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Efficient catalysts for asymmetric Mannich reactions

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Efficient chiral catalysts for direct asymmetric three-component Mannich reactions of ketones, aldehydes and an amine (*p*-anisidine) have been developed. The corresponding β-amino carbonyl compounds (Mannich adducts) were obtained in good chemical yields and excellent enantio- and diastereoselectivities. The reaction conditions have been optimized by invoking ultrasonication and the influence of some structural moieties of the catalysts on the chemical yield and stereoselectivity of the Mannich products has been evaluated.

Introduction

The synthesis of chiral, enantiomerically pure compounds is an important aspect of synthetic organic chemistry due to the importance of single stereoisomers in industrial sectors (*e.g.* pharma and food). As a result, the design and synthesis of appropriate catalysts for asymmetric reactions is crucial to be able to create chiral products in a highly enantioselective manner.

The asymmetric Mannich reaction is synthetically useful for the construction of nitrogen-containing chiral molecules.[1,2] An efficient proline-promoted three-component Mannich reaction was developed by List *et al.*[3,4] Similar results concerning proline-catalyzed Mannich reactions were described by Barbas and co-workers,[5] albeit the latter approach involved the use of preformed imines.

Recent developments on asymmetric Mannich reactions include asymmetric catalysis using enantiopure scandium(III),[6,7] copper,[8,9] and palladium complexes.[10] Nevertheless, the majority of Mannich reactions are still based on enamine catalysis and new examples keep emerging, thereby continuously increasing the scope. List *et al.* developed a method for the one-pot asymmetric synthesis of diaminoaldehydes with very high stereoselectivities from acetaldehyde and various *N*-Boc imines.[11] One year later, an enantioselective route to carbamate- and benzoate-protected β-aminoaldehydes and β-amino acids was reported by Zhao and co-workers.[12] In the same year, Sebesta and co-workers introduced L-proline-derived sulfonamides as very efficient catalysts in the Mannich reaction of cyclohexanone with *N*-PMP-protected α-imino ethylglyoxylate in different solvents.[13] More recently, Maruoka and co-workers reported a stereocontrolled synthesis of vicinal diamines by asymmetric Mannich reaction of *N*-protected aminoacetaldehydes.[14]

In the past few years, we designed a series of chiral organocatalysts, containing hydroxyl, sulfinyl and amino moieties, with two stereogenic centers, one located on the sulfinyl sulfur atom and the other on the carbon atom in the amine moiety[15] (Fig. 1). These catalysts were shown to efficiently catalyze various enantioselective reactions for asymmetric carbon–carbon bond formation. In particular, the catalysts containing secondary amines turned out to be useful for the stereoselective nitroaldol (Henry) reaction,[16] the aza-Henry reaction[17] and the asymmetric direct aldol reaction.[18]

The ones bearing chiral aziridinyl substituents proved efficient for enantioselective diethylzinc and phenylethynylzinc additions to aldehydes,[19,20] and enantioselective conjugate Michael addition of diethylzinc to enones.[21] Moreover, it was possible to access both enantiomeric products of these reactions using readily available enantiopure diastereomeric catalysts. Following up on the aforementioned results, we decided

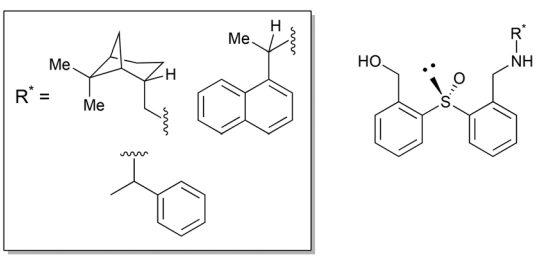

Fig. 1 Enantiopure sulfoxide-based catalysts bearing chiral amines.

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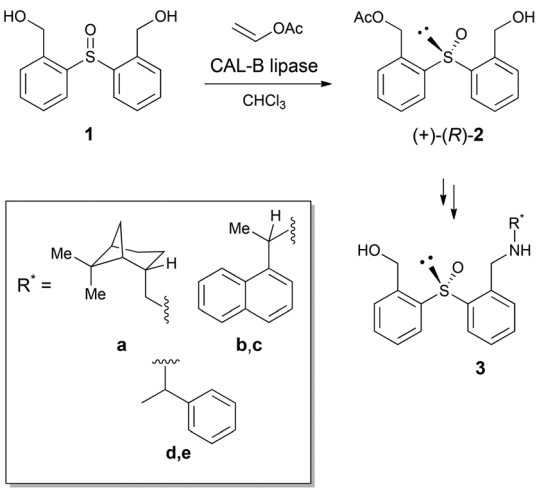
to apply our catalysts in three-component Mannich reactions using the standard enamine-mediated Mannich conditions.[4]

Results and discussion

Synthesis and screening of the ligands

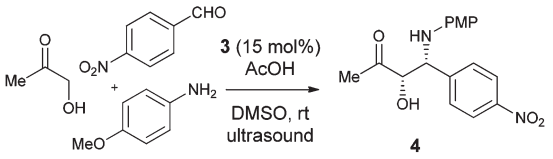
Five chiral catalysts **3a–e**, derived from (−)-*cis*-myrtanylamine (**a**), (−)-(*S*)- and (+)-(*R*)-1-(1′-naphthyl)ethylamine (**b** and **c**, respectively) and (−)-(*S*)- and (+)-(*R*)-phenylethylamine (**d** and **e**, respectively), were synthesized as described previously (Scheme 1).[15] In order to study the catalytic activity of the catalysts in the asymmetric three-component Mannich reaction, we chose the process involving hydroxyacetone, *p*-anisidine and *p*-nitrobenzaldehyde (Table 1) as a benchmark reaction. Initially, standard Mannich conditions were applied (DMSO as solvent, room temperature) using 35 mol% of catalyst **3c**. Since the reaction proceeded rather slowly, a catalytic amount (15 mol%) of acetic acid was added. This resulted after 48 h in the formation of the corresponding Mannich adduct in good ee (around 80%), but unsatisfactory chemical yield (approximately 40%). In order to enhance the reaction rate, we were inspired by a publication from the Kantam group,[22] who demonstrated an advantageous effect of ultrasound treatment on Mannich reactions both in terms of yield and ee. Thus, the reaction was repeated under identical conditions, but now subjected also to ultrasound. Gratifyingly, after 1 h, TLC showed complete conversion of the reaction. The results for the other catalysts are collected in Table 1.

It shows that catalyst **3a**, bearing the (−)-*cis*-myrtanylamine moiety and catalysts **3d–e** (bearing (−)-(*S*)- and (+)-(*R*)-phenylethylamine), exhibited only moderate catalytic activity in this process (entries 1, 4 and 5, respectively). On the other hand, catalysts **3b** and **c**, containing the enantiomeric 1-(1′-naphthyl)-ethylamine moieties, appeared more effective (entries 2 and 3), providing product **4** in high yield and excellent ee. Considering the outcome, we assume that the main stereocontrol is exerted by the stereogenic centers located on the amine moieties.



Scheme 1 Synthesis of catalysts **3a–c**.

Table 1 Screening of catalysts **3**



		Product **4**			
Entry	Catalyst	Yield [%]	$[\alpha]_D$ [a]	ee[b] (%)	dr[c]
1	**3a**	62	−2.0	57	13 : 1
2	**3b**	80	+3.3	91	18 : 1
3	**3c**	85	−3.5	97	20 : 1
4	**3d**	58	+1.9	54	12 : 1
5	**3e**	60	−2.0	56	13 : 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.

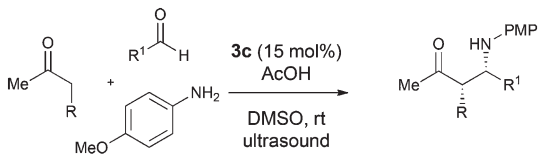
Catalysts **3b** and **c** have the same absolute configuration at the sulfinyl sulfur atom (*R*) and opposite configurations on the amine moieties ((*S*) and (*R*), respectively) leading to opposite enantiomers of product **4.** The slight differences in ee between entries 2 and 3 might be explained in terms of 'matched' and 'mismatched' interactions with the stereogenic sulfinyl center.

An additional experiment using lower catalyst **3c** loading (10 mol%) was performed and the corresponding Mannich adduct **4** was obtained in lower chemical yield and ee (79% and 88%, respectively).

Asymmetric Mannich reactions in the presence of catalyst 3c

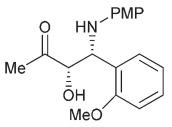
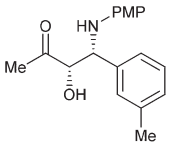
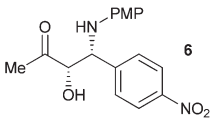
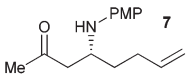
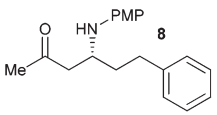
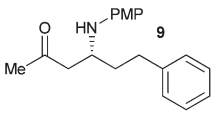
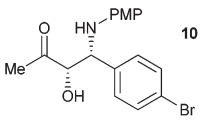
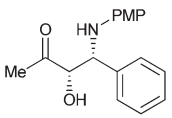
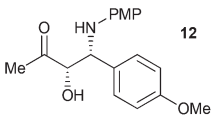
On the basis of the screening results, we decided to determine the scope of the activity of catalyst **3c**. It was therefore applied in asymmetric three-component Mannich reactions involving acetone (R = H) or hydroxyacetone (R = OH) as ketone, various aldehydes and *p*-anisidine as starting materials under identical reaction conditions as in the screening experiments (Scheme 2). The results of these Mannich transformations are shown in Table 2.

Inspection of Table 2 makes it clear that catalyst **3c** efficiently catalyzes the title reaction leading to the appropriate Mannich adducts **4–12.** Only in the case of entry 2, where an aliphatic aldehyde was applied, the corresponding chiral product was obtained in lower chemical yield and lower enantioselectivity (65 and 78%, respectively). In the other entries, the enantiopure Mannich adducts were formed in high chemical yields (82–93%), excellent enantioselectivities (94–99% ee) and generally high diastereoselectivities. In the reaction of hydroxyacetone and *p*-methoxybenzaldehyde (entry



Scheme 2 Mannich reaction promoted by catalyst **3c**.

Table 2 Asymmetric Mannich reactions promoted by catalyst **3c**

		Characterization			
Entry	Mannich product	Yield (%)	$[\alpha]_D$ [a]	ee[b] (%)	dr[c]
1	 **4**	92	+2.1	89	4 : 1
2	 **5**	91	+8.2	91	6 : 1
3	 **6**	85	−3.5	97	20 : 1
4	 **7**	65	+7.6	78	—
5	 **8**	82	+11.2	95	—
6	 **9**	91	−13.5	99	15 : 1
7	 **10**	93	+1.0	96	15 : 1
8	 **11**	86	+52.6	94	9 : 1
9	 **12**	90	−1.4	65	3 : 1

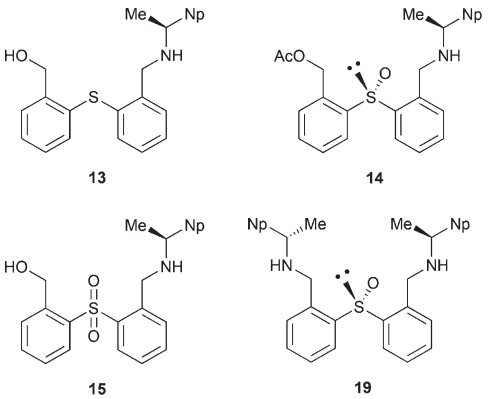
[a] In chloroform (c = 1). [b] Determined by chiral HPLC for the major diastereoisomer. [c] Based on ^{1}H NMR data of the crude product.

9), the product was formed in good chemical yield, but with a lower ee value. Similar findings for L-proline-catalyzed Mannich reaction were reported in the literature.[4]

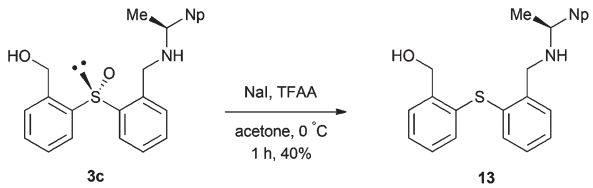
Influence of hydroxyl and sulfinyl groups on the stereochemistry of the process

In order to verify the influence of the sulfinyl and hydroxy moieties on the stereochemical outcome and chemical yield of the Mannich reactions, compounds **13–15** and **19** were synthesized (Scheme 3).

Compound **13** contains the sulfide instead of the sulfinyl moiety and was obtained in 40% yield from catalyst **3c** using a mild reduction method as described by Oae and Drabowicz[23]



Scheme 3 Catalysts **13**, **14**, **15** and **19**.



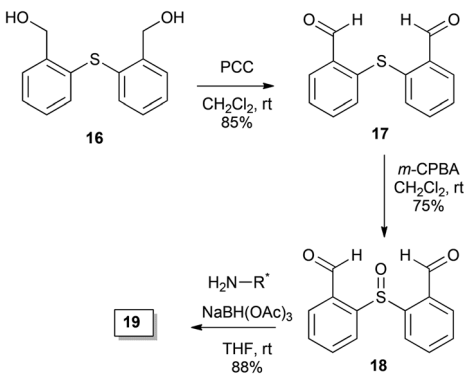
Scheme 4 Synthesis of catalyst **13**.

involving treatment with trifluoroacetic anhydride in the presence of sodium iodide in acetone at 0 °C (Scheme 4).

The acetylated derivative **14** was synthesized as described previously.[15] Sulfone **15** was obtained by oxidation of catalyst **3c** with *m*-CPBA. Diamine **19** was synthesized starting from bis(hydroxymethylphenyl)sulfide **16**, which upon PCC-mediated oxidation[24] of the diol to dialdehyde **17**, oxidation to the sulfoxide **18** with *m*-CPBA and subsequent reductive amination[25] with the aid of sodium triacetoxyborohydride gave the final diamine structure **19** in an overall yield around 60% (Scheme 5).

All amines **13–15** and **19** were tested as catalysts under the optimal Mannich conditions using hydroxyacetone, *p*-nitrobenzaldehyde and *p*-anisidine as starting materials (Table 3).

Table 3 clearly shows that modification of the catalyst, either by the protection of the alcohol (entry 2), or removal of



Scheme 5 Synthesis of catalyst **19**.

Table 3 Studies on the influence of the sulfinyl and hydroxy groups

		Product **4**			
Entry	Catalyst	Yield (%)	$[\alpha]_D$ [a]	ee[b] (%)	dr[c]
1	**13**	62	−1.8	50	9 : 1
2	**14**	58	−1.9	53	9 : 1
3	**15**	52	−1.7	48	7 : 1
4	**19**	94	−3.6	99	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.

the sulfinyl stereogenic center by reduction or oxidation (entries 1 and 3, respectively), leads to the corresponding Mannich adduct in moderate chemical yield and considerably lower enantiomeric excess. These data show that, although the main stereocontrol is exerted by the stereogenic centers located on the amine moiety (*vide supra*), the combination of the free alcohol and the sulfinyl moiety in the catalyst has a positive effect on the enantioselectivity of the title reaction. On the other hand, replacement of the hydroxy group by a chiral amine moiety, to produce the diamino derivative **19**, caused an enhancement in chemical yield and stereoselectivity of the Mannich product (entry 4). As the absolute configuration of both amino moieties is the same, the sulfinyl group is not a stereogenic centre anymore, which again shows the more decisive role of the stereogenic centre located in the amine part of the catalyst in the stereoselectivity of the reaction. Hence, diamine catalysts seem to be more efficient than amino alcohols in asymmetric three-component Mannich reactions.

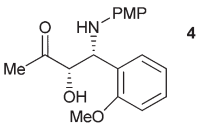
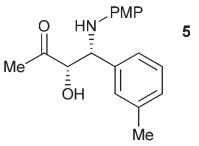
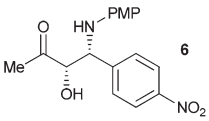
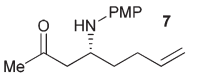
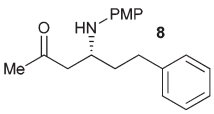
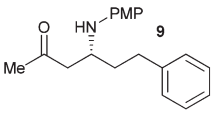
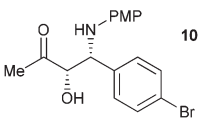
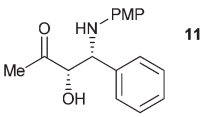
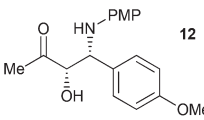
Asymmetric Mannich reactions in the presence of catalyst 19

Since catalyst **19** exhibited the highest efficiency in terms of chemical yield and stereoselectivity of the chiral Mannich product, we decided to reassess all the substrates from Table 2 and subjected them to the title reaction under optimized conditions (Scheme 6).

The results of these transformations are shown in Table 4.

Inspection of Table 4 clearly shows that all the results in terms of chemical yield and stereoselectivities have been improved by the use of diamine catalyst **19**.

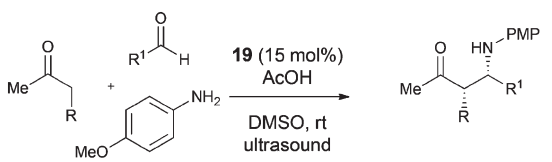
Table 4 Asymmetric Mannich reactions promoted by catalyst **19**

		Characterization			
Entry	Mannich product	Yield (%)	$[\alpha]_D$ [a]	ee[b] (%)	dr[c]
1	 **4**	96	+2.2	89	4 : 1
2	 **5**	95	+8.6	91	6 : 1
3	 **6**	94	−3.6	99	20 : 1
4	 **7**	70	+8.2	84	—
5	 **8**	88	+11.7	99	—
6	 **9**	95	−13.5	99	15 : 1
7	 **10**	98	+1.0	98	15 : 1
8	 **11**	91	+54.3	97	9 : 1
9	 **12**	90	−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.

Conclusions

Efficient chiral catalysts bearing two stereogenic centers, one located on the sulfinyl sulfur atom and the other on the carbon atom in the chiral amine moiety, were found to be efficient in effecting asymmetric three-component Mannich reactions. By systematically modifying the catalyst, we showed that the chiral amine moiety had the largest influence on the stereochemistry of the reaction. The introduction of a second chiral amine moiety in the catalyst improved both chemical yield and stereoselectivity of the asymmetric Mannich process.



Scheme 6 Mannich reaction promoted by catalyst **19**.

Experimental section

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 F_{254}) with the indicated solvent mixture. Detection was performed with UV-light. Optical rotations were determined with a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a Bruker DMX 300 spectrometer at 300 MHz in $CDCl_3$. Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as an internal standard. Coupling constants are reported as *J*-values in Hz. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI) or a MAT900 (EI, CI and ESI). The enantiomeric excess (ee) values were determined by chiral HPLC (Chiralpak AD-H).

Synthesis of catalysts 3a–e

Chiral diastereomeric catalysts **3a–e** and **14** were synthesized according to procedures described previously.[15]

Synthesis of catalyst 13

Catalyst **13** was synthesized using a procedure described by Drabowicz and Oae.[23] A round-bottom flask was charged with acetone (3 mL), catalyst **3c** (200 mg, 0.48 mmol) and sodium iodide (174 mg, 1.16 mmol). The flask was immersed in an ice bath (0 °C) and an acetone solution of trifluoroacetic anhydride (264 mg, 1.25 mmol, 0.175 mL) was slowly added with stirring. After 0.5 h, TLC showed completion of the reduction of the sulfoxide. After acetone has been evaporated, water was added and the mixture was extracted with diethyl ether (7 mL). The ether extract was washed with a sodium thiosulfate solution and water. Upon evaporation of ether from the dried extract, virtually pure sulfide was obtained. Final purification was performed by filtration through a short silica gel column with heptane as an eluent to yield **13** (77 mg, 40%) as a yellowish oil. $[\alpha]_D = -24.6$ ($CHCl_3$, $c = 1$); ^{1}H NMR ($CDCl_3$): δ = 1.44 (d, J = 6.0 Hz, 3H), 2.80 (br s, 2H), 3.85 (s, 2H), 4.65 (s, 2H), 4.55 (q, J = 6.0 Hz, 1H), 7.10–8.13 (m, 15H); ^{13}C NMR ($CDCl_3$): δ = 22.16 (CH_3), 50.21 (CH), 57.64 (CH_2N), 63.52 (CH_2O), 124.38 (C_{ar}), 124.87 (C_{ar}), 125.38 (C_{ar}), 126.12 (C_{ar}), 126.35 (C_{ar}), 126.78 (C_{ar}), 127.1 (C_{ar}), 127.37 (C_{ar}), 127.48 (C_{ar}), 127.95 (C_{ar}), 128.38 (C_{ar}), 129.88 (C_{ar}), 130.52 (C_{ar}), 131.54 (C_{ar}), 131.67 (C_{ar}), 132.19 (C_{ar}), 132.78 (C_{ar}), 133.56 (C_{ar}), 133.59 (C_{ar}), 134.76 (C_{ar}), 134.79 (C_{ar}), 142.68 (C_{ar}); HRMS (ESI) calcd for $C_{26}H_{25}NOS$: 400.3624; found: 400.3628 (M + H).

Synthesis of catalyst 15

Catalyst **3c** (0.10 g, 0.24 mmol) was dissolved in dry dichloromethane (10 mL) and MCPBA (0.17 g, 0.98 mmol) was added and the solution was stirred for 24 h at room temperature. After this time the reaction mixture was washed with 5% aqueous Na_2CO_3, extracted with dichloromethane and dried over anhydrous $MgSO_4$. After evaporation of the solvent the crude mixture was purified *via* column chromatography on silica gel using a mixture of ethyl acetate with heptane (in gradient) as an eluent to afford the corresponding sulfone **15** as yellowish foam (0.078 g, 78%); $[\alpha]_D = -8.3$ ($CHCl_3$, $c = 1$); ^{1}H NMR ($CDCl_3$): δ = 1.93 (d, J = 6.9 Hz, 3H), 4.44–4.62 (m, 4H), 5.89 (q, J = 6.9 Hz, 1H), 7.10–8.10 (m, 15H); ^{13}C NMR ($CDCl_3$): δ = 20.9 (CH_3), 39.91 (CH), 60.91 (CH_2N), 61.75 (CH_2O), 125.22 (C_{ar}), 125.43 (C_{ar}), 126.81 (C_{ar}), 127.34 (C_{ar}), 127.52 (C_{ar}), 127.75 (C_{ar}), 128.33 (C_{ar}), 128.54 (C_{ar}), 129.13 (C_{ar}), 129.22 (C_{ar}), 129.85 (C_{ar}), 130.12 (C_{ar}), 130.32 (C_{ar}), 131.10 (C_{ar}), 133.72 ($C_{q\ ar}$), 134.12 ($C_{q\ ar}$), 136.72 ($C_{q\ ar}$), 137.93 ($C_{q\ ar}$), 138.56 ($C_{q\ ar}$), 138.63 ($C_{q\ ar}$), 140.0 ($C_{q\ ar}$); HRMS (ESI) calcd for $C_{26}H_{24}NO_3S$: 431.3267; found: 431.3264 (M + H).

Synthesis of catalyst 19

Bis(hydroxymethylphenyl)sulfide **16** was synthesized according to the procedure described previously.[15] The next step leading to dialdehyde **17** was performed by following the procedure described by Hsu and co-workers.[24] A mixture of pyridinium chlorochromate (PCC) (6.86 g, 31.5 mmol) in dry dichloromethane (42 mL) was added dropwise to a solution of **16** (2.02 g, 8.23 mmol) in dry dichloromethane (30 mL). After stirring at room temperature for 4 h, the reaction mixture was filtered. The residue was washed with dichloromethane (3 × 20 mL) and diethyl ether (20 mL). The filtrate and washings were combined and concentrated *in vacuo* to give **17** as a yellowish solid (1.7 g, 85%), m.p. 97 °C; ^{1}H NMR ($CDCl_3$): δ = 7.15 (d, J = 6.0 Hz, 2H), 7.40–7.51 (m, 4H), 7.95 (dd, J = 6.0, 3.0 Hz, 2H), 10.35 (s, 1H).

Oxidation of the sulfide **17** to the corresponding sulfoxide **18** was performed by following a procedure described by Daines *et al.*[26] Sulfide (dialdehyde) **17** (1.5 g, 6.20 mmol) was dissolved in dry dichloromethane (15 mL) and cooled to 0 °C. MCPBA (1.33 g, 6.55 mmol) was added and the solution was stirred for 30 min at room temperature. After this time the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent the crude mixture was purified *via* column chromatography on silica gel using a mixture of ethyl acetate with heptane (in gradient) as an eluent to afford the desired sulfoxide as yellowish foam (1.20 g, 75%); ^{1}H NMR ($CDCl_3$): δ = 7.57–7.61 (m, 2H), 7.98–8.01 (m, 2H), 8.08–8.10 (m, 2H), 10.7 (s, 1H).

Reductive amination of dialdehyde (sulfoxide) **18** was carried out using a method described by Abdel-Magid *et al.*[25] Dialdehyde **18** (0.8 g, 4.40 mmol) and (+)-(*R*)-1-(1′-naphthyl)-ethylamine (1.50 g, 8.77 mmol) were dissolved in anhydrous THF (30 mL) and then treated with sodium triacetoxyborohydride (2.61 g, 12.31 mmol). The reaction mixture was stirred at room temperature for 2 h. Finally, the mixture was quenched by adding a saturated aqueous solution of $NaHCO_3$, and the product was extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated to give the crude product. Column chromatography on silica gel (ethyl acetate with heptane in gradient as an eluent) provided the catalyst **19** as a yellowish oil (2.21 g, 88%); $[\alpha]_D = -47.3$ ($CHCl_3$, $c = 1$); ^{1}H NMR ($CDCl_3$): δ = 1.41 (d, J = 6.9 Hz, 6H), 3.95 (s, 2H), 4.29 (q, J = 6.0 Hz, 2H), 6.89–8.01 (m, 22H); ^{13}C NMR ($CDCl_3$): δ = 22.48 ($2CH_3$), 49.10 ($2CH$), 60.34 ($2CH_2N$), 123.92 ($2C_{ar}$), 124.32 ($2C_{ar}$), 125.63 ($2C_{ar}$), 126.15 ($2C_{ar}$), 126.82 ($2C_{ar}$), 127.10 ($2C_{ar}$), 127.62 ($2C_{ar}$), 127.95 ($2C_{ar}$), 128.42 ($2C_{ar}$), 128.57 ($2C_{ar}$), 130.11 ($2C_{ar}$), 131.24 ($2C_{ar}$), 134.23

($2C_{ar}$), 135.72 ($2C_{ar}$), 137.23 ($2C_{ar}$), 141.52 ($2C_{ar}$); HRMS (ESI) calcd for $C_{38}H_{36}N_2OS$: 569.3579; found: 569.3584 (M + H).

Asymmetric three-component Mannich reaction – general procedure

A round-bottom flask containing a mixture of the catalyst (0.15 mmol), *p*-anisidine (0.123 g, 1 mmol), ketone (2 mL in the case of acetone and 0.74 g, 10 mmol in the case of hydroxyacetone), glacial acetic acid (10 μL, 0.15 mmol) and an aldehyde (1.1 mmol) in DMSO (8 mL) was immersed in an ultrasonic bath and was sonicated for 1 h at room temperature. After this time, a phosphate buffer solution (pH 7.4) was added and the mixture was extracted with ethyl acetate. After drying with anhydrous $MgSO_4$ and evaporation of the solvent, the crude mixture was subjected to column chromatography (heptane with ethyl acetate in gradient as an eluent) to afford chiral Mannich products **4–10**. The values of their chemical yields, optical rotations, ee's and dr's are collected in Tables 1–3, respectively.

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenylamino)-4-(2-methoxyphenyl)butan-2-one (**4**), a yellow oil; ^{1}H NMR ($CDCl_3$): 2.37 (s, 3H), 3.71 (s, 3H), 3.78 (br s, 1H), 3.99 (s, 3H), 4.40 (br s, 1H), 4.57 (d, J = 2.0 Hz, 1H), 5.39 (d, J = 2.0 Hz, 1H), 6.48–6.51 (m, 2H), 6.68–6.97 (m, 2H), 6.86–6.97 (m, 2H), 7.22–7.32 (m, 2H). Other spectroscopic data are in agreement with the literature.[27]

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenylamino)-4-(3-methylphenyl)butan-2-one (**5**), yellowish foam; ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H), 2.37 (s, 3H), 3.72 (s, 3H), 3.77 (br s, 1H), 4.34 (br s, 1H), 4.43 (d, J = 2.6 Hz, 1H), 4.87 (d, J = 2.6 Hz, 1H), 6.52–6.54 (m, 2H), 6.70–6.72 (m, 2H), 7.08–7.29 (m, 4H). Other spectroscopic data are in agreement with the literature.[27]

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenylamino)-4-(4-nitrophenyl)butan-2-one (**6**), yellowish foam; ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3H), 3.62 (s, 3H), 3.88 (br s, 1H), 4.25 (br s, 1H), 4.40 (d, J = 1.0 Hz, 1H), 5.00 (d, J = 1.0 Hz, 1H), 6.49–6.50 (m, 2H), 6.68–6.74 (m, 2H), 7.51–7.53 (m, 2H), 8.25–8.27 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(*R*)-4-(4-Methoxyphenylamino)oct-7-en-2-one (**7**), a yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.58–1.65 (m, 2H), 2.12 (s, 3H), 2.51–2.74 (m, 2H), 3.49 (br s, 1H), 3.75–3.80 (m, 1H), 3.75 (s, 3H), 4.94–5.05 (m, 2H), 5.75–5.85 (m, 1H), 6.52–6.54 (m, 2H), 6.75–6.57 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(*R*)-4-(4-Methoxyphenylamino)-6-phenylhexan-2-one (**8**), a yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.85 (m, 2H), 2.12 (s, 3H), 2.52–2.83 (m, 4H), 3.49 (br s, 1H), 3.74–3.76 (m, 1H), 3.75 (s, 3H), 6.49–6.52 (m, 2H), 6.74–6.76 (m, 2H), 7.18–7.25 (m, 3H), 7.26–7.30 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenylamino)-4-(4-cyanophenyl)-butan-2-one (**9**), yellowish foam; ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 3.25 (br s, 1H), 3.60 (s, 3H), 3.85 (br s, 1H), 4.40 (d, J = 1.0 Hz, 1H), 4.92 (d, J = 1.0 Hz, 1H), 6.42–6.47 (m, 2H), 6.60–6.63 (m, 2H), 7.45–7.48 (m, 2H), 7.54–7.60 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(3*S*,4*R*)-4-(4-Bromophenyl)-3-hydroxy-4-(4-methoxyphenylamino)butan-2-one (**10**), a yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3H), 3.27 (br s, 1H), 3.65 (s, 3H), 3.95 (br s, 1H), 4.42 (d, J = 1.0 Hz, 1H), 4.90 (d, J = 1.0 Hz, 1H), 6.48–6.51 (m, 2H), 6.61–6.67 (m, 2H), 7.39–7.45 (m, 2H), 7.50–7.54 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenylamino)-4-phenylbutan-2-one (**11**), a colorless solid; ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3H), 3.30 (br s, 1H), 3.62 (s, 3H), 4.38 (br s, 1H), 4.42 (d, J = 1.0 Hz, 1H), 4.86 (d, J = 1.0 Hz, 1H), 6.42–6.48 (m, 2H), 6.65–6.71 (m, 2H), 7.24–7.28 (m, 2H), 7.31–7.37 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

(3*S*,4*R*)-3-Hydroxy-4-(4-methoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (**12**), a yellowish oil; ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3H), 3.35 (br s, 1H), 3.72 (s, 3H), 3.83 (s, 3H), 4.28 (br s, 1H), 4.44 (d, J = 2.0 Hz, 1H), 4.95 (d, J = 2.0 Hz, 1H), 6.52–6.58 (m, 2H), 6.71–6.76 (m, 2H), 6.92–6.98 (m, 2H), 7.38–7.45 (m, 2H). Other spectroscopic data are in agreement with the literature.[4]

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Notes and references

1 (*a*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29; (*b*) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, 5797; (*c*) S. Hoekman, J. M. M. Verkade and F. P. J. T. Rutjes, in *Enantioselective organocatalyzed reactions II*, ed. R. Mahrwald, Springer, Heidelberg, pp. 343–378.

2 For general reviews on organocatalysis, see *e.g.*: *Asymmetric organocatalysis*, ed. A. Berkessel and H. Gröger, Wiley-VCH, Weinheim, 2005; *Enantioselective organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007.

3 B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336.

4 B. List, P. Pojarliev, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827.

5 W. Notz, S. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka and C. F. Barbas III, *Adv. Synth. Catal.*, 2004, **346**, 1131.

6 C. Xiao-Hua, G. Hui and X. Bing, *Eur. J. Chem.*, 2012, **3**, 258.

7 Q. Zhang, Y. H. Hui, X. Zhou, L. L. Lin, X. H. Liu and X. M. Feng, *Adv. Synth. Catal.*, 2010, **352**, 976.

8 G. Liang, M.-C. Tong, H. Y. Tao and C.-J. Wang, *Adv. Synth. Catal.*, 2010, **352**, 1851.

9 T. Arai, A. Mishiro, E. Matsumura, A. Awata and M. Shirasugi, *Chem.–Eur. J.*, 2012, **18**, 11219.

10 Y. K. Kang and D. Y. Kim, *Tetrahedron Lett.*, 2011, **52**, 2356.
11 C. Chandler, P. Galzerano, A. Michrowska and B. List, *Angew. Chem., Int. Ed.*, 2009, **48**, 1978.
12 L. Deiana, G.-L. Zhao, P. Dziedzic, R. Rios, J. Vesely, J. Ekstr and A. Cordova, *Tetrahedron Lett.*, 2010, **51**, 234.
13 E. Veverkova, J. Strasserova, R. Sebesta and S. Toma, *Tetrahedron: Asymmetry*, 2010, **21**, 58.
14 T. Kano, R. Sakamoto, M. Akakura and K. Maruoka, *J. Am. Chem. Soc.*, 2012, **134**, 7516.
15 M. Rachwalski, M. Kwiatkowska, J. Drabowicz, M. Kłos, W. M. Wieczorek, M. Szyrej, L. Sieroń and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2008, **19**, 2096.
16 M. Rachwalski, S. Leśniak, E. Sznajder and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2009, **20**, 1547.
17 M. Rachwalski, S. Leśniak and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2011, **22**, 1087.
18 M. Rachwalski, S. Leśniak and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2011, **22**, 1325.
19 S. Leśniak, M. Rachwalski, E. Sznajder and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2009, **20**, 2311.
20 M. Rachwalski, S. Leśniak and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2010, **21**, 2687.
21 M. Rachwalski, S. Leśniak and P. Kiełbasiński, *Tetrahedron: Asymmetry*, 2010, **21**, 1890.
22 M. Lakshmi Kantam, C. V. Rajasekhar, G. Gopikrishna, K. Rajender Reddy and B. M. Choudary, *Tetrahedron Lett.*, 2006, **47**, 5965.
23 J. Drabowicz and S. Oae, *Synthesis*, 1977, 404.
24 J.-J. Jiang, T.-C. Chang, W.-L. Hsu, J.-M. Hwang and L.-Y. Hsu, *Chem. Pharm. Bull.*, 2003, **51**, 1307.
25 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.
26 R. A. Daines, P. A. Chambers, I. Pendrak, D. R. Jakas, H. M. Sarau, J. J. Foley, D. B. Schmidt and W. D. Kingsbury, *J. Med. Chem.*, 1993, **36**, 3321.
27 C. Wu, X. Fu and S. Li, *Tetrahedron: Asymmetry*, 2011, **22**, 1063.