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A Highly Efficient Solvent-Free Asymmetric Direct Aldol Reaction Organocatalyzed by Recoverable (*S*)-Binam-L-Prolinamides. ESI-MS Evidence of the Enamine−Iminium Formation

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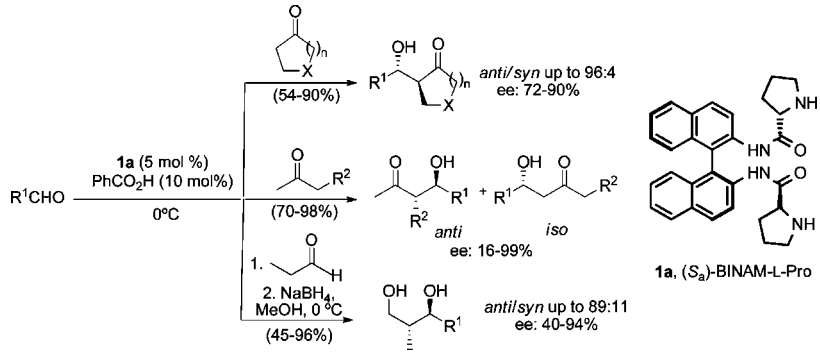

Recoverable (S_a)-binam-L-prolinamide in combination with benzoic acid is used as catalysts in the direct aldol reaction between cycloalkyl, alkyl, and α-functionalized ketones and aldehydes under solvent-free reaction conditions. Three different methods are assayed: simple conventional magnetic stirring, magnetic stirring after previous dissolution in THF and evaporation, and ball mill technique. These procedures allow one to reduce not only the amount of required ketone to 2 equiv but also the reaction time to give the aldol products with regio-, diastereo-, and enantioselectivities comparable to those in organic or aqueous solvents. Generally *anti*-isomers are mainly obtained with enantioselectivities up to 97%. The reaction can be carried out under these conditions also using aldehydes as nucleophiles, yielding after in situ reduction of the aldol products the corresponding chiral 1,3-diols with moderate to high enantioselectivities mainly as *anti*-isomers. The aldol reaction has been studied by the use of positive ESI-MS technique, providing the evidence of the formation of the corresponding enamine−iminium intermediates.

Introduction

Catalytic enantioselective processes[1] are the most attractive alternative to produce chiral compounds with high selectivity and efficiency.[2] In this field, the use of transition metal catalysts was the preferred option at the end of the last century. Nowadays, the use of metal-free processes, so-called organocatalysis,[3] is regarded as an environmentally benign strategy due to the advantages related to handling, cost, and safety issues. Organocatalysts are usually more stable, less expensive, readily available, and can be applied in less demanding reaction conditions than transition metal catalysts, and their use reduces the toxicity of products. In addition, this type of strategy allows the suppression of protection−deprotection steps, and therefore, the direct synthesis of structurally complex chiral molecules can be achieved by a highly efficient chemical process. However, most of the reactions involving organocatalysts are equilibrium processes, which generally need a huge excess of one of the reactants, normally the nucleophile, to generate the products with high yields. Besides this drawback, normally long reaction times and high catalyst loading are needed. In the pursuit of a more efficient and greener process,[4] the application of solvent-free reaction conditions[5] in organocatalyzed processes should be regarded as an improvement in the synthesis of complex molecules.[6]

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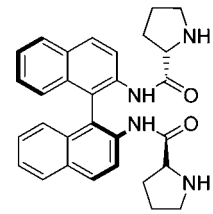
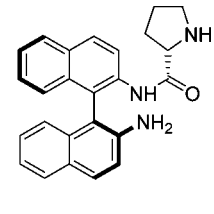
On the other hand, the aldol reaction[7] is extensively applied in industry either in bulk or in fine chemical manufacture and pharmaceutical target production, and therefore, the application of "green conditions" is of great interest.[8] This C−C bond-forming reaction provides a molecule which bears one or more stereogenic centers.[9] Among other asymmetric catalytic methods, organocatalyzed processes have been extensively applied in this reaction.[10] Several reaction conditions have been developed[11] in order to achieve higher efficiencies, and only recently the use of solvent-free conditions has been reported.[6b,d,e] Thus, L-proline (10 mol %) has been used as organocatalyst for the aldol condensation of alkyl symmetrical ketones and aldehydes using a ball milling[12] technique, affording the expected aldol with high yields (53−99%) mainly as *anti*-isomers (dr's from 1:1 to 93:7) and with good enantioselectivities (ee's from 56 to 99%) in short reaction times (5–36 h) and with 2 equiv of ketone.[6b,e] The use of conventional magnetic stirring for the same solvent-free reactions gave similar results, but longer reaction times were required (1−4 days). These conditions have also been applied to the aldehyde−aldehyde aldol reaction, giving after 1−4 days mainly the *anti*-aldol products with good yields (40−91%) and diastereo- (dr's from 77:23 to 93:7) and enantioselectivities (ee's from 92 to 98%).[6d]

Prolinamides derived from 1,1′-binaphthyl-2,2′-diamine (**1a** and **1b**) have been studied as catalysts in the aldol reaction under different reaction conditions using cyclic or acyclic alkyl[13] and α-functionalized[14] ketones as nucleophiles. Bisprolinamides (S_a)-binam-L-Pro **1a** and its enantiomer were more efficient than other bis- or monoprolinamide derivative **1b**,[13a] with the addition of benzoic acid as cocatalyst in the reaction being crucial to obtaining a great acceleration in the reaction. Under these reaction conditions, less reactive ketones, such as butanone[13c] and α-functionalized ketones, can be used as nucleophile source in organic solvents or even in the presence of water[13f,14] to give the corresponding aldols products with a high level of selectivity. Catalyst **1a** can also be recovered by simple extractive workup after the reaction completion.[13a,c]

Recently, we have reported the enantioselective direct intermolecular aldol under solvent-free conditions catalyzed by (*S*)-binam-L-prolinamide **1a** (5 mol %) and benzoic acid (10 mol %) under simple conventional magnetical stirring, in short reaction times and using only 2 equiv of several cyclic and acyclic aliphatic and α-functionalized ketones with 4-nitrobenzaldehyde, giving the corresponding aldol products with enantioselectivities highly dependent on the ketone.[15] Herein, we report a full account and the mechanistic studies about the aldol reaction under solvent-free conditions, catalyzed by binam-derived prolinamides in this type of transformation.



1a



1b

Results and Discussion

Catalyst **1a** was synthesized by coupling of commercially available (*S*)-1,1′-binaphthyl-2,2′-diamine [(*S*)-binam] and the in situ generated Fmoc-L-Pro chloride (2.1 equiv) followed by

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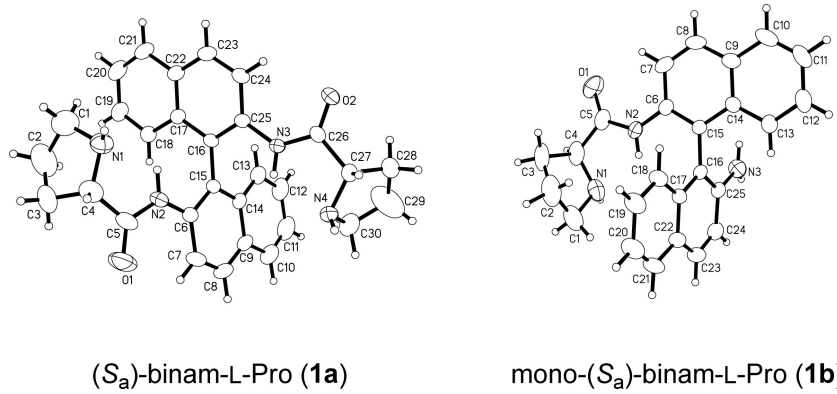
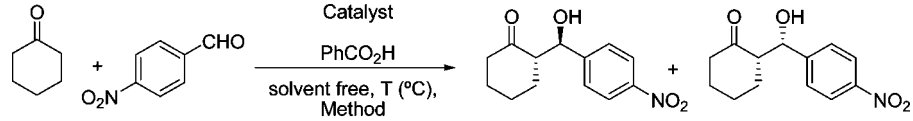


FIGURE 1. Single-crystal X-ray structure of compounds **1a** and **1b**.

TABLE 1. Optimization of the Used Method under Solvent-Free Conditions for the Reaction of Cyclohexanone and 4-Nitrobenzaldehyde[a]



2a **3a** *anti*-**4aa** *syn*-**4aa**

entry	method[b]	catalyst (mol %)	benzoic acid (mol %)	ketone (equiv)	T (°C)	t (h)	conversion (%)[c]	*anti*/*syn*[d]	ee (%)[e]
1	A	**1a** (10)	20	2	25	1.0	99	67:33	88
2	B	**1a** (10)	20	2	25	1.5	99	72:28	89
3	C	**1a** (10)	20	2	25	1.5	100	69:31	88
4	A	**1a** (10)	20	2	0	1.5	80	83:17	90
5	B	**1a** (10)	20	2	0	2.0	94	89:11	93
6	A	**1a** (10)	20	1	0	1.5	65	82:18	88
7	B	**1a** (10)	20	1	0	5.5	98	92:8	93
8	A	**1a** (5)	10	2	0	2.0	99	90:10	86
9	B	**1a** (5)	10	2	0	4.0	94	93:7	90
10	A	**1a** (5)	0	2	0	4.0	82	97:3	90
11	B	**1a** (5)	0	2	0	4.0	94	96:4	90
12	A	**1b** (5)	10	2	0	8.0	85	87:13	83
13	B	L-Pro (10)	-	2	0	24	34	96:4	96
14	B	L-Pro (10)	10	2	0	24	60	94:6	94

[a] General reaction conditions: the reaction was carried out using 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (2 or 1 equiv). [b] Method A: Conventional magnetic stirring. Method B: 4-Nitrobenzaldehyde, catalyst, and benzoic acid were dissolved in dry THF (0.5 mL), and the solvent was evaporated previous to the addition of the cyclohexanone. Method C: The grinding bowl containing the reaction mixture was rotated in a ball mill at a rotation speed of 400 rpm. [c] Conversion based on the amount of the unreacted aldehyde. [d] Determined by ^{1}H NMR of the crude product. [e] Determined by chiral phase HPLC analysis for the *anti*-**4aa** isomer.

deprotection with piperidine. After chromatographic purification, pure system **1a** was obtained in 97% overall yield. When only 1.1 equiv of Fmoc-L-Pro chloride was used in the coupling step, catalyst **1b** was obtained as the main product and isolated in 58% yield after purification. Suitable crystals for X-ray diffraction experiment of both compounds were obtained from $CHCl_3$/Et_2O at −20 °C, showing that the dihedral angle between the binaphthyl groups in compound **1a** was 81.51°, whereas for compound **1b**, it was of 83.45° (Figure 1).[16]

The organocatalyzed solvent-free aldol reaction was carried out with cyclohexanone (**2a**) and 4-nitrobenzaldehyde (**3a**) as a model, and different parameters were studied, such as the amount of ketone, the catalyst, the temperature, method to carry out the process, and comparing the obtained results with those obtained under similar reaction conditions with L-proline.

Three different methods were tested: conventional magnetic stirring (method A), conventional magnetic stirring with previous solution in THF (method B),[17] and ball milling conditions (method C), under different temperatures and equivalents of cyclohexanone (Table 1). The reaction of 4-nitrobenzaldehyde and 2 equiv of cyclohexanone at 25 °C using 10 mol % of **1a** and 20 mol % of benzoic acid was carried out using these three

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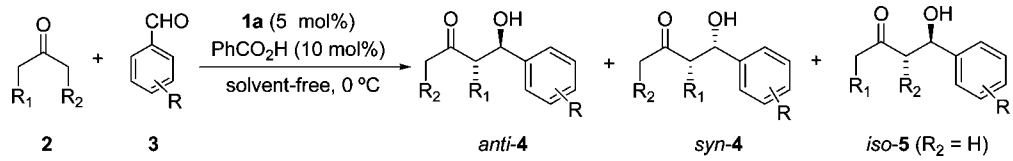
SCHEME 1. Aldol Reaction Catalyzed by 1a/Benzoic Acid of Different Ketones with Different Aldehydes under Solvent-Free Conditions



different methods. The expected products were obtained after only 1−1.5 h, with similar results for all of them, 99−100% conversions and 88−89% ee and moderate dr (Table 1, entries 1−3) but in shorter reaction time using method A (Table 1, entry 1). Conversely to the previous reported results with L-proline,[6b,e] the use of the ball milling technique (method C, Table 1, entry 3) did not render the aldol product in shorter reaction time or with better results than those obtained using conventional magnetical stirring. Therefore, the optimization of other reaction parameters was done by using methods A and B using simple conventional magnetic stirring. Then, the influence of the reaction temperature and the amount of cyclohexanone (**2a**) in the results was studied using methods A and B. Decreasing the temperature to 0 °C, using 10 mol % of **1a** and 20 mol % of benzoic acid, and methods A and B, we observed a slight increase of the reaction time with better diastereo- and enantioselectivities up to 93% ee (Table 1, entries 4 and 5).

By reduction of the amount of cyclohexanone to 1 equiv, using method A or B, longer reaction times were needed for the reaction completion (Table 1, compare entries 4 with 6, and 5 with 7), but compound **4aa** was obtained with similar selectivities. Reducing the amount of catalyst **1a** and benzoic acid to 5 and 10 mol %, respectively, led to an increase in the reaction time, with a slight increase in the achieved diastereoselectivities and a small decrease in the obtained enantioselectivities being observed (Table 1, entries 8 and 9). In the absence of benzoic acid, a decrease in the reaction rate but an increase in the diastereoselectivity and the enantioselectivity by using method A was observed (Table 1 compare entry 8 with 10). Using method B, the absence of acid did not have any considerable effect on the reaction rate, diastereo-, and enantioselectivities obtained (Table 1, compare entries 9 and 11).

Catalyst **1b** (5 mol %) and benzoic acid (10 mol %) were less efficient than catalyst **1a**, affording product **4aa** in 8 h with lower enantioselectivity (Table 1, compare entries 8 and 12). When L-proline (10 mol %) was used as catalyst under method B conditions, low conversion was observed even after 24 h reaction time, but product **4aa** was achieved in excellent diastereo- and enantioselectivities (Table 1, entry 13). In order to increase the conversion, benzoic acid (10 mol %) was added to the reaction mixture, achieving aldol **4aa** with higher conversion (60%) after the same time, but with slightly lower diastereo- and enantioselectivities (Table 1, compare entries 13 and 14). Other conditions tested with L-proline as catalyst gave better conversion but afforded the aldol product with much lower diastereoselectivities and enantioselectivities. In view of the obtained results, some conclusion about the appropriate amount of catalyst **1a** and benzoic acid can be made. The best compromise between the reaction rate, yield, amount of ketone, and diastereo- and enantioselectivities was achieved by using 2 equiv of cyclohexanone, 5 mol % of **1a** in the presence of 10 mol % of benzoic acid, with longer reaction times required using method B but with increased selectivity (Table 1, entries 8 and 9). For comparison, when the same reaction was carried out in DMF/H_2O (1:1) at −20 °C using a higher catalyst loading of **1a** (10 mol %) and benzoic acid (20 mol %), a large excess of cyclohexanone (26.4 equiv) must be used. This reaction took place in 2 h with full conversion affording product **4aa**, with 98% de and 97% ee for the *anti*-isomer.[13c] Alternatively, pure H_2O at 0 °C was used under the same reaction conditions, affording mainly *anti*-**4aa** with 99% conversion in only 1.5 h with 90% de and 94% ee.[13c]

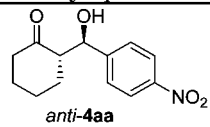
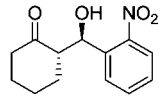
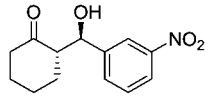
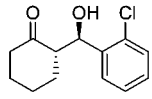
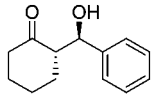
The scope of the solvent-free process using method A was studied using several aromatic aldehydes and cyclohexanone as donor (Scheme 1 and Table 2).

When different aromatic activated aldehydes were allowed to react with cyclohexanone under **1a**/benzoic acid catalysis, the corresponding aldol products were obtained in 80−86% yields, 80−90% de, and 84−90% ee, mainly as *anti*-isomers (Table 2, entries 1−4). Comparing these results with those obtained with L-proline (10 mol %) using ball milling conditions, the reaction times were similar, giving the aldol products in slightly higher yields and ee but with lower de.[6e] When nonactivated aldehyde, such as benzaldehyde, was used as electrophile, longer reaction time was needed for the completion of reaction and lower yields were obtained although the diastereo- and enantioselectivities for the *anti*-**4ae** were rather high (Table 2, entry 5). In this case, the use of ball milling conditions and L-proline (10 mol %) as catalyst afforded the aldol product in shorter reaction time with similar yields but with lower diastereo- and enantioselectivities.[6e]

Then, the reaction of different cyclic ketones with 4-nitrobenzaldehyde was studied using methods A, B, and C (Scheme 1 and Table 3). Whereas cyclohexanone gave exclusively the *anti*-**4aa** product with high enantioselectivities using methods A and B (Table 3, entries 1 and 2), the use of cyclopentanone afforded a nearly 1:2 mixture of *anti*/*syn*-**4ba** isomers with higher ee for the *anti*-isomer (Table 3, entries 3 and 4). In solution, using 10 mol % of catalyst **1a**, 20 mol % of benzoic acid, and 26.4 equiv of cyclopentanone in DMF/H_2O (1:1) at −20 °C, the *syn*-isomer was mainly obtained (44:66 dr) after 1.5 h in 61% ee. Carrying the reaction in pure H_2O at 0 °C gave results comparable to those achieved in DMF/H_2O but after 1 h of reaction time.[13c] Heterocyclic ketones **2c**−**2e** are also suitable nucleophiles for the aldol reaction,[18] affording under solvent-free conditions the expected products mainly as *anti*-isomers. The purification of such compounds (**4ca**, **4da**, and **4ea**) was carried out by filtration through a small pad of silica gel or by removal of the catalyst by acid extraction and subsequent purification of the aldols by recrystallization since epimerization of the aldol products was observed under column chromatography purification. Whereas ketones **2c** and **2d** gave high ee exclusively for the *anti*-**4ca** and *anti*-**4da** aldols, respectively, (Table 3, entries 5−8), the

(18) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198–8202.

TABLE 2. Reaction of Aldehydes with Cyclohexanone under Solvent-Free Conditions Using Method A[a]

entry	major product	t (h)	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	 *anti*-**4aa**	2	80	90:10	86
2	 *anti*-**4ab**	8	83	94:6	88
3	 *anti*-**4ac**	9	81	95:5	90
4	 *anti*-**4ad**	8	86	93:7	84
5	 *anti*-**4ae**	22	54	96:4	86

[a] General reaction conditions: aldehyde (0.25 mmol), cyclohexanone (0.5 mmol), (S_a)-binam-L-Pro **1a** (5 mol %), and benzoic acid (10 mol %) at 0 °C. [b] Yield of the pure product after flash column chromatography. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral phase HPLC analysis.

use of *N*-Boc-protected piperidin-4-one (**2e**) led to a mixture of *anti*-**4ea**/*syn*-**4ea** in 76% ee for the *anti*-isomer (Table 3, entry 11).

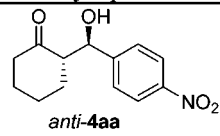
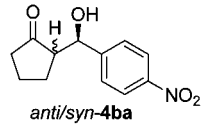
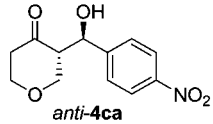
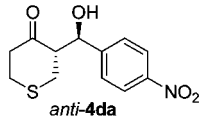
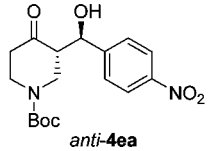
For ketone **2c**, using method B, the results were comparable to those obtained using method A, but longer reaction times were needed. However, for solid ketones, **2d** and **2e**, it was necessary to use method B or method C in order to obtain the corresponding aldol products in high yields. Using method C, product *anti*-**4da** was achieved with a yield and enantioselectivity higher than that obtained with method B (Table 3, entries 7 and 9), whereas *anti*-**4ea** was obtained with lower yield and enantioselectivity but with slightly better diastereoselectivity than with method B (Table 3, entries 11 and 13). The use of L-proline (10 mol %) as catalyst under method B conditions gave the corresponding aldol products in much longer reaction time but with similar diastereo- and enantioselectivities for product *anti*-**4da** (Table 3, entries 8 and 12). Under ball milling conditions using L-proline as catalyst,[6e] compound *anti*-**4da** was achieved with similar yield and slightly higher de and ee (Table 3, entry 10). For solid ketone **2e**, longer reaction time was required, obtaining *anti*-**4ea** with similar yield, higher de but lower ee (Table 3, entry 14).[6e]

Then, several acyclic alkyl ketones, such as acetone and butanone and α-functionalized ketones as nucleophiles, were tested in the reaction with 4-nitrobenzaldehyde (Scheme 1 and Table 4). Acetone was tested as nucleophile, affording the aldol product **4fa** in only 3 h in 86% yield and 74% ee using method A. Using method B, similar results were obtained but longer reaction time was required (Table 4, entries 1 and 2). These results were better than those reported by using the ball milling technique (Table 4, entry 3).[6b,e] Longer reaction time (8 h) was required by carrying out the reaction in DMF/H_2O (1:1) at −20 °C using catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of acetone, achieving compound **4fa** in higher 94% yield and 86% ee.[13c] When H_2O at 0 °C was used as solvent under similar reaction conditions, the aldol product was obtained after 20 h with quantitative yield but with 75% ee.[13c] In the case of 2-butanone, a mixture of *anti*-**4ga** (62% yield) and *iso*-**5ga** (38% yield) with excellent 97 and 91% ee was obtained in only 1 day (Table 4, entry 4). The use of method B led to similar results but in longer reaction times (Table 4, entry 5). For comparison, carrying out the reaction in solution, DMF/H_2O (1:1) at −20 °C using catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of ketone, gave similar results after 1 day and in pure H_2O at 0 °C as solvent; the results were similar in only 12 h reaction time.[13c]

When α-functionalized ketones were tested as nucleophiles, the results were dependent on the functionality. Thus, when α-chloroacetone (**2h**) was used as nucleophile, the aldol product *anti*-**4ha** was mainly obtained with a 94:6 regioisomer ratio **4**/**5**, 81:19 dr, and 72% ee. Due to the lability of the aldol **4ha** toward column chromatography purification, the obtained mixture was converted by treatment with Et_3N in CH_2Cl_2 to the corresponding *trans*-α,β-epoxycarbonyl compound **6ha** in 76% yield and 66% ee (Table 4, entry 6, and Scheme 2).[14c] Using the same protocol in solution, DMF/H_2O (1:1) at 0 °C, catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of ketone, after treatment with Et_3N in CH_2Cl_2, the epoxide **6ha** was obtained with 45% yield and 83% ee.[14c]

Using α-fluoroacetone (**2i**) as source of nucleophile, a double loading of catalyst **1a** (10 mol %) and benzoic acid (20 mol %) was needed in order to achieve the aldol product in good yield and moderate regioselectivity (50%) and 38% de (Table 4, entry 7). Longer reaction times and lower diastereoselectivity were observed by using method B (Table 4, entry 8). However, using the same catalyst loading and 26.4 equiv of α-fluoroacetone (**2i**) in DMSO at 25 °C, aldol **4ia** was obtained after 48 h in

TABLE 3. Reaction of 4-Nitrobenzaldehyde with Cyclic Ketones under Solvent-Free Conditions[a]

entry	method[b]	major product	t (h)	yield (%)[c]	*anti*/*syn*[d]	ee (%)[e]
1	A	 *anti*-**4aa**	2	80	90:10	86
2	B		4	85	96:4	90
3	A	 *anti*/*syn*-**4ba**	3	64	30:70	80 (46)[f]
4	B		7	86	28:72	80 (43)[f]
5	A	 *anti*-**4ca**	17	68[g]	84:16[g]	72[g]
6	B		21	71[g]	86:14[g]	76[g]
7	B[h]	 *anti*-**4da**	4	64[g]	93:7[g]	80[g]
8	B[i]		48	76[g]	94:6[g]	72[g]
9	C[h]		8	75[i]	88:12[i]	84[i]
10	C[k]		34	79	96:4	90
11	B[h]	 *anti*-**4ea**	48	69[g]	65:35[g]	76[g]
12	B[i]		192	77	92:8	90
13	C[h]		8	43[g]	73:26	70
14	C[k]		36	50	86.14	55

[a] General reaction conditions: 4-nitrobenzaldehyde (0.25 mmol), ketone (2 equiv), (S_a)-binam-L-Pro **1a** (5 mol %), and benzoic acid (10 mol %) at 0 °C, unless otherwise stated. [b] As in Table 1. [c] Yield of the pure product after flash chromatography. [d] Determined by ^{1}H NMR of the pure product. [e] Determined by chiral phase HPLC analysis. [f] In parentheses is the ee for the *syn*-isomer. [g] Yields, de, and ee determined after purification of the crude reaction mixture by filtration through a small pad of silica gel. [h] The reaction was carried out at 25 °C. [i] The reaction was carried out using L-Pro (10 mol %) at 25 °C. [j] Yields, de, and ee determined after purification of the crude reaction mixture by acidic extraction and recrystallization. [k] Previously reported results on ref 6e obtained with L-Pro as catalyst.

94% conversion and excellent regioselectivity (>99:1), high 84% de, and 93% ee.

When α-oxygenated ketones were used as donors, good yields and regioselectivities were achieved (Table 4, entries 9−15). However, whereas α-hydroxyacetone (**2j**) gave poor ee (Table 4, entries 9 and 10), α-methoxyacetone (**2k**) and α-benzyloxylacetone (**2 L**) gave mainly the *anti*-aldols **4ka** and **4la**, respectively, with good ee's (Table 4, entries 11−15). In order to obtain aldol product **4ja** with good results, the reaction must be carried out as previously described in DMSO at 0 °C using 20 mol % of catalyst **1a** and 26.4 equiv of α-hydroxyacetone, giving after 24 h mainly *anti*-**4ja** (96% yield, 80:20 regioisomeric ratio, 70:30 dr) with 80% ee.[14b] In the case of α-methoxyacetone (**2k**), best results concerning enantioselectivity (80%) were obtained by using method B, although longer reaction time was required (Table 4, entries 11 and 12).

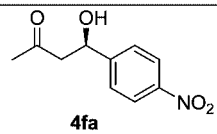
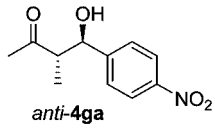
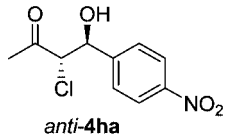
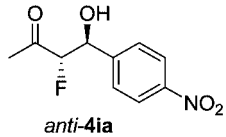
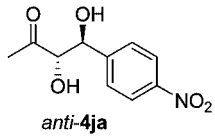
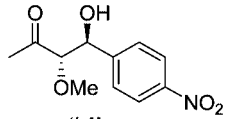
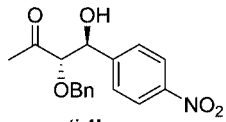
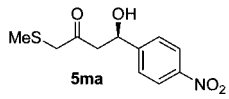
In solution, similar results were achieved by using catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of **2k** in DMF/H_2O (1:1) at 0 °C after 25 h.[14b] For the case of α-benzyloxylacetone (**2l**), *anti*-**4al** aldol was mainly obtained with similar diastereo- and enantioselectivities by using method A or B, but in higher yield, regioisomeric ratio, and shorter reaction time with method A (Table 4, entries 14 and 15). In DMF as solvent and using catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of **2l**, aldol **4la** was obtained after 39 h with high conversion, but with lower regio- and diastereoselectivities and in 88% ee.[14b]

Using α-(methylsulfanyl)acetone (**2m**) as nucleophile afforded mainly the *iso*-**5ma** product with a regioselectivity of 1:5 and 86% ee using method A (Table 4, entry 16). Under method B conditions, longer reaction time was required (7 days), giving lower yield and regioselectivity with slightly better ee (Table 4, entry 17). Carrying the reaction in solution, best results were achieved using H_2O at 0 °C as solvent and catalyst **1a** (10 mol %), benzoic acid (20 mol %), and 26.4 equiv of ketone, giving after 21 h mainly the *iso*-**5ma** (ratio **4**/**5** 1:8) with 93% ee.[14b] For the case of ketones **2k**, **2i**, **2k**, and **2l**, L-proline (10 mol %) was tested as catalyst under method B conditions. Only in the case of α-methoxyacetone (**2k**) was the aldol product obtained with low yield (Table 4, entry 13).

Finally, the recovery of the catalyst was studied in the reaction between cyclohexanone and 4-nitrobenzaldehyde. For that purpose, after the reaction was finished, the dissolved reaction mixture in AcOEt was treated with 6 M HCl. The aqueous phase containing the catalyst was treated with saturated NaOH until pH 10 and extracted with ethyl acetate. After flash chromatographic purification, 86% of the catalyst was recovered and reused in another catalytic cycle, affording results similar to that obtained in the first use, 81% yield, 91:9 *anti*/*syn* ratio, 84% ee for *anti*-**4aa** (compare with Table 2, entry 1).

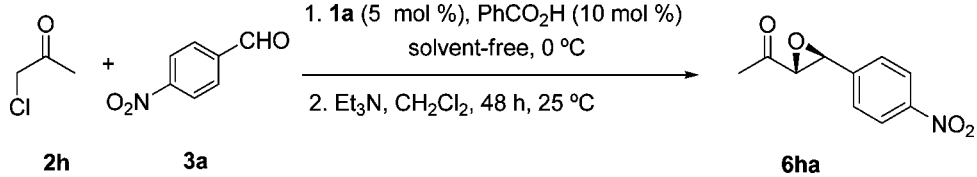
The use of solvent-free conditions can be also applied to the more challenging aldol reaction between aldehydes. Therefore, several aromatic aldehydes were allowed to react with propanal (5 equiv) at 0 °C using catalyst **1a** (5 mol %) and benzoic acid (10 mol %). After 5−7 days reaction time, the obtained aldol products were reduced in situ to give diols **8** in moderate to good yields, mainly as *anti*-isomers with high enantioselectivities (Table 5). Thus, when 4-nitrobenzaldehyde was used as acceptor, the reaction took place in 6 days, yielding, after in situ reduction, the corresponding diol **8aa** in 45% yield, 56% de,

TABLE 4. Reaction of 4-Nitrobenzaldehyde with Acyclic Ketones under Solvent-Free Conditions[a]

entry	method[b]	major product	t (h)	Yield (%)[c]	regioisomer **4**/**5**	*anti*/*syn*[d]	ee (%)[e]
1	A	 **4fa**	3	86	-	-	74
2	B		8	88	-	-	74
3	C[f]		19	73	-	-	56
4	A	 *anti*-**4ga**	24	96	63:37	>99:1	97 (91)[g]
5	B		40	97	55:45	>99:1	90 (99)[g]
6	A	 *anti*-**4ha**	45	76[h]	94:6	81:19	66[h]
7[i]	A	 *anti*-**4ia**	17	86	75:25	69:31	80
8[i]	B		40	98[j]	75:25	50:50	78
9	A	 *anti*-**4ja**	4	76[j]	>99:1	75:25	16
10	B		21	92[k]	49:1	64:36	20
11	A	 *anti*-**4ka**	4	78[j]	94:6	83:17	60
12	B		21	84	91:9	83:17	80
13	B[k]		48	3	89:11	80:20	94
14	A[l]	 *anti*-**4la**	78	78	97:3	86:14	84
15	B		89	70	88:12	83:17	86
16	A	 **5ma**	48	74	16:84	50:50	86
17	B		168	70	17:73	49:51	90

[a] As in Table 3. [b] As in Table 3. [c] As in Table 3. [d] As in Table 3. [e] As in Table 3. [f] Previously reported results in ref 6e obtained with L-Pro as catalyst. [g] In parentheses is the ee of *iso*-**5ga**. [h] Yield and ee of the pure epoxide. [i] Reaction carried out with **1a** (10 mol %) and benzoic acid (20 mol %) at 25 °C. [j] Conversion based on the amount of the unreacted aldehyde. [k] The reaction was carried out using L-Pro (10 mol %) at 25 °C. [l] The reaction was carried out at −20 °C.

SCHEME 2. Formation of Chiral α-Epoxy Ketone 6ha by a Subsequent Aldol Condensation−S_N2 Displacement

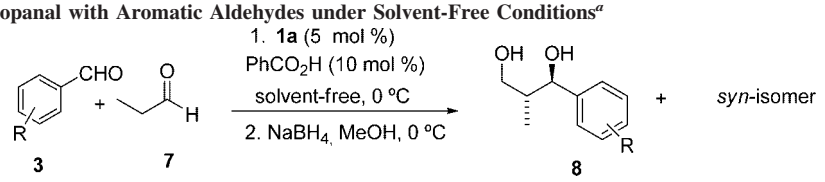


2h **3a** **6ha**

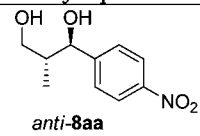
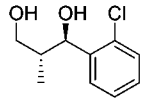
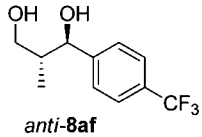
and 85% ee (Table 5, entry 1). However, the more hindered 2-chlorobenzaldehyde (**3d**) gave the diol with lower diastereo- and enantioselectivities (Table 5, entry 2). When 4-trifluoromethylbenzaldehyde was used as electrophile, again the diol product **8af** was achieved in high yield (96%), diastereoselectivity (78% de), and enantioselectivity (94% ee) (Table 5, entry 3). In this transformation, the use of a less activated aldehyde such as benzaldehyde as electrophile led to poor results (ca. 20% conversion) after 7 days reaction time.

The possible mechanism in the aldol reaction catalyzed by proline and its derivatives has been extensively discussed, with the enamine formation being assumed to be involved in the rate-determining step.[10,19] For the case of L-proline-catalyzed reaction, the formation of such an intermediate has been detected by employing electrospray-ionization mass spectrometry (ESI-MS);[20] this technique was also successfully applied for the aldol reaction catalyzed by L-prolinethioamides.[21] For the (S_a)-binam-L-Pro, one or both proline residues can be involved in the

TABLE 5. Reaction of Propanal with Aromatic Aldehydes under Solvent-Free Conditions[a]



3 7 8

entry	major product	t (d)	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	 *anti*-**8aa**	6	45	78:22	85
2	 *anti*-**8da**	7	60	59:41	40
3	 *anti*-**8af**	5	96	89:11	94

[a] General reaction conditions: the reaction was carried out using propanal (5 equiv), aldehyde (0.25 mmol), catalyst **1a** (5 mol %), and benzoic acid (10 mol %) at 0 °C. [b] Yield of the pure diol after flash chromatography. [c] Determined by ^{1}H NMR of the crude diol product. [d] Determined by chiral phase HPLC analysis for the *anti* isomer.

enamine formation, with the detection of such intermediates being possible by the use of ESI-MS experiments. For this purpose, to a mixture of catalyst **1a** and benzoic acid was added dry acetone at 0 °C, and the reaction mixture was stirred for 65 min. An aliquot of the mixture was diluted with methanol and analyzed by ESI-MS showing the signals *m*/*z* 479, 519, 559, and 599 corresponding to catalyst **1a**·H$^+$, monoenamine **9**·H$^+$, dienamine **10**·H$^+$, and dienamine **10**·H$_2$O·Na$^+$, respectively (Figure 2b). When the same experiment was carried out in the absence of benzoic acid, only the signals *m*/*z* 501 and 541 corresponding to catalyst **1a**·Na$^+$ and monoenamine **9**·Na$^+$, respectively, appeared (Figure 2a). Therefore, the presence of benzoic acid promotes the additional formation of dienamine **10**.

When 4-nitrobenzaldehyde was added to the above reaction mixture, that is, catalyst **1a**, benzoic acid, and dry acetone, after 3.5 h, very complicated *m*/*z* spectra were obtained having all the above-mentioned peaks and also three small signals *m*/*z* 231, 692, and 732, respectively, corresponding to the aldol product **4fa**·Na$^+$ and intermediates **11**·Na$^+$ and **12**·Na$^+$, showing that both or either enamine **9** or **10** can be involved in the formation of the aldol products (Figure 2c). However, only one arm is working in the aldol process. When the same experiment was carried out in the absence of benzoic acid, only the formation of the monoenamine **9**·Na$^+$ and a small peak corresponding to the intermediate **11**·Na$^+$ were detected (see Supporting Information). With these results, the catalytic cycle depicted in Figure 3 can be proposed as a possible reaction pathway, although other short-lived intermediates which cannot be detected by this MS technique cannot be excluded.

In summary, catalyst (S_a)-binam-L-Pro **1a** in combination with benzoic acid can be used under solvent-free reaction conditions under simple and conventional magnetic stirring with a wide scope of ketones and aldehydes. This procedure permitted us to reduce the amount of required ketone to 2 equiv, achieving the aldol products in shorter reaction times compared to the results in solvents[13,14] with high regio-, diastereo-, and enantioselectivities when alkyl and α-functionalized ketones are used as nucleophilic source. Generally *anti*-isomers were mainly obtained with enantioselectivities from 16 to 97%, which were highly dependent on the ketone. These results are comparable and sometimes better than those previously reported using the ball milling technique and L-proline as catalyst,[6b,e] with the additional advantage that conventional magnetic stirring is used. Under these conditions, the aldol reaction between aldehydes was also possible, yielding after in situ reduction mainly chiral 1,3-diols with moderate to high enantioselectivities. The application of ESI-MS techniques has permitted us to propose an enamine−iminium mechanism in which both proline moieties are involved, with the addition of benzoic acid being crucial

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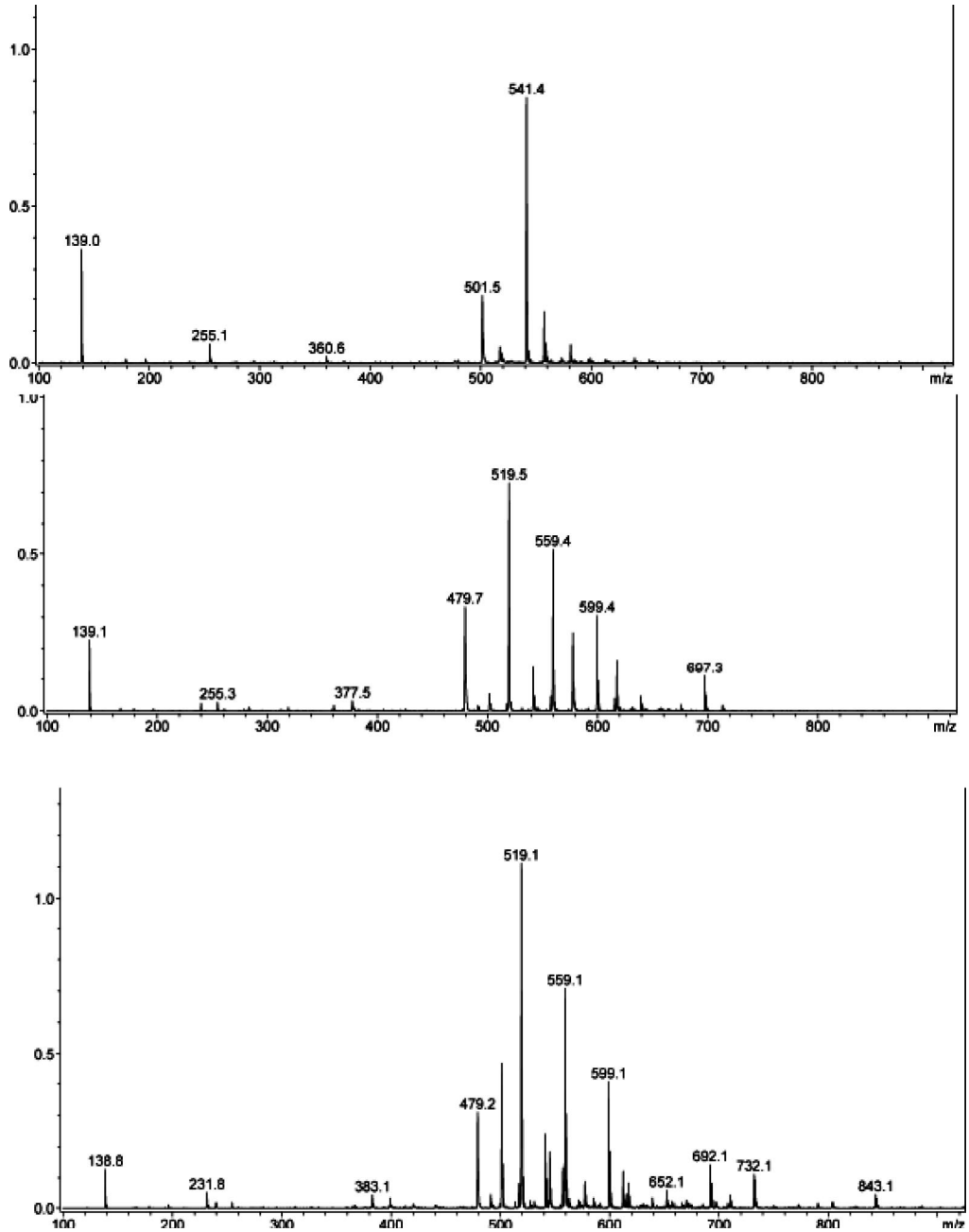

FIGURE 2. ESI-MS spectra for the aldol reaction catalyzed by prolinamide **1a**; (a) **1a** and acetone; (b) **1a**, benzoic acid, and acetone; (c) **1a**, benzoic acid, acetone, and 4-nitrobenzaldehyde.

for providing the enamine−iminium species and therefore to accelerate the reaction rates.

Experimental Section

Typical Procedure for the Aldehyde−Ketone Aldol Reaction Catalyzed by (S_a)-Binam-L-Prolinamide 1a under Solvent-Free Conditions. Method A: To a mixture of the 4-nitrobenzaldehyde (0.25 mmol, 0.037 g), catalyst **1a** (0.0125 mmol, 6 mg), and benzoic acid (0.025 mmol, 3 mg) under argon atmosphere at the indicated temperature was added cyclohexanone (0.5 mmol, 0.052 mL). The reaction was stirred until the aldehyde was consumed (monitored by TLC). Then, the crude product was diluted in CH_2Cl_2 (10 mL), silica gel was added, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (hexanes/AcOEt) to yield the pure aldol product. **Method B:** To a mixture of the 4-nitrobenzaldehyde (0.25 mmol, 0.037 g), catalyst **1a** (0.0125 mmol, 6 mg), and benzoic acid (0.025 mmol, 3 mg) under argon atmosphere at the indicated temperature was added dry THF (0.5 mL), and the corresponding mixture was stirred for 5 min. Then, the solvent was completely evaporated in vacuo during 15 min. The reaction flask was cooled to the indicated temperature, and cyclohexanone (0.5 mmol, 0.052 mL) was added. The reaction was stirred until the aldehyde was consumed, and the above workup procedure was carried out to yield the pure aldol product. **Method C:** To a mixture of the 4-nitrobenzaldehyde (0.25 mmol, 0.037 g), catalyst **1a** (0.0125 mmol, 6 mg), and benzoic acid (0.025 mmol, 3 mg) at 25 °C in a ball mill vessel was added cyclohexanone (0.5 mmol, 0.052 mL). The reaction mixture was stirred in a grinding bowl using a ball mill with a rotation speed of 400 rpm for 30 + 5 min pause periods until the aldehyde

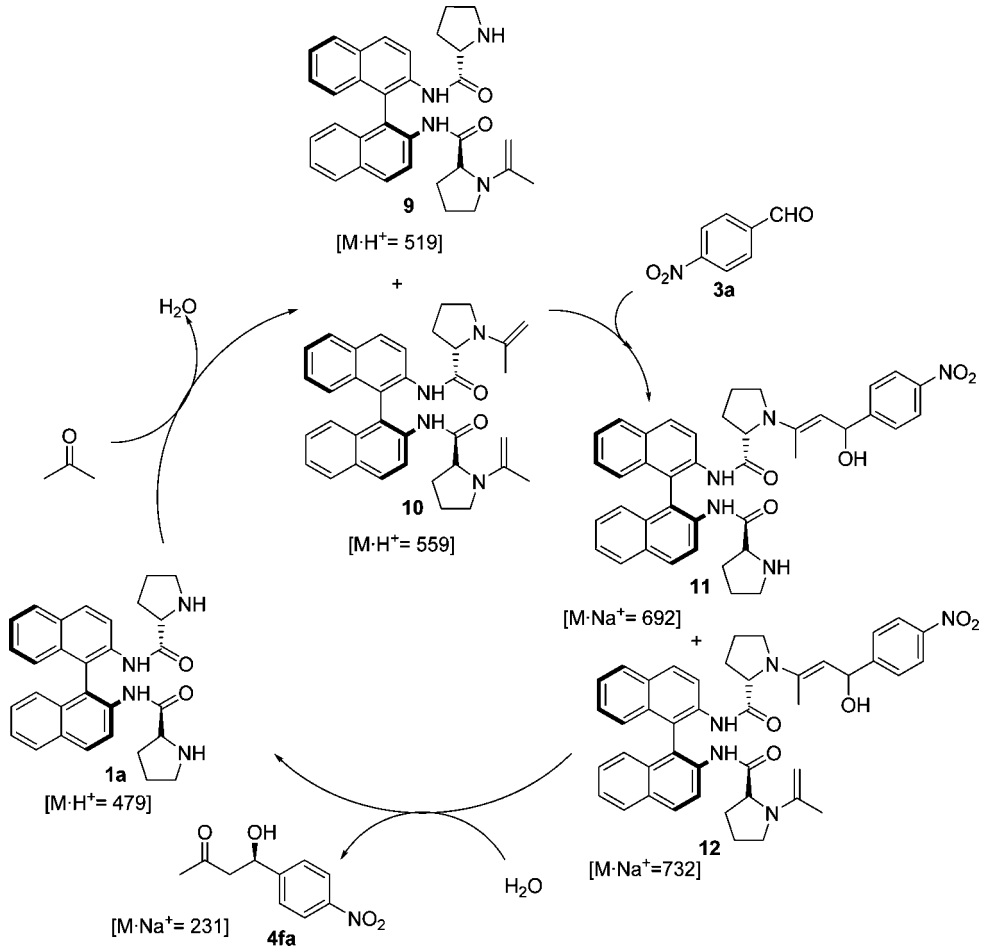

FIGURE 3. Possible catalytic cycle for the aldol reaction mediated by binam-prolinamide **1a**.

was consumed, and the above workup procedure was carried out to yield the pure aldol product **4**.

Compound 4aa: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28−1.49 (m, 1H), 1.52−1.73 (m, 3H), 1.79−1.83 (m, 1H), 2.06−2.14 (m, 1H), 2.21−2.31 (m, 1H), 2.33−2.50 (m, 1H), 2.54−2.63 (m, 1H), 3.12 (br s, 1H *syn*), 4.02 (br s, 1H *anti*), 4.88 (d, J = 8.4 Hz, 1H *anti*), 5.46 (s, 1H *syn*), 7.49 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *anti* 24.6, 27.5, 30.6, 42.6, 57.1, 73.9, 123.5, 127.8, 147.4, 148.3, 214.6; ^{13}C NMR (75 MHz, $CDCl_3$) δ *syn* 24.7, 25.8, 27.7, 42.5, 56.7, 70.0, 123.4, 126.5, 147.5, 149.2, 213.9.

Typical Procedure for Catalyst Recovery: To a mixture of 4-nitrobenzaldehyde (4.2 mmol, 0.625 g), catalyst **1a** (0.21 mmol, 100 mg), and benzoic acid (0.42 mmol, 52 mg) under argon atmosphere at 0 °C was added cyclohexanone (2 equiv, 8.4 mmol, 0.88 mL). The reaction was stirred for 6 h until the aldehyde was consumed (monitored by TLC). Then, the crude product was diluted in AcOEt (30 mL), and 6 M HCl (30 mL) was added, and the mixture was stirred for 10 min. The resulting emulsion was treated with saturated NaCl solution (3 × 15 mL). The aqueous layer was basified with saturated NaOH until pH 10 and extracted with EtOAc (3 × 30 mL). The organic phase was dried with $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (hexanes/AcOEt) to yield catalyst **1a** (75 mg, 81% recovery yield), which was used in the next reaction cycle.

Typical Procedure for the Aldehyde−Aldehyde Aldol Reaction Catalyzed by (S_a)-Binam-L-Prolinamide 1a under Solvent-Free Conditions: To a mixture 4-nitrobenzaldehyde (0.25 mmol, 0.037 g), catalyst **1a** (0.0125 mmol, 6 mg), and benzoic acid (0.025 mmol, 3 mg) under argon atmosphere at 0 °C was added propanal (1.25 mmol, 0.09 mL). The reaction was stirred for 5−7 days until the aromatic aldehyde was consumed (monitored by TLC). Then, the crude product was diluted with MeOH (0.8 mL), and $NaBH_4$ (1.25 mmol, 0.048 g) was added at 0 °C, and the mixture was stirred for 2 h. The resulting residue was purified by flash chromatography (hexanes/AcOEt 4:1) to afford pure products **8**.

Compound 8aa: $[\alpha]^{20}_D$ −56.7 (c = 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ *anti* 0.78 (d, J = 7.0 Hz, 3H), 2.01−2.06 (m, 1H), 2.74 (br s, 1H), 3.72−3.85 (m, 3H), 4.72 (d, J = 7.8 Hz, 1H *anti*), 7.54 (d, J = 8.7 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *anti* 13.6, 41.5, 67.4, 79.3, 123.6, 127.5, 147.4, 150.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ *syn* 0.82 (d, J = 7.2 Hz, 3H), 2.01−2.06 (m, 1H), 3.28 (d, J = 3.6 Hz, 1H), 3.67−3.84 (m, 3H), 5.14 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *syn* 9.8, 41.1, 66.6, 75.4, 123.3, 128.3, 147.6, 150.6.

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Supporting Information Available: Synthesis, characterization, ^{1}H and ^{13}C NMR spectra and X-ray structure of catalysts of catalysts **1a** and **1b**, and crystallographic information files. ESI-MS spectra of catalyst **1a** in the presence or absence of benzoic acid. General procedure for the aldol reaction. NMR and HPLC data for aldol products. NMR spectra and HLPC chromatograpms from aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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