonable to assume, that initial formation of an imine from the substrates—aldehydes and *p*-anisidine—takes place. The chiral catalyst, whose tertiary amine moiety acts as a Brønsted base and hydroxy groups as hydrogen bond donors,[17] induce a stereoselective attack of the ketone enolate on the imine formed.

3. Conclusions

The newly synthesized polydentate ligands, containing the hydroxyl group, stereogenic sulfinyl group and enantiomerically pure prolinol moieties with a free hydroxyl group proved very efficient

Table 3
Mannich reaction in the presence of catalysts **9a**, **9b**, **10a**, **10b**



Entry	Catalyst	Product			
		Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	*dr*[c]
1	**9a**	91	+3.3	90	18:1
2	**9b**	90	−3.2	89	18:1
3	**10a**	94	+3.4	94	20:1
4	**10b**	95	−3.5	96	20:1

[a] In chloroform (*c*=1).
[b] Determined by chiral HPLC for the major diastereoisomer.
[c] Based on ^{1}H NMR data of the crude product.

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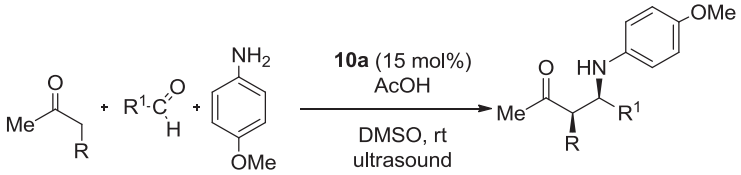
Table 4
Screening of aldehydes and ketones in the Mannich reaction using catalyst **10a**



Entry	R	R^1	Mannich product			
			Yield [%]	$[\alpha]_D$[a]	Ee [%][b]	d.r.[c]
1	OH	*o*-$MeOC_6H_4$	90	−2.1	87	4:1
2	OH	*m*-Tol	92	−8.2	91	6:1
3	OH	*p*-$O_2NC_6H_4$	94	+3.4	94	20:1
4	H	$CH_2CH_2CH{=}CH$	62	−7.1	73	—
5	H	CH_2CH_2Ph	80	−10.8	92	—
6	OH	CH_2CH_2Ph	89	+13.1	96	12:1
7	OH	*p*-BrC_6H_4	94	−1.0	96	15:1
8	OH	Ph	84	−52.6	94	9:1
9	OH	*p*-$MeOC_6H_4$	91	+1.4	65	3:1

[a] In chloroform (*c*=1).
[b] Determined by chiral HPLC for the major diastereoisomer.
[c] Based on ^{1}H NMR data of the crude product.

catalysts in some reactions of the asymmetric C–C bond formation, i.e., the diethylzinc addition to aldehydes, the aldol condensation and the three-component Mannich reaction. Replacement of the central hydroxyl group in these ligands with the second prolinol moiety of the same absolute configuration gave new ligands in which the sulfinyl group was not a stereogenic centre anymore. Nevertheless, these ligands proved almost equally efficient as catalysts for the reactions investigated. The absolute configuration of the proline moiety exerted a decisive impact on the stereochemistry of these reactions, hence, decided about the absolute configuration of the products formed.

4. Experimental

4.1. General information

Unless otherwise specified, all the reagents were purchased from commercial suppliers and used as received. Reactions were followed using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV-light. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter (*c* 1). Column chromatography was carried out using Merck 60 silica gel. ^{1}H NMR spectra were recorded at 200 or 500 MHz and ^{13}C NMR spectra at 101 or 126 MHz in $CDCl_3$ and CD_3OD as solvents. Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as an internal standard. Coupling constants are reported as *J* values in Hz. Mass spectra (MS) were recorded using chemical ionization technique on Finningan MAT 95 spectrometer. The enantiomeric excess (*ee*) values were determined by chiral HPLC Column: Lux 5μ Cellulose – 1 (Phenomenex).

4.2. Synthesis of prochiral bis(2-hydroxymethylphenyl) sulfoxide 1

*4.2.1. Bis(2-tetrahydropyranyloxymethylphenyl) sulfoxide (**8**).* Magnesium (0.504 g, 21.0 mmol) was placed in a three-necked flask and a solution of **7** (0.1143 g, 0.45 mmol) in THF (4 ml) was added. The mixture was refluxed for 1 h and the remaining substrate **7** (5.194 g, 20.37 mmol) in THF (30 ml) was added. The reaction mixture was slowly cooled to 0 °C and the solution of dimethyl sulfite in THF was added dropwise. Stirring was continued for 24 h at room temperature. A solution of 10% HCl (40 ml) was added, the layers were separated and the aqueous layer was extracted with Et_2O (3×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography ($CHCl_3$:MeOH 100:1) to give **8** as a colorless oil (7.1451 g, 83.7%). ^{1}H NMR ($CDCl_3$) δ 1.45–1.79 (m, 12H), 3.47–3.53 (m, 2H), 3.76–3.90 (m, 2H), 4.58–4.63 (m, 2H), 4.65–4.92 (m, 4H), 7.40–7.55 (m, 6H), 7.69–7.72 (m, 2H).

*4.2.2. Bis(2-hydroxymethylphenyl) sulfoxide (**1**).* Sulfoxide **8** (7.145 g, 16.6 mmol) was dissolved in ethanol (100 ml) and PPTS (10%-mol) was added. The reaction mixture was heated under reflux for 3 h and reaction was monitored by TLC ($CHCl_3$:MeOH 20:1). After completion of the reaction the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 ml) and washed with water (100 ml). Aqueous layer was extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography ($CHCl_3$:MeOH 20:1) to give **1** as white crystals (4.239 g, 86.5%). ^{1}H NMR (CD_3OD) δ 4.69 (s, 4H), 4.88 (s, 2H), 7.43–7.69 (m, 8H).[1]

Enzymatic desymmetrization of prochiral sulfoxide **1** and mesylation of **2** were performed according to the literature procedure.[1]

4.3. Synthesis of hydroxymethylphenyl *N*-prolinylmethylphenyl sulfoxides 9a and 9b

4.3.1. Acetoxymethylphenyl N-prolinylmethylphenyl sulfoxides. To acetoxymethyl-phenyl mesyloxymethylphenyl sulfoxide **3**[1] (0.311 g, 0.81 mmol), dissolved in $CHCl_3$ (20 ml), triethylamine (0.11 ml, 0.81 mmol) and (*S*)-prolinol (80 μl, 0.81 mmol) were added. The mixture was stirred at room temperature for 72 h, and the reaction progress was controlled by TLC (AcOEt:MeOH 20:1). After completion of the reaction the solvent was evaporated and the crude product was purified by column chromatography to give acetoxymethylphenyl *N*-prolinylmethylphenyl sulfoxide as a white solid (0.288 g, 91.4%, $[\alpha]_D$=−25.3, c 1). To confirm its structure, two-dimensional NMR spectra were recorded (COSY, HSQC, HMBC). ^{1}H NMR ($CDCl_3$) δ 1.70–1.78 (m, 2H), 1.82 (s, 3H), 1.93–1.96 (m, 2H), 2.20–2.24 (m, 1H), 2.82 (m, 1H), 2.90 (m, 1H), 3.51 (dd, 1H, *J*=2.2,

9.0 Hz), 3.53 (d, 1H, *J*=12.5 Hz), 3.95 (dd, 1H, *J*=2.2, 9.0 Hz), 4.64 (d, 1H, *J*=12.5 Hz), 4.92–5.03 (AB, 2H, *J*=13.0 Hz), 7.24–7.66 (m, 7H), 8.17 (d, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ 20.50; 24.01; 27.72; 54.28; 56.48; 62.25; 62.82; 65.35; 126.11; 128.77; 129.51; 130.18; 130.34; 131.14; 131.4; 131.81; 133.12; 140.54; 141.67; 142.32; 170.31. MS (CI) *m*/*z* 388.2 (M+H) $C_{21}H_{25}O_4SN$.

The same reaction was performed using (*R*)-prolinol. Yield 0.290 g (91.7%), $[\alpha]_D$=+34.6, c 1. ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 1.77–1.99 (m, 3H), 2.46–2.58 (m, 1H), 2.74–2.83 (m, 1H), 3.14–3.24 (m, 3H), 4.09 (AB, 2H, *J*=13.32 Hz), 4.24 (bs, 1 H), 5.01 (AB, 2H, *J*=12.81 Hz), 7.07 (d, 1H, *J*=7.69 Hz), 7.20–7.68 (m, 6H), 8.16 (d, 1H, *J*=7.69 Hz).

4.3.2. Hydroxymethylphenyl N-(S)-prolinylmethylphenyl sulfoxide ***(9)***. Acetoxymethylphenyl *N*-prolinylmethylphenyl sulfoxide (0.274 g, 0.71 mmol) was dissolved in methanol (6 ml) and sodium (0.016 g, 0.71 mmol) was slowly added. The mixture was stirred at room temperature for 30 min. After this time the solvent was evaporated and the residue was purified by column chromatography (AcOEt:MeOH 10:1) to give the desired product-s **9** as white crystals;

9a: (0.213 g, 87.5%); $[\alpha]_D$=−72.0. ^{1}H NMR ($CDCl_3$) δ 1.63–1.75 (m, 2H), 1.78–1.85 (m, 1H), 1.87–1.94 (m, 1H), 2.26–2.31 (m, 1H) 2.84–2.89 (m, 2H), 3.39 (dd, 1H, *J*=3.2 Hz, 11.1 Hz), 3.62 (dd, 1H, *J*=3.2 Hz, 11.1 Hz), 3.70 (d, 1H, *J*=13.0 Hz), 4.30 (d, 1H, *J*=13.0 Hz), 4.49 (s, 2H), 7.31–7.35 (m, 1H), 7.37–7.46 (m, 6H), 7.78–7.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 23.63 (CH_2), 27.51 (CH_2), 54.52 (CH_2), 56.57 (CH), 61.79 (CH_2N), 62.85 (CH_2O), 65.46 (CH_2O-prolinol), 125.81 (C_{Ar}), 127.74 (C_{Ar}), 128.30 (C_{Ar}), 128.90 (C_{Ar}), 129.09 (C_{Ar}), 130.42 (C_{Ar}), 131.14 (C_{Ar}), 131.58 (C_{Ar}), 139.06 (qC), 139.81 (q C), 140.78 (qC), 142.03 (qC). MS (CI) *m*/*z* 346.3 (M+H) $C_{19}H_{23}O_3SN$. HRMS: *m*/*z* calcd for $C_{19}H_{23}O_3NS$: 345.1399; found: 345.13987.

9b: (0.1346, 55.3%); $[\alpha]_D$=+38.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.63–1.65 (m, 1H), 1.71–1.78 (m, 1H), 1.81–1.88 (m, 1H), 1.89–1.96 (m, 1H), 2.39 (q, 1H, *J*=9.9 Hz), 2.76 (bs, 1H), 2.94 (t, 1H, *J*=2.9 Hz), 3.52 (dd, 1H, *J*=3.3 Hz, *J*=12.1 Hz), 3.57 (d, 1H, *J*=12.7 Hz), 3.68 (dd, 1H, *J*=2.8 Hz, 12.1 Hz), 4.23 (d, 1H, *J*=13.4 Hz), 4.45 (d, 1H, *J*=13.4 Hz), 4.64 (d, 1H, *J*=12.8 Hz), 7.23 (d, 1H, *J*=7.9 Hz), 7.28–7.32 (m, 2H), 7.36–7.42 (m, 2H), 7.44 (t, 1H, *J*=7.5 Hz), 7.51 (t, 1H, *J*=7.5 Hz), 8.01 (d, 1H, *J*=7.7 Hz). ^{13}C NMR ($CDCl_3$): 23.23; 26.80; 54.92; 57.18; 62.43; 62.62; 66.77; 126.22; 128.14; 128.98; 129.65; 130.88; 130.91; 131.70; 138.70; 139.81; 141.52; 143.32.

4.4. Synthesis of bis(*N*-prolinylmethylphenyl) sulfoxides 10a and 10b

4.4.1. Bis(mesyloxymethylphenyl) sulfoxide. Sulfoxide **1** (0.518 g, 2 mmol) was dissolved in methylene chloride (100 ml) and triethylamine was added (0.63 ml, 4.54 mmol). To this solution mesyl anhydride (0.791 g, 4.54 mmol) was dropped. The reaction mixture was stirred at room temperature for 45 min (TLC monitoring ethyl acetate:methanol 20:1). After completion of the reaction 50 ml of water was added, the layers were separated, and the aqueous layer was extracted with methylene chloride (3×20 ml). The combined organic layer was drying over anhydrous $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography (ethyl acetate) to give 0.801 g of a colorless oil (96.9%). ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6H), 5.38 (AB, 4H, *J*=7.0 Hz), 7.58–7.78 (m, 8H).

4.4.2. Bis[N-(S)-prolinylmethylphenyl] sulfoxide ***10a***. In a round bottom flask bis(mesyloxymethylphenyl) sulfoxide (0.856 g, 2.22 mmol) and triethylamine (0.62 ml, 4.44 mmol) were dissolved in 40 ml of chloroform. (*S*)-prolinol (0.43 ml, 4.44 mmol) was added dropwise. The reaction mixture was stirred for 24 h (TLC monitoring ethyl acetate: methanol 5: 1). After completion of the reaction chloroform was evaporated and the crude product was purified by column chromatography (ethyl acetate: MeOH in gradient, 100:0–10:1) to give 0.6241 g (76.4%) of **10a** as a yellow oil; $[\alpha]_D$=−63.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.57–1.64 (m, 4H) 1.67–1.73 (m, 3H), 1.70–1.79 (m, 2H), 1.82–1.88 (m, 2H), 1.98 (bs, 1H), 2.32 (q, 1H, *J*=9.0 Hz), 2.57–2.62 (m, 1H), 2.70–2.78 (m, 2H), 2.95 (t, 1H, *J*=7.0 Hz), 3.18 (dd, 1H, *J*=3.0, 11.5 Hz), 3.27 (dd, 1H, *J*=3.0, 11.5 Hz), 3.38 (dd, 1H, *J*=3.0, 11.5 Hz), 3.42 (br s, 1H), 3.63 (dd, 1H, *J*=3.0, 11.5 Hz), 3.73 (d, 1H, *J*=13.5 Hz), 3.83 (d, 1H, *J*=13.5 Hz), 4.22–4.29 (m, 1H), 7.31–7.34 (m, 1H), 7.35–7.44 (m, 5H), 7.46 (bs, 1H), 7.49 (d, 1H, *J*=7.5 Hz), 7.60 (d, 1H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 23.40 (CH_2), 23.50 (CH_2), 27.39 (CH_2), 27.68 (CH_2), 54,23 (CH_2), 55.27 (CH_2), 55.43 (CH), 57.06 (CH), 62.51 (CH_2N), 62.84 (CH_2N), 65.28 (CH_2O), 65.67 (CH_2O), 126.84 (C_{Ar}), 126.93 (C_{Ar}), 126.99 (C_{Ar}), 128.29 (C_{Ar}), 128.38 (C_{Ar}), 129.42 (C_{Ar}), 130.01 (C_{Ar}), 131.14 (C_{Ar}), 131.19 (C_{Ar}), 139.28 (qC), 141.21 (qC), 141.77 (qC), MS (CI) *m*/*z* 429.3 (M+H) $C_{24}H_{32}O_3SN_2$. HRMS: *m*/*z* calculated for $C_{24}H_{32}O_3SN_2$: 428.2134; found 428.21336.

4.4.3. Bis[N-(R)-prolinylmethylphenyl] sulfoxide ***10b***. Bis[*N*-(*R*)-prolinylmethylphenyl] sulfoxide **10b** was obtained in the same way as **10a**, starting from bis(mesyloxymethylphenyl) sulfoxide and (*R*) prolinol. 0.5996 (73.4%); $[\alpha]_D$=+62.8 (*c* 1, $CHCl_3$).

4.5. The reactions of asymmetric synthesis

The reactions of asymmetric synthesis were performed according to the literature procedures: the diethylzinc addition to benzaldehyde,[7] the aldol condensation[18] and the Mannich reaction.[6] The detailed descriptions are given in the Supplementary data.

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Supplementary data

Supplementary data (NMR spectra of **9** and **10**; general methods of the asymmetric syntheses and selected HPLC analyses of their products) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.05.103.

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