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BINAM-prolinamides as recoverable catalysts in the direct aldol condensation

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Abstract—New BINAM-prolinamides were developed and tested as organocatalysts in the direct aldol condensation between aldehydes and several aliphatic ketones. C_2-symmetrical (*Sa*)-BINAM-L-prolinamide gives the best enantioselectivities for this transformation, being recovered and reused after the reaction by simple extractive techniques. The reaction was performed in DMF/H_2O at 0 °C to give the aldol products in up to 95% ee for acetone. For 2-butanone, the corresponding *iso*-regioisomers were regioselectively obtained in up to 96% ee working in DMF at rt. In the case of cyclohexanone, dr up to 10:1 in favour of the *anti* products, which were obtained in 90–93% ee, was achieved.

1. Introduction

The direct generation of carbanion equivalents via an asymmetric enamine intermediate and reaction with electrophiles is one of the most elegant and straightforward methods to build a C–C bond in an enantioselective and catalytic way.[1] In this sense, small organic molecules, known as organocatalysts,[2] have shown their synthetic efficiency in the direct aldol reaction.[3] Using this strategy, pre-generation of enolates is not needed and a wide substrate scope can be achieved. In this field, proline is a cornerstone in the direct intramolecular aldol reaction,[4,5] its reactivity and stereoselectivity as an organocatalyst being attributed to the formation of cyclic transition states in which the presence of an acidic proton seems to be crucial.[6] However, the development of new organocatalysts, in which the highly acidic proton of proline is replaced by another less acidic one has shown that it is the ability to form hydrogen bonds and not the proton acidity, that is a necessary condition for successful enantioselection. For instance, prolinamides[7] and small peptides[8] are efficient and selective catalysts in this transformation. Moreover, these new systems permit the enhancement of the structural diversity of the catalysts and therefore the ability to fine tune their reactivity.

Some of these proline derivatives were designed to resemble the peptides involved in the active pocket of an enzyme. In that case, the achieved stereoselectivity is reasoned due to the presence of several amide bonds with restricted rotation, which creates a non-covalent bonding environment similar to that of an enzyme. The goal of our approach was to find a new system with the broad substrate scope of proline and the specificity of aldolase enzymes for the direct aldol reaction.[9] Herein, we report the synthesis of new prolinamides derived from 2,2′-diamino-1,1′-binaphthalene (BINAM) and their application as catalysts.[10] The design of these catalysts is based on the following facts: the binaphthyl moiety would provide restricted rotation around the biaryl axis due to steric hindrance of the aryl groups. This structural motif would look like the β-turn pocket associated with the presence of proline residues in the active sites of several enzymes, and it could work as specifically as the proper enzyme. Moreover, the modification of this binaphthyl moiety would allow further modulation of catalytic activity. Furthermore, the presence of the aryl counterpart might increase the solubility of the catalyst in common organic solvents and would make feasible the recovery of the catalyst by acid/base extractive techniques. Finally, the presence of a binaphthyl derivative would allow us to study the influence of

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the axial stereoelement in the stereochemical outcome of the reaction products.

2. Results and discussion

The synthesis of the BINAM-prolinamides **1**[11] was performed by coupling the commercially available (*S*)- or (*R*)-BINAM with the acyl chloride derived from Fmoc-L-Pro or Fmoc-D-Pro followed by final deprotection with piperidine in the yields indicated in Figure 1. Once the catalysts were prepared, they were tested in the classical model aldol reaction between acetone and *p*-nitrobenzaldehyde, to examine the efficiency of catalysts **1** (Table 1).[12]

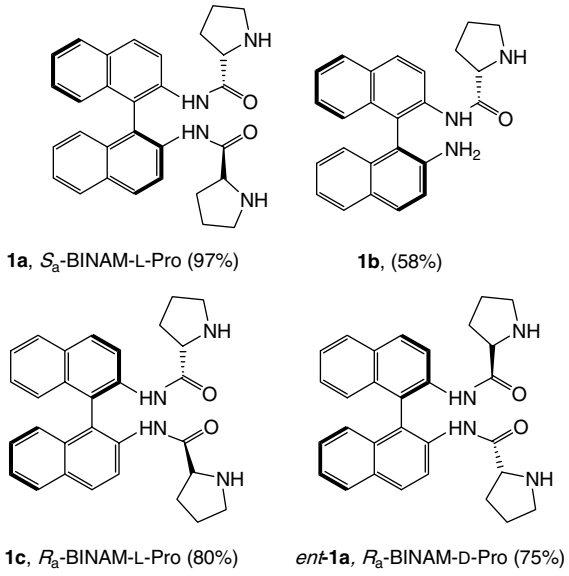
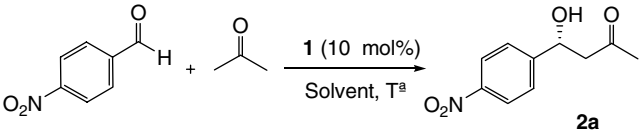


Figure 1. BINAM-derived prolinamides.

Concerning the reaction time and chemical yield, catalyst **1a** (96% yield, 11% ee) was more efficient than **1b** (28% yield, 36% ee, Table 1, compare entries 1 and 2) in THF at rt. Changing the solvent to DMSO and using catalyst **1a**, the aldol product was obtained in 52% ee (Table 1, entry 3), with the reaction time being very long (8 d). Under these conditions and using proline as catalyst, a 76% ee was achieved.[4] In DMF, the reaction time was shorter (3 d) but the enantioselectivity decreased to 35% (Table 1, entry 4). Recently, it has been reported that the addition of an amount of water to the solvent accelerated the reaction rate.[13] When the reaction was carried out in a 1/1 mixture DMF/H_2O at 25 °C, the reaction took place in only 1 d although with a poor 15% ee (Table 1, entry 5). Decreasing the temperature to 0 °C, increased the ee up to 79%, with the reaction time being 3 d (Table 1, entry 6). The addition of a higher amount of water had a negative effect on the enantioselectivity and reaction time (Table 1, entry 7). As comparison and, once the best reaction conditions were found, we tested the catalytic efficiency of L-Pro under the same conditions, achieving a 60% yield and a nearly racemic product **2a**, after 5 d (Table 1, entry 8). Decreasing the catalyst loading to 5 mol %, **2a** was obtained in

Table 1. Direct aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by **1**[a]



Entry	Cat.	Solvent	*T* (°C)	*t* (d)	Yield (%)[b]	ee (%)[c]
1	**1a**	THF	25	3	96	11
2	**1b**	THF	25	7	28	36
3	**1a**	DMSO	25	8	76	52
4	**1a**	DMF	25	3	71	35
5	**1a**	DMF/H_2O[d]	25	1	85	15
6	**1a**	DMF/H_2O[d]	0	3	99	79
7	**1a**	DMF/H_2O[e]	0	5	83	54
8	L-Pro	DMF/H_2O[d]	0	5	60	1
9	**1a**	DMF/H_2O[d,f]	0	6	67	51
10	**1c**	DMF/H_2O[d]	0	3	97	45
11	*ent*-**1a**	DMF/H_2O[d]	0	3	87	60[g]
12	**1a**[h]	DMF/H_2O[d]	0	6	80	80
13	**1a**[i]	DMF/H_2O[d]	0	6	81	79

[a] The reaction was carried out using 27.6 equiv of acetone per equivalent of aldehyde in the presence of 10 mol % of catalyst in 1 mL of solvent.
[b] Isolated products after column chromatography.
[c] Determined by HPLC (Chiracel AS, hexane/isopropanol: 85:15), the absolute configuration of the major enantiomer being *R*.
[d] 1:1.
[e] 1:4.
[f] 5 mol % of catalyst **1a** was used.
[g] The opposite enantiomer was obtained.
[h] Second cycle with the recovered catalyst.
[i] Third cycle with the recovered catalyst.

67% yield and 51% ee (Table 1, entry 9). Thus, 10 mol % of catalyst **1a** seems to be the appropriate loading to carry out the reaction. Other prolinamide catalysts such as those derived from chiral β-amino alcohols (**I**)[7f] or C_2-symmetric bisprolinamide (**II**)[7i] (Fig. 2) led to **2a**, with up to 99% ee in both cases but decreasing the reaction temperature to −25 °C or −35 °C, respectively.

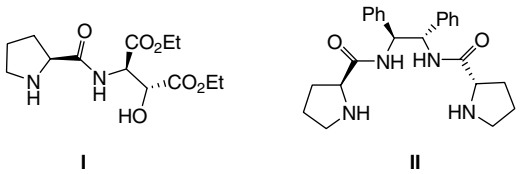
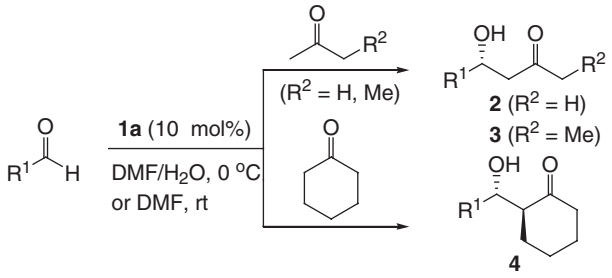


Figure 2. Prolinamides used as catalysts in the direct aldol reaction.

The recovery of the catalyst after the reaction had finished was carried out by quenching with 6 M HCl and the aldol product was extracted into the organic layer. The acidic aqueous extract was treated with NaOH until pH ~ 11 and then extracted with AcOEt to recover the catalyst, which was recrystallized from $CHCl_3/Et_2O$. This recovered prolinamide **1a** was re-used in two subsequent cycles as catalyst in the reaction of *p*-nitrobenzaldehyde and acetone in DMF/H_2O 1:1 giving the same

Table 2. Direct aldol reaction of catalyzed by BINAM-prolinamide **1a**[a]

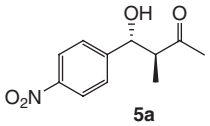


Entry	R^1	Ketone	No.	*t* (d)	Yield %[b]	dr[c]	ee %[d]
1	4-$NO_2C_6H_4$		**2a**	3	99	—	79
2	2-$NO_2C_6H_4$		**2b**	3	99	—	85
3	2-ClC_6H_4		**2c**	1.5	98	—	95
4	Ph		**2d**	4.5	75	—	65
5	C_6H_{11}		**2e**	2.5	52	—	78
6[e]	4-$NO_2C_6H_4$		**3a**	11	96[f]	—	96
7[e]	$(CH_3)_2CH$		**3f**	8	53	—	86
8	4-$NO_2C_6H_4$		**4a**	3	98	10:1	93 (44)
9	2-ClC_6H_4		**4b**	2.5	98	8:1	92 (7)
10	Ph		**4c**	4.5	99	4.3:1	90 (72)

[a] The reaction was carried out using 27.6 equiv of ketone per equivalent of aldehyde in the presence of 10 mol % of catalyst in 1 mL of solvent.
[b] Isolated products after column chromatography.
[c] Determined by ^1H NMR.
[d] Determined by HPLC. In parenthesis the ee for the *syn*-isomer.
[e] The reaction was carried out in DMF at rt.
[f] 4% of *anti*-**5a** in 31% ee was also obtained.

results as the freshly prepared catalyst, although with longer reaction times (Table 1, compare entries 6, 12 and 13). Once the best catalyst **1a** (10 mol %) and reaction conditions (DMF/H_2O: 1:1, 0 °C) were found, we extended its application to the reaction of acetone with different aldehydes, the obtained results being summarized in Table 2.

With acetone, the best enantioselectivities (up to 95%) were achieved when *ortho*-susbstituted aromatic aldehydes were used as nucleophiles (Table 2, entries 2 and 3). The use of less activated aldehydes, such as benzaldehyde or cyclohexanecarboxaldehyde led to a decrease in the reaction yields, the enantioselectivities being 65% and 78%, respectively (Table 2, entries 4 and 5). Then, a non-symmetrical ketone, such as 2-butanone, was used as a substrate and the reaction carried out in DMF at rt. Using *p*-nitrobenzaldehyde as nucleophile, the major product was the expected *iso*-isomer **3a**, and 4% of the *anti*-isomer **5a**. Compound **3a** had a 96% ee, while the *anti*-isomer was obtained with a 3% ee. (Table 2, entry 6). When L-proline was used as catalyst under these reaction conditions, 67% of product **3a** (96% ee) and 33% of the *anti*-isomer **5a** (13% ee) were obtained.



5a

The aldol reaction of 2-butanone also took place with less reactive and hindered aldehydes, such as isobutyraldehyde, to afford *iso*-isomer **3f** as the only product with an 86% ee (Table 2, entry 7). As a comparison and using L-proline or prolinamide **II** as catalysts in DMSO the only detected products with *p*-nitrobenzaldehyde and isobutyraldehyde were the *iso*-isomers but with lower ees (77% and 80%, respectively).[4] Surprisingly, β-amino alcohol derived prolinamides **I** led only to the diastereomeric mixture of *anti:syn* products for *p*-nitrobenzaldehyde and 2-butanone.[7f]

When cyclic ketones, such as cyclohexanone, were used as nucleophiles, remarkably high diasteroselectivities (up to 10:1) were observed using activated aldehydes, such as *p*-nitrobenzaldehyde or *o*-chlorobenzaldehyde, the *anti*-isomer being the major one in both cases. For these *anti*-compounds **4a** and **4b**, the enantioselectivities found were also very high, 93% and 92%, respectively (Table 2, entries 8 and 9). Barbas et al. used L-proline as catalysts in DMSO for this reaction, obtaining lower diasteroselectivities (dr. 2:1) and enantioselectivities (89% ee for *anti*-**4a**).[4] On the other hand, β-amino alcohol derived prolinamides **I** gave product **4a** with excellent diastereoselectivity (95:5) but lower ee for *anti*-**4a** (79% ee).[7f] Meanwhile, with C_2-symmetric bisprolinamides **II**, a 97:3 *anti:syn* ratio was obtained for **4a**, the enantioselectivity for the major isomer being comparable to our results (93% ee).[7i] For catalyst **1a**, the reaction between benzaldehyde and cyclohexanone was less diastereoselective, affording the *anti*:*syn* mixture of diastereoisomers with a 4.3:1 ratio. In this case, both isomers were obtained with high enantioselectivity (90% ee for the *anti*-isomer and 72% ee for the *syn*, Table 2, entry 10).

3. Conclusion

In conclusion, C_2-symmetrical (*Sa*)-BINAM-L-prolinamide **1a** has shown to be an efficient catalyst for the direct aldol reaction between several ketones and aldehydes, its recovery being possible by extractive techniques. The reaction conditions were mild, involving aqueous DMF at 0 °C in reasonable reaction rates. The aldol products were obtained with high enantioselectivities, comparable or even better to those obtained with L-proline and related prolinamide systems. For 2-butanone, the *iso*-isomers were obtained regioselectively and for cyclohexanone the corresponding *anti*-isomers were formed diastereoselectively. The scope of this reaction and the application of this catalyst to other related transformations are currently being studied.

Acknowledgements

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11. Compound **1a**: $[\alpha]_D^{26} = +108.6$ (*c* 1, MeOH); Mp 230 °C ($CHCl_3$, Et_2O); $R_f = 0.70$ (AcOEt/MeOH 1:1); $\nu = 3335$, 3192, 2964, 2869, 1676, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$, 1.26, 1.48, 1.71, 1.87, 2.34, 3.55, 7.15, 7.24, 7.41, 7.93, 8.04, 8.79, 9.69; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$, 30.6, 46.1, 60.6, 119.3, 119.7, 124.9, 125.0, 126.9, 128.2, 129.6, 130.9, 132.4, 135.1, 173.9; HRMS (*m*/*z*): Calcd for $C_{30}H_{32}O_2N_4$: 480.2525; found: 480.2501.
    Compound **1b**: $[\alpha]_D^{29} = -87.4$ (*c* 1, MeOH); Mp 265 °C ($CHCl_3$, Et_2O); $R_f = 0.40$ (AcOEt/MeOH 1:1); $\nu = 3466$, 3345, 3203, 3055, 2970, 1668, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$, 1.75, 2.36, 3.55, 3.68, 6.90, 7.29, 7.71, 7.83, 7.92, 7.99, 8.82, 9.73; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.2$, 30.7, 46.2, 60.7, 111.4, 118.1, 119.9, 120.2, 122.5, 123.6, 124.8, 125.1, 126.8,126.9, 128.0, 128.3, 129.2, 129.9, 131.0, 132.3, 133.6, 135.2, 142.6, 173.9; HRMS (*m*/*z*): Calcd for $C_{25}H_{23}ON_3$: 381.1841; found: 381.1818.
    Compound **1c**: $[\alpha]_D^{25} = +6.7$ (*c* 1, MeOH); Mp 120 °C ($CHCl_3$, Et_2O); $R_f = 0.21$ (AcOEt/MeOH 1:1); $\nu = 3349$, 3203, 3059, 2968, 1685, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$, 1.49, 1.73, 1.93, 2.22, 2.57, 3.52, 7.14, 7.25, 7.40, 7.93, 8.04, 8.79, 9.68; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.7$, 30.7, 46.6, 60.6, 119.1, 119.7, 124.8, 125.0, 126.9, 128.2, 129.6, 130.9, 132.4, 135.1, 173.6; HRMS (*m*/*z*): Calcd for $C_{30}H_{32}O_2N_4$: 480.2525; found: 480.2521.
12. *Typical procedure:* To a solution of aldehyde (37.8 mg, 0.25 mmol), in dry solvent (1 mL) under argon was added the corresponding ketone (5.5 mmol). The catalyst was added (10 mol%) to the resulting solution in one portion, and the resulting mixture stirred at the corresponding temperature. The reaction was monitored by ^1H NMR spectroscopy and quenched with a 6 M aqueous solution of hydrochloric acid (5 mL) and ethyl acetate (5 mL). The mixture was stirred vigorously for 10 min. The emulsion was separated (3×5 mL satd NaCl) and the aqueous phase treated with a satd NaOH solution until pH >9 and then ethyl acetate was added (3×15 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated recovering pure catalyst (85%). The organic phase from the acidic workup was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography yielding pure aldol products.
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