Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2754–2760

A multifunctional proline-based organic catalyst for enantioselective aldol reactions

Stefania Guizzetti, Maurizio Benaglia,* Luca Pignataro and Alessandra Puglisi

Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano—via Golgi, 19, I-20133 Milano, Italy

Received 11 August 2006; revised 11 October 2006; accepted 16 October 2006

Dedicated to Professor Mauro Cinquini for his 65th birthday

Abstract—The synthesis of multifunctional organic catalysts, easily obtained by the condensation of (*S*)-proline with 1,1′-binaphthyl-2,2′-diamine is reported. These C_2 as well as C_1 symmetric prolinamides were shown to be able to promote the direct aldol condensation between acetone, methoxyacetone or cyclohexanone and different aldehydes in very good yields and high enantioselectivities.

1. Introduction

Recently a great deal of attention has been devoted to the possibility of developing enantioselective catalytic processes with high levels of chemical efficiency and stereocontrol promoted, not by organometallic species but by wholly organic molecules.[1] Over the last five years, properly called 'the golden age of organocatalysis', for many reactions once promoted only by metal-based catalysts one or more organocatalytic versions have been developed, where an organic catalyst has been defined as 'an organic molecule of relatively low molecular weight able to promote a reaction in substoichiometric quantity'.[2]

In this field, a landmark was reached by the seminal work of List and Barbas, which employed (*S*)-proline to promote the direct intermolecular aldol condensation of acetone and hydroxyacetone with aldehydes.[3]

Since then, several proline[4] derivatives[5] have been prepared and tested in aldol reactions,[6] however a large loading of the catalyst (30 mol %) is often required and in most cases only fair enantioselectivities were observed for reactions with aromatic aldehydes, with a few exceptions.[7,8]

Prompted by recent contributions in the field,[8] we herein report the synthesis of a family of multifunctional organic catalysts, easily obtained by the condensation of (*S*)-proline with 1,1′-binaphthyl-2,2′-diamine,[9] that were shown to be able to promote the direct aldol condensation between acetone or cyclohexanone and different aldehydes in very good yields and high enantioselectivities.[10]

2. Results and discussion

Following our interest in the development of chiral organic catalysts easily prepared from inexpensive, commercially available, enantiopure materials whose manipulation should be kept to a minimum,[11] we decided to attach the proline moiety to a 1,1′-binaphthyl-2,2′-diamine scaffold, which offers the possibility of preparing C_2 as well as C_1 symmetric compounds.

The simple condensation of (*S*)-Cbz proline with the racemic 1,1′-binaphthyl-2,2′-diamine followed by deprotection through hydrogenolysis afforded in only two steps the two diastereoisomeric, enantiomerically pure organocatalysts **1** and **2** in quantitative yield, easily separated by chromatographic purification (Fig. 1).

The bis-prolinamide derivatives were tested in the aldol condensation between acetone and 4-nitro benzaldehyde, in two different solvent systems, acetone only and a ketone/chloroform mixture (Scheme 1).[12] Both catalysts were seen to be very reactive at rt, affording the product in quantitative yield after 12 h of reaction time (Table 1,

* Corresponding author. Tel.: +39 025031 4171; fax: +39 025031 4159; e-mail: maurizio.benaglia@unimi.it

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.10.018

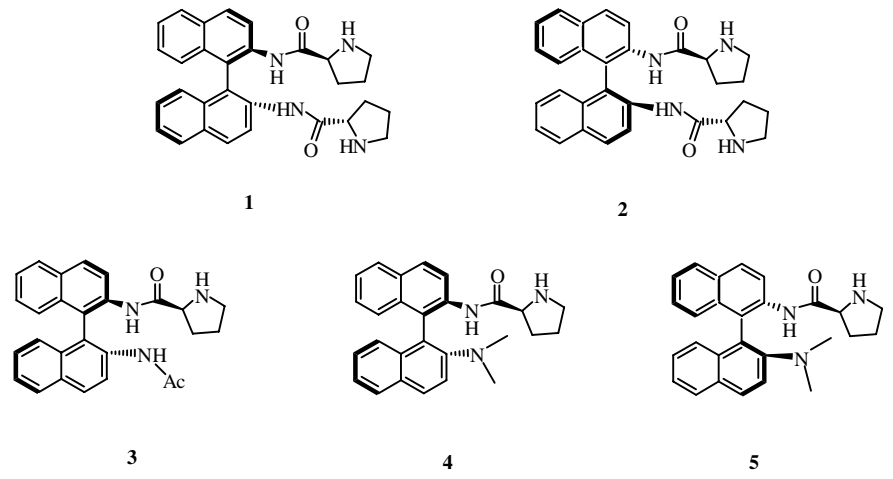
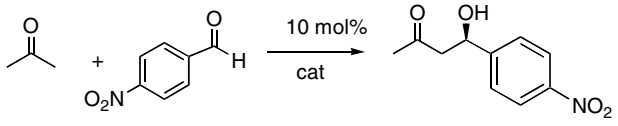


Figure 1. (*S*)-Proline-based catalysts **1**–**5**.



Scheme 1. Aldol reaction promoted by catalysts **1**–**5**.

entries 1, 4 and 9) and comparable enantioselectivities (about 45% ee). The reaction medium does not seem to play a predictable role in the reaction outcome.

Lowering of the reaction temperature allowed us to improve the enantioselectivity of the process, even though longer reaction times were necessary to obtain the product in good yields. Interestingly, catalyst **1** seems to be moderately effected by the condensation temperature (enantioselectivity was increased from 44% at rt to 67% at −27 °C, but it was not further improved at −50 °C, entries 2, 3 and 5). However, the diastereoisomeric catalyst **2** was shown to be more sensitive to the temperature and promoted the aldol condensation with 67% ee at −27 °C and with 85% ee at −50 °C[13] (entries 10 and 11).

In order to further explore possible catalyst structure modification, based on the recent work by Gong,[7] and Xiao and Zhao,[8] we decided to prepare also multifunctional, C_1-symmetric prolinamides, bearing only one proline residue.

Following a known procedure,[14] (*R*)-1,1′-binaphthyl-2,2′-diamine was monoacetylated and then coupled to (*S*)-Boc proline to give, after deprotection, catalyst **3** in 65% overall yield. Starting from the mono *N*-acetyl (*R*)-binaphthyl diamine, catalyst **4** was synthesised in only four steps and in 75% overall yield. Analogously by employing (*S*)-1,1′-binaphthyl-2,2′-diamine, organocatalyst **5** was prepared in 71% yield over five steps and with only one chromatographic purification.

The results of the new C_1-symmetric organocatalysts employed in the test reaction with 4-nitro benzaldehyde are shown in Table 2.

Both prolinamides **3** and **4** catalysed the reaction with high enantioselectivity at rt, affording the product with 85% ee.[15] However, while the stereochemical efficiency of **3** did not change by running the reaction at a low temperature (entries 1 and 2 vs entry 3) and the aldol product could be obtained with 80% ee even by running the condensation at 60 °C (entry 4); catalyst **4** showed a more marked dependence on the temperature. At −27 °C in acetone, prolina-

Table 1. Enantioselective aldol reaction promoted by organic catalysts **1** and **2**

Entry	Solvent	Temperature (°C)	Reaction time (h)	Catalyst	Yield[a] (%)	ee[b] (%)
1	Acetone	25	12	**1**	98	44
2	Acetone	−27	88	**1**	74	67
3	Acetone	−50	88	**1**	30	67
4	Acetone/$CHCl_3$	25	12	**1**	80	60
5	Acetone/$CHCl_3$	−27	88	**1**	55	65
6	Acetone	25	12	**2**	98	45
7	Acetone	−27	88	**2**	41	55
8	Acetone	−50	88	**2**	21	65
9	Acetone/$CHCl_3$	25	12	**2**	98	44
10	Acetone/$CHCl_3$	−27	88	**2**	57	67
11	Acetone/$CHCl_3$	−50	88	**2**	41	85

[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Chiracel OJ-H).

Table 2. Enantioselective aldol reaction promoted by organic catalysts **3**–**5**

Entry	Solvent	Temperature (°C)	Reaction time (h)	Catalyst	Yield[a] (%)	ee[b] (%)
1	Acetone	25	12	**3**	65	85
2	Acetone/$CHCl_3$	25	12	**3**	64	87
3	Acetone/$CHCl_3$	−27	88	**3**	40	87
4	Acetone/$CHCl_3$	60	8	**3**	71	80
5	Acetone	25	12	**4**	90	85
6	Acetone	−27	88	**4**	92	90
7	Acetone/$CHCl_3$	25	12	**4**	91	45
8	Acetone/$CHCl_3$	−27	88	**4**	55	91
9	Acetone	25	12	**5**	98	67
10	Acetone/$CHCl_3$	25	12	**5**	98	61
11	Acetone/$CHCl_3$	−27	88	**5**	65	87

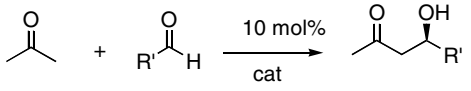
[a] Yields determined after chromatographic purification.
[b] Enantiomeric excess determined by HPLC (Chiracel OJ-H).

mide **4** catalysed the reaction in 92% yield and 90% ee (entries 5 and 6). Comparable enantioselectivities, but lower chemical yields were obtained in an acetone/chloroform mixture (entries 7 and 8).

Finally, catalyst **5** was seen to be less stereoselective at rt than its diastereoisomer **4** (entry 5 vs 9) but promoted the reaction with a similar level of enantioselectivity at −27 °C (87% ee vs 91% ee)[16] (Table 2, entry 11).

It must be noted that all organocatalysts **1**–**5** catalysed the reaction to always afford the same major enantiomer of the β-hydroxy ketone, indicating that the stereochemical outcome of the condensation is regulated by the proline residue. The stereogenic axis of the binaphthyl diamine seems to play an important role in helping the stereocontrol of the condensation. However at this point, it is not easy to identify the matching configurations of the stereogenic elements in the molecule.[17]

The new multifunctional organocatalysts were selected in order to study the aldol condensation of acetone with different aldehydes (Scheme 2). For example, catalyst **4** was also shown to efficiently promote the condensation of aliphatic aldehydes, such as cyclohexanecarboxaldehyde or



Scheme 2. Aldol condensation between acetone and different aldehydes.

pivalaldehyde with 99% ee and 91% ee, respectively (Table 3, entries 2 and 3). The addition of *N*,*N*-dimethylformamide to the reaction mixture allowed us to increase the chemical yield in the condensation of acetone with less reactive aromatic aldehydes; for example, the aldol condensation with benzaldehyde was promoted in 91% yield and 71% ee at 0 °C (Table 3, entry 5 vs entry 4).

Organocatalysts **5** and **4** were also shown to efficiently control the stereochemistry of the reaction of cyclohexanone with 4-nitrobenzaldehyde (Table 4).

The product was obtained after 12 h at rt as an 81/19 *anti*/*syn* mixture with **5** and 84/16 ratio with **4** (entries 1 and 2). Both the diastereo- and enantio-selectivities increased by running the reaction at −27 °C; by employing **4**, a 96/4 *anti*/*syn* ratio was obtained with a 85% ee for the *anti* isomer that was isolated basically as a single product by using catalyst **5** (entries 3 and 4).

In order to further improve the enantioselectivity of the process, the effect of added water was briefly investigated.[18] In the condensation of cyclohexanone with 4-nitrobenzaldehyde, the addition of 3 mol/equiv of water exerted a beneficial effect both on the chemical and the stereochemical efficiency of the catalyst (entry 5). A single isomer was isolated in very high yield and with 95% enantiomeric excess.[19]

The condensation of cyclohexanone with other aldehydes was also studied. While catalyst **4** promoted the reaction with benzaldehyde with modest yield and enantioselectivity

Table 3. Aldol condensation between acetone and different aldehydes

Entry	R′	Catalyst	Temperature (°C)	Reaction time (h)	Yield[a] (%)	ee[b] (%)
1	4-NO_2Ph	**4**	−27	88	92	90
2	Cy	**4**	25	12	90	99
3	*t*-Bu	**4**	25	12	81	91
4	Ph	**4**	0	88	15	69
5[c]	Ph	**4**	0	88	91	71

[a] Yields determined after chromatographic purification. Reaction conditions: acetone (0.8 mL), catalyst (0.02 mmol), aldehyde (0.2 mmol).
[b] Enantiomeric excess determined by HPLC on a chiral stationary phase.
[c] Reaction run in the presence of 5 mol/equiv of DMF.

Table 4. Aldol condensation of cyclohexanone with different aldehydes

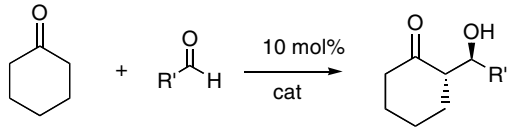
Entry	Catalyst	Reaction time (h)	Temperature (°C)	R	Yield[a] (%)	dr[b] (%)	ee[c] (%)
1	**5**	12	25	*p*-NO_2Ph	55	81/19	71[d]
2	**4**	12	25	*p*-NO_2Ph	60	84/16	57[d]
3	**4**	88	−27	*p*-NO_2Ph	98	96/4	85[d]
4	**5**	88	−27	*p*-NO_2Ph	71	>98/2	87[d]
5[e]	**5**	88	−27	*p*-NO_2Ph	91	>98/2	95[d]
6[f]	**5**	88	−27	*p*-NO_2Ph	67	>98/2	90[d]
7[e]	**4**	88	−27	Ph	35	>98/2	68[d]
8[e]	**4**	88	−27	*o*-ClPh	83	>98/2	85[d]
9[e]	**4**	88	−27	C_6H_{11}	88	>98/2	87[d]

[a] Yields determined after chromatographic purification. Reaction conditions: cyclohexanone (0.8 mL), catalyst (0.02 mmol), aldehyde (0.2 mmol).
[b] Diastereoisomeric ratio determined by NMR and confirmed by HPLC analysis.
[c] Enantiomeric excess determined by HPLC on a chiral stationary phase.
[d] Ee of *anti*-isomer.
[e] Reaction run in the presence of 3 mol/equiv of water.
[f] Reaction run in the presence of 3 mol/equiv of DMF.

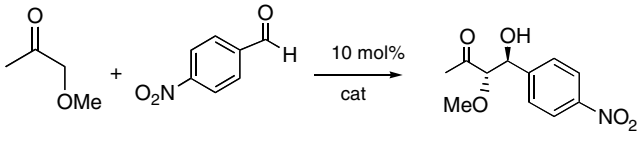
(entry 7), the reaction at −27 °C with *o*-chlorobenzaldehyde afforded the product basically as an *anti* isomer only, in 83% yield and 85% ee (entry 8). Also from the condensation between cyclohexanone and cyclohexane–carboxaldehyde, the product was obtained in very high stereo- and enantio-selectivities (entry 9) (Scheme 3).

The new binaphthyl diamine-based prolinamides were also tested in the aldol condensation of methoxy acetone with 4-nitrobenzaldehyde (Scheme 4 and Table 5). In this case, the C_1-symmetric organocatalysts showed a marked superior efficiency over the C_2-symmetric derivatives; at room temperature *N*-acetyl derivative **3** catalysed the reaction with an 83/17 *anti*/*syn* ratio and 87% ee for the *anti*-isomer (entries 1 vs 2).[20] In this reaction, catalyst **3** performed even better than catalysts **4** and **5**. At −27 °C, catalyst **3** was able to promote the reaction in 91% yield to afford the product as a single isomer in 91% ee (Table 5, entries 3–5).[21]

It is worth mentioning that a preliminary investigation showed that **4** was able to promote a multicomponent Mannich reaction between 4-nitrobenzaldehyde, 4-methoxyaniline and acetone to afford the β-amino ketone with 51% ee at rt[22] (Scheme 5).



Scheme 3. Aldol condensation of cyclohexanone and different aldehydes.

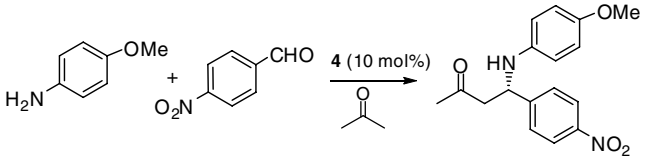


Scheme 4. Aldol condensation between 4-nitrobenzaldehyde and methoxyacetone.

Table 5. Aldol condensation between 4-nitrobenzaldehyde and methoxyacetone

Entry	Catalyst	Reaction time (h)	Temperature (°C)	Yield[a] (%)	dr[b] (%)	ee[c] (%)
1	**2**	12	25	67	70/30	27[d]
2	**3**	12	25	61	83/17	87[d]
3	**3**	88	−27	91	>98/2	91[d]
4	**4**	88	−27	90	77/23	77[d]
5	**5**	88	−27	45	70/30	67[d]

[a] Yields determined after chromatographic purification. Reaction conditions: methoxyacetone (0.8 mL), catalyst (0.02 mmol), aldehyde (0.2 mmol).
[b] Diastereoisomeric ratio determined by NMR and confirmed by HPLC analysis.
[c] Enantiomeric excess determined by HPLC on a chiral stationary phase.
[d] Ee of *anti*-isomer.



Scheme 5. Enantioselective Mannich reaction.

3. Conclusions

In conclusion a new class of multifunctional organocatalyst, easily prepared in a few steps, has been prepared and successfully tested in the aldol condensation of acetone and cyclohexanone with aldehydes. Preliminary experiments showed that these new, versatile organocatalysts were also able to promote with high enantioselectivity, the aldol condensation of methoxy acetone and the Mannich reaction. Further studies regarding the catalyst structure optimisation, investigation of the role of the stereogenic axis of the binaphthyl diamine and application of the novel catalysts in other reactions are currently underway in our group.[23]

4. Experimental

4.1. General methods

TLC was performed on Merck silica gel 60 TLC plates F254 and visualised using either UV or phosphomolibdic acid. Flash chromatography was carried out on silica gel (230–400 mesh). ^{1}H NMR were recorded at 300 MHz with the indicated solvent. ^{13}C NMR were obtained at 75 MHz. Chemical shifts were determined relative to tetramethylsilane (for hydrogen atoms) and residual solvent peaks (for carbon atoms). Optical rotations were obtained on a Perkin–Elmer 241 polarimeter at 589 nm. HPLC for ee determination was performed on Agilent 1100 instrument under the conditions reported below. Catalysts **1** and **2** are known compounds.[10]

4.2. Synthesis of catalyst 3

To a stirred solution of (*S*)-Boc-proline (0.085 g, 0.39 mmol) in dry $CHCl_3$ (2 mL), EDC (0.075 g, 0.39 mmol) and HOBT (0.053 g, 0.039 mmol) were added and the reaction mixture cooled to 0 °C. After (*R*)-*N*-acetyl binaphthyl diamine (0.070 g, 0.21 mmol) in $CHCl_3$ (1 mL) was added, the resulting mixture was allowed to stir at rt for 15 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL), and the organic phase was separated, washed with water, dried over Na_2SO_4, filtered and concentrated under vacuum at room temperature to afford the crude product, which was purified by flash chromatography with a 6/4 hexanes/ethyl acetate mixture as eluant (yield 98%). The deprotection of the Boc group was accomplished by stirring the prolinamide in DCM/TFA (1/1 2 mL) at rt for 15 h. The mixture was cooled at 0 °C, diluted with DCM (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ until the pH was basic. The aqueous phase was extracted twice with DCM and all the organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum at room temperature to afford the product in >98% yield.

Compound **3** white solid, mp 69 °C, then dec. $[\alpha]_D^{23} = +25.3$ (*c* 0.31, DCM); IR (DCM): *v* 1667, 1645, 1501, 1427, 1265 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.47 (d, $J = 8.5$ Hz, 1H), 8.39 (d, $J = 7.9$ Hz, 1H), 8.07 (m, 2H), 7.97 (m, 2H), 7.49 (m, 2H), 7.33 (m, 2H), 7.20 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.3$ Hz, 1H), 7.05 (br s, 1H), 3.80 (br s, 1H), 3.67 (m, 1H), 2.70 (m, 1H), 2.30 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 169.1, 134.9, 134.7, 132.6, 132.5, 131.5, 131.3, 129.9, 129.3, 128.3, 128.1, 127.2, 127.0, 125.6, 125.3, 125.2, 125.0, 122.9, 122.5, 121.9, 121.7, 60.5, 46.5, 30.1, 25.5. Elem. Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.63; H, 5.97; N, 9.87.

4.3. Synthesis of catalyst 4

Starting from the (*R*)-*N*,*N*-dimethyl-binaphthyl diamine, following the procedure described above, catalyst **4** was prepared. Compound **4** pale yellow solid, mp 77 °C, then dec. $[\alpha]_D^{23} = -95.9$ (*c* 0.21, DCM); IR (DCM): *v* 1677, 1598, 1455, 1427, 1260 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.55 (d, $J = 8.5$ Hz, 1H), 7.99 (d, $J = 7.1$ Hz, 1H), 7.93 (m, 1H), 7.91 (m, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.30 (m, 1H), 7.20–7.10 (m, 4H), 6.95 (d, $J = 7.5$ Hz, 1H), 3.45 (dd, $J = 6.5$ Hz, $J = 2.1$ Hz, 1H), 2.72 (m, 1H), 2.52 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 130.1, 129.6, 129.0, 128.5, 128.2, 128.1, 127.1, 127.0, 126.6, 126.3, 126.2, 125.6, 125.2, 124.9, 124.5, 124.0, 123.7, 120.7, 120.0, 119.0, 60.8, 46.8, 43.4, 30.6, 29.7 25.8. Elem. Anal. Calcd for $C_{27}H_{27}N_3O$: C, 79.19; H, 6.65; N, 10.26. Found: C, 79.21; H, 6.67; N, 10.21.

4.4. Synthesis of catalyst 5

Starting from the (*S*)-*N*,*N*-dimethyl-binaphthyl diamine, following the above described procedure, catalyst **5** was prepared. Compound **5** pale yellow solid, mp 65 °C, then dec. $[\alpha]_D^{23} = -16.2$ (*c* 0.35, DCM); IR (DCM): *v* 1679, 1618, 1595, 1504, 1453, 1428, 1265 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 8.60 (d, $J = 8.8$Hz, 1H), 8.00 (d, $J = 7.1$ Hz, 1H), 7.97–7.83 (m, 2H), 7.70 (d, $J = 7.6$ Hz, 1H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.30–7.15 (m, 4H), 7.15 (d, $J = 7.5$ Hz, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 3.55 (dd, $J = 6.9$ Hz, $J = 2.1$ Hz, 1H), 2.62 (m, 1H), 2.50 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.45 (m, 1H), 1.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 131.1, 129.8, 128.6, 128.0, 127.9, 127.7, 127.5, 126.5, 126.0, 125.9, 125.0, 124.8, 124.2, 123.9, 122.5, 121.5, 120.7, 120.0, 119.8, 109.5, 60.7, 46.3, 43.4, 31.6, 27.3, 24.8. Elem. Anal. Calcd for $C_{27}H_{27}N_3O$: C, 79.19; H, 6.65; N, 10.26. Found: C, 79.15; H, 6.63; N, 10.29.

4.5. Aldol reaction

General procedure: To a stirred solution of catalyst (0.02 mmol) in acetone (0.8 mL) (or acetone/$CHCl_3$ 1/1 mixture) at a given temperature after 15 min, the aldehyde (0.2 mmol) was added. The mixture was allowed to stir for a given time, then the solvent was evaporated and the crude product analysed. If necessary, the crude products were purified by flash chromatography with different hexanes/ethyl acetate mixture as eluents. Yields and ee for each reaction are indicated in the Tables. The assignment of absolute configuration to the predominant isomer formed in each reaction rests on comparison of the sign of the specific rotation with those reported in the literature.

4.6. (*R*)-4-(4-Nitrophenyl)-4-hydroxy-2-butanone

This product was purified with a hexanes/ethyl acetate 7:3 mixture as eluant. It had ^{1}H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiracel OJ column (hexane/isopropanol 70:30; flow rate 0.8 mL/min; λ 220 nm): $t_R = 11.6$ min, $t_S = 12.9$ min.

4.7. (*R*)-4-Cyclohexyl-4-hydroxy-2-butanone

This product had ^{1}H NMR data in agreement with those reported in the literature. The enantiomeric excess was

determined by HPLC on a Chiracel OJ-H column (hexane/isopropanol 70:30; flow rate 0.8 mL/min; λ 270 nm): $t_{major} = 4.63$ min, $t_{min} = 3.63$ min.

4.8. (*R*)-4-*tert*-Butyl-4-hydroxy-2-butanone

This product had ^{1}H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiracel AD column (hexane/isopropanol 97:3; flow rate 0.8 mL/min; λ 270 nm): $t_{major} = 8.3$ min, $t_{min} = 9.4$ min.

4.9. (*R*,*R*)-2-[1-(4-Nitrophenyl)-hydroxymethyl]-cyclohexanone

This product had ^{1}H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel OJ-H column (hexane/isopropanol 70:30; flow rate 0.8 mL/min; λ 230 nm): *t syn*$_{major} = 10.5$ min, *t syn*$_{min} = 12.3$ min; *t anti*$_{min} = 11.3$ min, *t anti*$_{major} = 16.8$ min.

4.10. 4-Nitrophenyl-4-(*N*-4-methoxyphenyl)-amino-2-butanone

This product had ^{1}H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiralpack AD column (hexane/isopropanol 60:40; flow rate 0.8 mL/min; λ 270 nm): $t_{major} = 11.1$ min, $t_{min} = 12.5$ min.

Acknowledgements

This work was supported by MIUR (Rome) within the national project 'Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali'. We thank Professor Cozzi for valuable discussion.

References

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; WILEY-VCH: Weinheim, Germany, 2005.
2. For a recent review on polymer-supported organic catalysts see: Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401–3429.
3. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5264.
4. For selected references see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–569; (b) Sakthivel, K.; Notz, W.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591; (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154; (d) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343–1345.
5. (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579; (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. *Org. Biomol. Chem.* **2005**, *3*, 84–89; (c) Marigo, M.; Wabnitz, T.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–796.
6. (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.; Jiang, Y.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5269; (b) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.
7. (a) Tang, Z.; Yang, Z.; Chen, X.-H.; Cun, L.; Mi, A.; Jiang, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9290; (b) Tang, Z.; Cun, L.; Cui, X.; Mi, A.; Jiang, Y.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263–1266.
8. (a) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321–5324; (b) Chen, J.-R.; Lu, H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543–4546.
9. Xiong, X.; Huang, X.; Gou, S.; Huang, J.; Wen, Y.; Feng, X. *Adv. Synth. Catal.* **2006**, *348*, 538–544; For the use of BINAM-derived bis imines as chiral ligands see: Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064–2069, and references cited therein.
10. While this manuscript was in preparation, three contributions about the use of BINAM-derived prolinamides were published: (a) Guillena, G.; Hita, M.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729–733; (b) Guillena, G.; Hita, M.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031; (c) Gryko, D.; Kowalczyk, B.; Zawadzki, L. *Synlett* **2006**, 1059–1062; For other recent contributions of the same groups see also: (d) Guillena, G.; Hita, M.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497; (e) Gryko, D.; Lipinski, R. *Eur. J. Org. Chem.* **2006**, 3864–3876.
11. Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.,* **2006**, *71*, 1458–1464.
12. The use of catalysts **1** and **2** in a chloroform/acetone mixture represents a useful alternative to the reaction in DMF/H_2O solvent system (see Ref. 10a), since it allowed to perform the reaction at −50 and to afford the product in 85% ee, with a easy work up.
13. These observations confirmed the trend reported by Gryko in Ref. 10c, where the (*S*)-BINAM-derived catalyst in acetone promoted the reaction with higher enantioselectivity than (*R*)-BINAM derived C_2-symmetric catalyst (65% ee vs 32% ee at 4 °C in acetone).
14. Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293–4296.
15. This result is also in good agreement with the one reported in Ref. 10c where an analogous *N*-benzoyl derivative promoted the aldol condensation in acetone at 4 °C in 83% ee.
16. Catalysts **3** and **5** promoted the reaction in acetone with slightly lower enantioselectivity.
17. The role of the stereogenic axis of binaphthyl diamine is currently under active investigation in our group. Preliminary studies showed that 1,1′-biphenyl-2,2′-diamine-based prolinamides catalysed the aldol condensation with slightly lower enantioselectivities than binaphthyl diamine-based prolinamides. Please note that also Gryko reported contradictory results in acetone and dioxane as reaction solvents that prevent any easy determination of the matching configurations of the stereogenic elements of the molecule.
18. Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891–1895.
19. Also in this case the C_1 symmetric catalytic systems in chloroform compare favourably to the C_2 symmetric ones in DMF (dr >99/1, 95% ee vs dr 10/1, 93% ee, see Ref. 10a).
20. It is worth mentioning that under the same experimental conditions, the use of hydroxyacetone brought us to the formation of racemic products. However the use of catalyst **2** in DMSO allowed to obtain the *anti*-isomer in 82% ee (see Ref. 10b). Please note that catalyst **2** in DMF at 0 °C promoted the reaction with methoxyacetone in 92% ee (see Ref. 10b).

21. The reaction with benzaldehyde and cyclohexanecarboxaldehyde did not afford the product in reasonable yield.
22. The role of addictives in the Mannich reaction and different experimental conditions in order to improve the enantioselectivity of the process are currently under study.
23. For recent contributions in the field see: (a) He, L.; Tang, Z.; Cung, L.-F.; Mi, A.; Jiang, Y.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346–351; (b) Guo, H.-M.; Cheng, L.; Cun, L.; Gong, L.-Z.; Mi, A.; Jiang, Y.-Z. *Chem. Commun.* **2006**, 429–431.