Bisprolinediamides with the Binaphthyl Backbone as Organocatalysts for the Direct Asymmetric Aldol Reaction

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Received 17 January 2006

Abstract: A series of L-prolineamides derived from various aromatic diamines including 1,1′-binaphthyl-2,2′-diamine, were prepared in good yields. They were evaluated as catalysts for the direct asymmetric aldol reaction. The presence of the binaphthyl and proline moieties in one molecule has beneficial effects on the stereochemical outcome of the reaction of acetone with a model aldehyde. Furthermore, it was shown that dioxane as the solvent significantly improved both yield and enantioselectivity, reaching 89% and 86%, respectively.

Key words: organocatalysis, aldol reaction, asymmetric synthesis, binaphtyl, proline

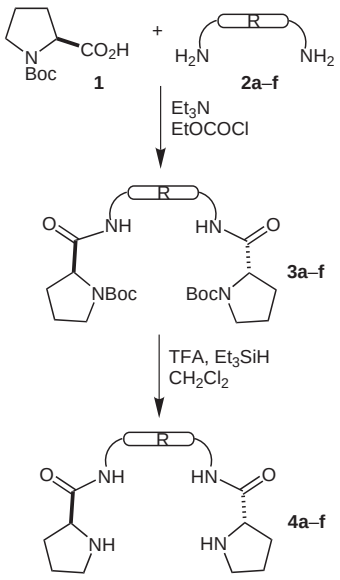
Asymmetric catalysis has received considerable attention over the past few decades and its contribution toward organic synthesis has become increasingly significant.[1,2] A wide variety of enantioselective transformations can be performed with catalytic amounts of a chiral promoter, providing a highly economic access to optically active compounds. All these catalytic transformations can fall into one of three categories: transition metal catalysis, organocatalytic transformations, or enzymatic processes. Over the past few years, rapid progress has been made in the development of organocatalyzed processes.[2,3] Since the pioneering work by List et al.[4] who demonstrated L-proline itself can catalyze the intermolecular aldol addition of acetone to 4-nitrobenzaldehyde, with fair enantioselectivities, proline itself has become a very attractive catalyst but its catalytic activity can be fine-tuned only by changing the reaction conditions. Since that time several proline-derived catalysts have been prepared.[5–16]

Recently, the simplest C_2-symmetric bisamide derived from L-proline and ethylenediamine showed very high activity but low stereoselectivity in the model aldol reaction.[17] The use of (1*S*,2*S*)-1,2-diphenylethylenediamine as a linkage improved the selectivity of the catalyst appreciably. The stereoselectivity of the aldol reaction catalyzed by C_2-symmetric bisprolinediamides were strongly influenced by the nature of the linkage. Though this work is elegant it has one major drawback, the reaction conditions vary from case to case (anhydrous acetone, CH_2Cl_2 for cyclopentanone, and THF for 2-hydroxyacetone) and good ee values were only obtained when these reactions were performed at –35 °C.

Furthermore, Xiao et al.[18] showed that the non-symmetric bisamide derived from (1*R*,2*R*)-1,2-cyclohexanediamine, L-proline, and 4-methylbenzoic acid is an effective catalyst for the aldol reaction of cyclohexanone with aromatic aldehydes giving products in good yield and up to 97% ee. Since the catalysts are believed to stabilize the transition state through hydrogen bonding to proline and its derivatives, small changes in the catalyst structure might influence the strength of hydrogen bonding and as a result change the selectivity of the reaction. It has also been shown that variation of the electronic properties of the acyl moiety on the catalyst could influence its activity and selectivity.[18]

With this in mind, we have synthesized bisprolinediamides **4a**–**d** derived from aromatic diamines (Scheme 1, Figure 1). Diamines of type **2** were coupled with *N*-Boc-L-proline **1** in the presence of Et_3N and ethyl chloroformate,[6b] affording their respective N-protected bisprolinediamides **3** in good yields; next they were treated with TFA and Et_3SiH[19] giving pure **4a**–**d**.

Newly prepared catalysts **4a**–**d** were tested in the model aldol reaction of acetone with 4-nitrobenzaldehyde (**6a**).



Scheme 1 Synthesis of bisprolinediamides of type **4**

SYNLETT 2006, No. 7, pp 1059–1062
Advanced online publication: 24.04.2006
DOI: 10.1055/s-2006-939701; Art ID: G01306ST

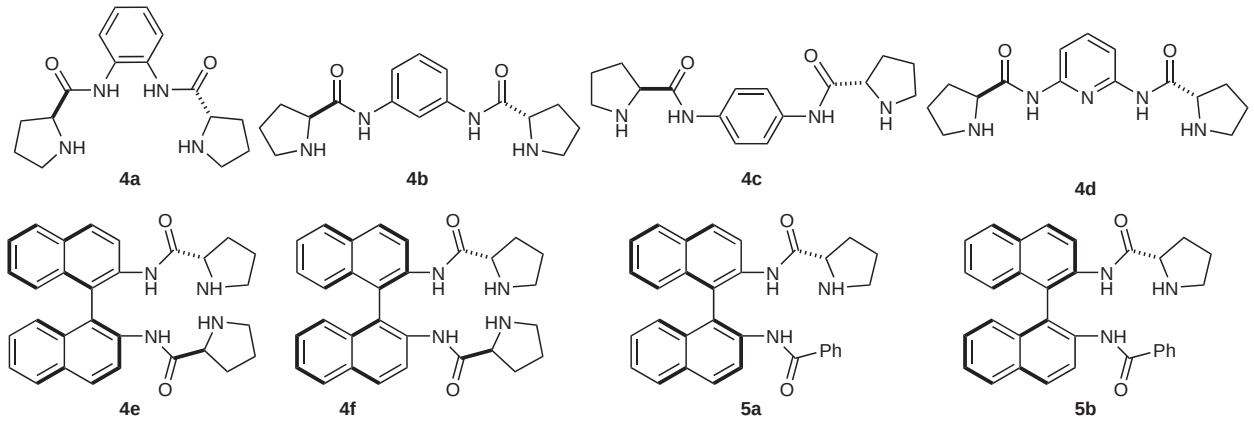


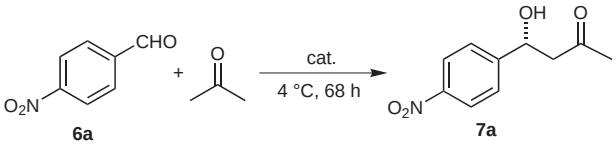
Figure 1 Bisprolinediamides **4** and **5** used as catalysts for the model aldol reaction of acetone with 4-nitrobenzaldehyde **6a**

The structure of the aromatic amine moiety had a small effect on the yield of **7a**, yields were usually in the range 50–70%. The reaction catalyzed by diamide **4b** gave the lowest yield and moderate ee (Table 1, entry 2). When 2,6-diaminopyridine was used as a linkage (catalyst **4d**) the yield of **7** increased to 67% (Table 1, entry 4). The presence of an electron-withdrawing group (pyridine moiety) in place of the phenyl substituent enhanced the acidity of the amide proton, thus, the reactivity of the catalyst was higher. Also, since the ee remained unchanged, we assumed that the nitrogen atom did not participate in the transition state.

The binaphthyl backbone has been widely used in transition-metal catalysis and is believed to be the factor, which determines the effectiveness of the catalyst. In addition, Maruoka et al.[13] have recently described a new axially chiral amino acid with a binaphthyl backbone, which has found application as a catalyst in the aldol reaction. The yields as well as the enantiomeric excesses for the model reaction of 4-nitrobenzaldehyde (**6a**) with acetone were higher than those reported for the proline-catalyzed reaction. Thus, we prepared new organocatalysts **4e** and **4f** which have the 1,1′-binaphthyl-2,2′-diamine **2** and L-proline joined, such that the organocatalyst possesses axial chirality. We designed our new catalyst in such a way that we could benefit from the profitable influence of both the binaphthyl backbone and the proline moiety. The obvious way in doing so was to utilize the approach described by Jurczak et al.[20] for the synthesis of 1,1′-binaphthyl-2,2′-diamides derived from natural amino acids. Thus racemic 1,1′-binaphthyl-2,2′-diamine **2** was coupled with *N*-Boc-L-proline **1**[6b] affording a mixture of diastereoisomeric products **3** (Scheme 1). After separation by column chromatography on silica gel and deprotection of the Boc-group,[19] pure products **4e** and **4f** were obtained.[21] It should be pointed out that these two optically pure catalyst were obtained from cheap, racemic diamine **2**. Both were used as catalysts for the model aldol reaction of 4-nitrobenzaldehyde (**6a**) with acetone (Table 1). We were delighted to discover that both reactions gave good yields (Table 1, entries 5, 6), as well as improved enantioselectivity when the reaction was carried out in dioxane. The catalyst **4e** afforded a superior level of stereocontrol to its diastereoisomer **4f**. This indicates that the *S* configuration of the binaphthyl moiety matches the L-proline, enhancing the stereoselectivity, whereas in the other case, the two fragments form a mismatched pair (catalyst **4f**).

The strength of hydrogen bonding might influence the catalytic properties of the catalyst since it is believed that the transition state in proline and its derivative is stabilized through hydrogen bonding. Xiao et al.[18] have also shown that the activity and selectivity of the catalyst can be tuned by changing one of the acyl moieties in the bisprolinediamides catalyst. With this in mind we have synthesized catalysts **5a** and **5b** possessing only one proline moiety.[22] The reaction of (*S*)- or (*R*)-1,1′-binaphthyl-2,2′-diamine with an equimolar amount of *N*-Boc-L-proline gave the

Table 1 The Aldol Addition of Acetone to 4-Nitrobenzaldehyde[a]



		Acetone		Dioxane	
Entry	Catalyst	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	**4a**	72	43	–	–
2	**4b**	48	51	–	–
3	**4c**	57	41	–	–
4	**4d**	67	51	–	–
5	**4e**	69	65	89	86
6	**4f**	70	32	–	–
7	**5a**	51	40	80	84
8	**5b**	70	83	73	74

[a] *Reagents and conditions*: 4-nitrobenzaldehyde (1 mmol), acetone (2 mL), catalyst (0.1 mmol), 4 °C, 68 h.
[b] Isolated yields.
[c] Determined by HPLC using an ASH column.

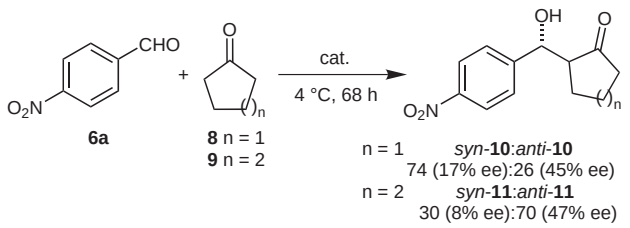
respective monoprolineamide in 43% yield. Subsequent reaction with benzoylchloride followed by treatment with TFA and Et_3SiH[19] yielded bisamides **5a** and **5b**. When compound **5a** catalyzed the reaction of acetone with 4-nitrobenzaldehyde (**6a**) the yield as well as the ee dropped substantially compared with **4e** (Table 1, entry 7). On the other hand its diastereoisomer **5b** afforded superior levels of stereocontrol (Table 1, entry 8). When the reactions were carried out in dioxane the enantioselectivity increased or remained at the same level. Since the results obtained in acetone and dioxane are contradictory, we cannot clearly state which configuration of the binaphthyl backbone matches the *S* configuration of proline.

The scope of the aldol reaction using symmetric catalyst **4e** was examined with a series of aryl aldehydes **6b**–**j** (Table 2) and ketone donors (Scheme 2). In most cases good yields and fair enantioselectivities were obtained. Unfortunately, reactions of 4-nitrobenzaldehyde (**6a**) with cyclopentanone (**8**) and cyclohexanone (**9**) afforded aldols **10** and **11**, respectively, with moderate diastereoselectivity and low enantioselectivity.

Table 2 Bisprolinediamide **4e** catalyzed aldol reaction[a]

Entry	R	Product	Yield (%)[b]	ee (%)[c]
1	C_6F_5	**7b**	79	71
2	4-CN-C_6H_4	**7c**	74	73
3	4-CF_3-C_6H_4	**7d**	72	88
4	2,6-Cl_2-C_6H_3	**7e**	75	85
5	2-Cl-C_6H_4	**7f**	73	62
6	4-Cl-C_6H_4	**7g**	53	77
7	4-Br-C_6H_4	**7h**	16	54
8	C_6H_5	**7i**	15	74
9	β-naphtyl	**7j**	9	50

[a] All reactions were performed with 1 mmol of aldehyde, 1 mL of acetone, 4 mL of dioxane and 0.1 mmol of catalyst at 4 °C for 68 h.
[b] Isolated yields.
[c] Determined by HPLC using ASH or ADH column.



Scheme 2 Aldol reactions of aldehyde **6a** with cyclic ketones

Further work on optimizing the reaction conditions as well as on the properties of the catalyst are currently underway.

In conclusion, we have synthesized new chiral organocatalysts, which connect an axially chiral binaphthyl backbone with the centrally chiral proline moiety. The highly skewed position of the naphtyl rings influences the catalytic activity of the proline moiety. The *S* configuration of the binaphthyl moiety matches the *S* configuration of the proline in symmetric catalysts **4e** and **4f**. Additionally, it was shown that the replacement of the binaphthyl moiety with other aromatic diamines in the diamide catalysts **4** causes a decrease in the enantioselectivity. Our studies have shown that to obtain efficient catalysis a certain conformation is required since the structure of the linkage influences the enantioselectivity of the model aldol reaction. We believe that the dihedral angle between both proline moieties is the determining factor. Furthermore the use of dioxane as a solvent for the direct asymmetric aldol reaction catalyzed by **4e** not only improved the yield and the stereochemical outcome of the reaction but also allowed the use of other donors. The aldol reaction of acetone with various aryl aldehydes **6** afforded aldols with moderate to good yield and fair enantioselectivities.

Our work underlines how difficult the rational design of efficient catalysts is and how much work is still needed.

Acknowledgment

We thank Prof. J. Jurczak for helpful discussions.

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(21) **Compounds of Type 4; Typical Procedure**
To a solution of N-Boc protected proline **1** (4.3 g, 20.0 mmol) in anhyd THF (50 mL), Et_3N (2.8 mL, 20.1 mmol) was added and the mixture was cooled to 0 °C, then ethyl chloroformate (2.5 mL, 20 mmol) was added dropwise over 15 min. The reaction temperature was maintained at 0 °C for 30 min, then a THF (10 mL) solution of racemic 1,1′-binaphthyl-2,2′-diamine (2.84 g, 10 mmol) was added dropwise over 15 min at 0 °C. The reaction mixture was stirred overnight and then refluxed for 4 h. Finally, after cooling to r.t., the white precipitate ($Et_3N{\cdot}HCl$) was removed by filtration, and the filtrate was concentrated in vacuo. Then the residue was purified by column chromatography (*n*-hexane–EtOAc, ca 4:1) to give two diastereomeric products **3e** (2.41 g, 3.6 mmol) and **3f** (2.46 g, 3.7 mmol) in 73% overall yield. To a solution of diamide **3e** (0.75 g, 1.1 mmol) in CH_2Cl_2 (3 mL), excess TFA (1.5 mL), and Et_3SiCl (1.5 mL) was added and the resulting mixture was stirred for 2 h at r.t. The solvent was removed and the pH of the residue was adjusted to <7 by the addition of an aq sat. solution of $NaHCO_3$, the product was extracted with CH_2Cl_2, and dried over $MgSO_4$. Removal of the solvent resulted in pure **4e** (0.45 g, 0.94 mmol, 85%).
4e Mp 203–208 °C (dec.); $[\alpha]_D^{25}$ –142.8 (*c* 0.94, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.70 (1 H, s), 8.82 (2 H, AB/2, *J* = 9.0 Hz), 8.04 (2 H, AB/2, *J* = 9.0 Hz), 7.44–7.15 (6 H, m), 3.62 (2 H, dd, *J* = 9.3, 4.4 Hz), 2.40 (2 H, ddd, *J* = 9.6, 6.6, 7.8 Hz), 1.96 (4 H, m), 1.57 (2 H, br s), 1.45 (2 H, ddd, *J* = 6.6, 9.8, 4.8 Hz), 1.35–1.17 (2 H, m), 0.98–0.77 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.0, 135.2, 132.5, 130.9, 129.6, 128.2, 126.9, 125.0, 124.9, 119.7, 119.2, 60.6, 46.2, 30.7, 25.4. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{31}N_4O_2$: 479.2442; found: 479.2458.

(22) **Compounds of Type 5; Typical Procedure**
To a solution of N-Boc protected proline **1** (0.43 g, 2 mmol) in anhyd THF (5 mL), Et_3N (0.24 mL, 2 mmol) was added and the mixture was cooled to 0 °C with stirring, then ethyl chloroformate (0.18 mL, 1.5 mmol) was added dropwise over 15 min. After the addition the reaction temperature was maintained at 0 °C for 30 min. Then a THF solution (1 mL) of (*R*)-1,1′-binaphthyl-2,2′-diamine (0.57 g, 2 mmol) was added dropwise over 5 min at 0 °C. The reaction was stirred overnight at r.t. and the white precipitate ($Et_3N{\cdot}HCl$) formed was removed by filtration. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (*n*-hexane–EtOAc, ca. 4:1) to yield (*S*)-*tert*-butyl 2-[(*R*)-1-(2-aminonaphthalen-1-yl)naphthalene-2-yl-carbamoyl]pyrrolidine-1-carboxylate (0.42 g, 0.87 mmol, 44%).
To a solution of (*S*)-*tert*-butyl 2-[(*R*)-1-(2-aminonaphthalen-1-yl)naphthalene-2-yl-carbamoyl]pyrrolidine-1-carboxylate (175 mg, 0.36 mmol) in anhyd THF (5 mL), Et_3N (50 μL, 0.36 mmol) was added and the resulting mixture was cooled to 0 °C. Then benzoyl chloride (45μL, 0.36 mmol) was added dropwise, the mixture was stirred for 2 h, and the white precipitate ($Et_3N{\cdot}HCl$) was removed by filtration. The filtrate was concentrated in vacuo and then the residue was purified by column chromatography (*n*-hexane–EtOAc, 7:3) to give (*S*)-*tert*-butyl 2-[(*R*)-1-(2-benzamido)naphthalene-1-yl]naphthalene-2-yl-carbamoylpyrrolidine-1-carboxylate (198 mg, 0.34 mmol) in 94% yield.
To a solution of (*S*)-*tert*-butyl 2-[(*R*)-1-(2-benzamido)naphthalene-1-yl]naphthalene-2-yl-carbamoyl-pyrrolidine-1-carboxylate (198 mg, 0.34 mmol) in CH_2Cl_2 (680 μL), excess TFA (340 μL), and Et_3SiCl (45 μL) was added. The resulting mixture was stirred for 2 h at r.t. The volatile compounds were removed and the pH of the residue was adjusted to <7 by the addition of a sat. aq solution of $NaHCO_3$, the product was extracted with CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed to give pure **5b** (160 mg, 0.33 mmol, 97%). Mp 80–82 °C; $[\alpha]_D^{25}$ +10.9 (*c* 0.80, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.70 (1 H, s), 8.80 (1 H, AB/2, *J* = 9.0 Hz), 8.55 (1 H, AB/2, *J* = 9.0 Hz), 8.09 (1 H, AB/2, *J* = 9.1 Hz), 8.08 (1 H, AB/2, *J* = 9.1 Hz), 7.95 (2 H, dd, *J* = 3.8, 8.1 Hz), 7.86 (1 H, br s), 7.68–7.11 (11 H, m), 3.58 (1 H, dd, *J* = 4.4, 9.4 Hz), 2.57 (1 H, dt, *J* = 9.9, 7.2 Hz), 1.90–1.82 (1 H, m), 1.59 (1 H, ddt, *J* = 12.5, 7.2, 4.9 Hz), 1.44–1.36 (1 H, m), 1.26 (1 H, s), 1.15 (1 H, dq, *J* = 20.0, 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 165.4, 135.2, 135.0, 134.4, 132.6, 132.5, 131.7, 131.2, 131.1, 130.2, 130.0, 128.6, 128.3, 128.2, 127.5, 127.1, 126.7, 125.6, 125.23, 125.19, 125.1, 121.2, 120.8, 60.6, 46.6, 30.5, 25.6. HRMS (ESI): *m*/*z* calcd for $C_{32}H_{28}N_3O_2$: 486.2176; found: 486.2171.

Aldol Reaction; General Procedure
To a stirred solution of a catalyst (0.1 mmol) in dioxane (4 mL) at 0 °C, acetone (1 mL) (or other ketones) and an aldehyde **6** (1 mmol) were added under air in a closed system. The reaction mixture was stirred at 4 °C for 68 h. Then the reaction mixture was diluted with EtOAc and washed with a sat. aq solution of NH_4Cl. The organic layer was separated and dried over Na_2SO_4. Column chromatography (silica gel, hexanes–EtOAc) gave pure aldol **7**.