DOI: 10.1002/adsc.200800814

Water *versus* Solvent-Free Conditions for the Enantioselective Inter- and Intramolecular Aldol Reaction Employing L-Prolinamides and L-Prolinethioamides as Organocatalysts

Diana Almaşi,[a] Diego A. Alonso,[a,*] Andrea-Nekane Balaguer,[a] and Carmen Nájera[a]

[a] Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante, Apartado 99, 03080, Alicante, Spain
Fax: (+34)-96-590-3549; e-mail: diego.alonso@ua.es or cnajera@ua.es

Received: December 29, 2008; Revised: February 3, 2009

Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800814.

Abstract: Organocatalysts **1**, derived from L-proline and (1*S*,2*R*)-*cis*-1-aminoindan-2-ol or (*R*)-1-aminoindane, are evaluated as promoters in the direct asymmetric aldol reaction between ketones and aromatic aldehydes in the presence of water and under solvent-free reaction conditions. L-Prolinethioamides **1c** and **1d** exhibited higher enantioselectivity than the corresponding prolinamides **1a** and **1b** in the model aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of 4-nitrobenzoic acid as cocatalyst. In particular, L-prolinethioamide **1d** (5 mol%), derived from L-proline and (*R*)-1-aminoindane, is shown as the most efficient organocatalyst studied promoting the direct aldol reaction of cycloalkyl, alkyl, and α-functionalized ketones with aromatic aldehydes in the presence of water and under solvent-free reaction conditions employing only 2 equivalents of nucleophile. Generally, *anti*-aldol products are obtained in high yields and excellent diastereo- and enantioselectivities (up to >98/2 *anti*/*syn*, up to 98% *ee*). Solvent-free conditions give slightly higher *dr* and *ee* than using water as solvent. In addition, organocatalyst **1d** can be easily recovered by extractive work-up and reused. Prolinethioamide **1d** (5 mol%) in combination with 4-$NO_2C_6H_4CO_2H$ (5 mol%) is also a very effective organocatalytic system for the asymmetric solvent-free intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction with comparable or higher levels of enantioselectivity (up to 88% *ee*) to other reported catalysts in organic solvents.

Keywords: aldol reaction; asymmetric organocatalysis; prolinethioamides; solvent-free reaction; water

Introduction

The direct asymmetric aldol reaction[1] is one of the most useful synthetic methods for the synthesis of chiral polyol derivatives. Asymmetric organocatalysis[2] has recently devoted a great emphasis to the design of efficient chiral organocatalysts for the aldol reaction *via in situ* generated enamine intermediates.[3] Organocatalyzed aldol reactions are very often environmentally friendly processes since no metal species are involved and the reactions can usually be performed without the use of inert atmosphere and anhydrous solvents. These reactions are typically performed under mild conditions in organic solvents such as DMSO, DMF, and chlorinated solvents or using a large excess of nucleophile which allows it to act as reaction medium as well. The necessity to further reduce sources of pollution, such as the sometimes employed chlorinated solvents, has prompted scientists to search for organic reactions performed in the presence of water[4] or under solvent-free conditions.[5] Organocatalysts that can perform in the presence of water are of current interest because water is a desirable solvent with respect to environmental concerns, safety, and cost.[6–8] On the other hand, organocatalyzed reactions under solvent-free conditions usually need shorter reaction times and result in simple and efficient work-up procedures.[9] For these reasons, or-

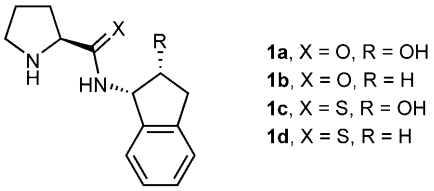


Figure 1. Prolineamide-derived organocatalysts for the direct aldol reaction.

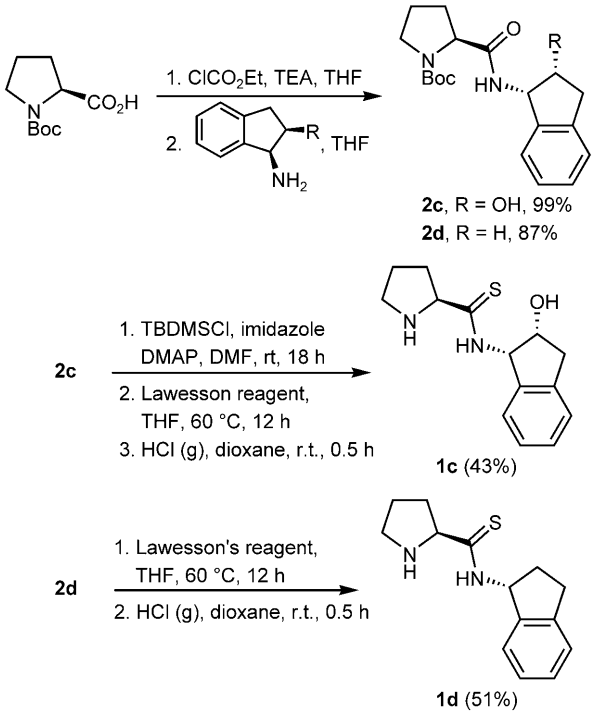
ganocatalyzed aldol reactions under solvent-free conditions or employing water as solvent have become a highly pursued goal in green chemistry.

Following our studies in the use of prolineamide-derived organocatalysts as efficient promoters for C–C bond forming processes, we have recently shown that prolineamide **1a**, derived from L-Pro and (1*S*,2*R*)-*cis*-1-amino-2-indanol (Figure 1), exhibits good catalytic activity in the asymmetric conjugate addition of ketones to nitrostyrenes in NMP as solvent.[10] On the other hand, we have communicated[11] that prolinethioamide **1d**, derived from L-Pro and (*R*)-1-aminoindane (Figure 1), is a very efficient and recyclable organocatalyst for the solvent-free direct aldol reaction with excellent levels of *anti*-diastereoselectivity (up to >96%) and enantioselectivity (up to 98% *ee*).[12] Herein, we report a full account about the direct inter- and intramolecular aldol reactions catalyzed by 1-aminoindane- and 1-aminoindanol-derived prolinamides and prolinethioamides using water as solvent and under solvent-free conditions.

Results and Discussion

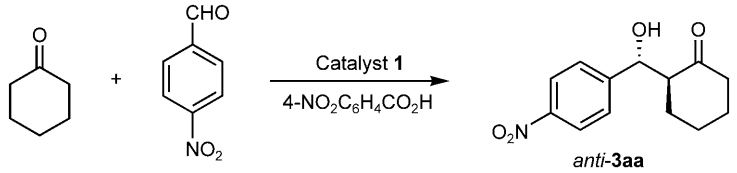
Prolinamides **1a** and **1b** were prepared in excellent yields by reaction of *N*-Cbz-L-Pro with (1*S*,2*R*)-*cis*-1-aminoindan-2-ol and (*R*)-1-aminoindane, respectively, and final hydrogenolysis (see Supporting Information).[10] On the other hand, catalysts **1c** and **1d** were prepared following reported procedures[12] from *N*-Boc-L-Pro instead due to Cbz hydrogenolysis problems associated with the presence of the thioamide moiety. Thus, reaction of *N*-Boc-L-Pro with commercially available (*R*)-1-aminoindane and (1*S*,2*R*)-*cis*-1-aminoindan-2-ol, led to *N*-Boc-L-prolinamide intermediates **2c** and **2d**, respectively (Scheme 1). Protection of the hydroxy function in **2c** with TBDMSCl, followed by thiation with Lawesson's reagent, and deprotection of the amine and hydroxy functions with a saturated solution of hydrogen chloride in dioxane led to prolinethioamide **1c** in good yield (Scheme 1). A similar procedure, except for the hydroxy protection, was followed to prepare prolinethioamide **1d** from intermediate **2d** in a 51% yield (Scheme 1).

The efficacy of organocatalysts **1** (20 mol%) using a carboxylic acid as cocatalyst (20 mol%) was first examined in the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of water (Method A) and under solvent-free conditions with conventional magnetic stirring (Method B) at room temperature (Table 1). A preliminary study (see Supporting Information) showed 4-nitrobenzoic acid (20 mol%) as the most efficient cocatalyst for the process in the presence of water. As depicted in Table 1 (entries 1–8) catalysts **1** exhibited high catalytic efficiency, especially prolinamide **1a** under solvent-free conditions (Method B), which provided a very fast cross-aldol reaction (10 min) although with moderate diastereo- and enantioselectivity (Table 1, entry 2). In general, the best results in terms of selectivity were obtained when the reaction was carried out in the presence of water (Method A) regardless of the catalyst employed. The highest diastereo- and enantioselectivity was observed with prolinethioamide **1d** (Table 1, entry 7) still under a very short reaction time [*anti*/*syn*: 91/9, 89% *ee* (*anti*), 3 h] employing water as solvent. Similar selectivities were observed for this catalyst under solvent-free conditions (entry 8, Method B), although a dramatic rate acceleration took place and the reaction was completed after 1 h. Similar results but with opposite enantioselectivity were obtained when *ent*-**1d** was used as catalyst under solvent-free conditions (entry 9). At this point, different reaction parameters were also studied in order to improve the selectivity of the process. For instance, under solvent-free conditions (Method B), the efficacy of catalyst **1d** was similar when the reaction was



Scheme 1. Synthesis of L-prolinethioamides **1c** and **1d**.

Table 1. Aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **1** in the presence of water (Method A) and under solvent-free conditions (Method B).



anti-**3aa**

Entry	**1** [mol%]	Method[a]	*T* [°C]	Time [h]	Conv. [%][b]	*anti*/*syn*[b]	*ee* [*anti*][c]
1	**1a** (20)	A	r.t.	3	95	87/13	81
2	**1a** (20)	B	r.t.	10 min	99	79/21	64
3	**1b** (20)	A	r.t.	3	97	77/23	71
4	**1b** (20)	B	r.t.	3	99	70/30	58
5	**1c** (20)	A	r.t.	3	99	88/12	87
6	**1c** (20)	B	r.t.	3	97	82/18	71
7	**1d** (20)	A	r.t.	3	99	91/9	89
8	**1d** (20)	B	r.t.	1	99	89/11	88
9	*ent*-**1d** (20)	B	r.t.	1	99	85/15	−88
10	**1d** (20)	B[d]	r.t.	1	98	91/9	86
11	**1d** (20)	B[e]	r.t.	1	98	87/13	74
12	**1d** (20)	A	12	5	96	91/9	89
13	**1d** (20)	B	0	5	97	92/8	88
14	**1d** (5)	A	12	8	98	98/2	94
15	**1d** (5)	B	0	8	99	94/6	93
16	**1d** (5)	A[f]	12	8	99	94/6	95
17	**1d** (5)	B[g]	0	24	95	98/2	93

[a] Method A: a mixture of the corresponding organocatalyst, 4-$NO_2C_6H_4CO_2H$, and cyclohexanone (4 equiv.) was stirred in water (0.5 mL mmol^{-1} aldehyde) for 20 min before addition of 4-nitrobenzaldehyde (1 equiv.). Then, the reaction mixture was stirred for the time indicated in the table. Method B: a mixture of the corresponding organocatalyst, 4-$NO_2C_6H_4CO_2H$, and cyclohexanone (2 equiv.) was stirred for 20 min before addition of 4-nitrobenzaldehyde (1 equiv). Then, the reaction mixture was stirred for the time indicated in the table.

[b] Determined by ^{1}HNMR over the crude reaction mixture.

[c] Determined by chiral phase HPLC analysis over the crude reaction mixture.

[d] The reaction was performed in a ball mill at 400 rpm.

[e] **1d**, 4-$NO_2C_6H_4CO_2H$, and 4-nitrobenzaldehyde were first dissolved in THF, then the solvent was evaporated and cyclohexanone (2 equiv.) was added to the mixture, which was stirred for 1 h.

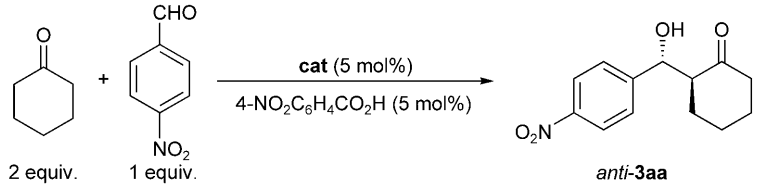
[f] 2 equiv. of ketone were used.

[g] 1 equiv. of ketone was used.

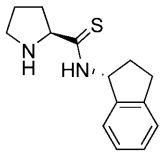
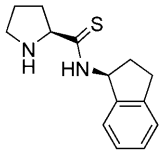
performed in a ball mill[9a,b] (Table 1, entry 10). Recently, a remarkable rate acceleration of solvent-free organic reactions has been described by Otera et al. by immediate solvent evaporation due to the enhancement of molecule to molecule contacts between reactants.[13] In our case, under conventional magnetic stirring with a pre-formed solution in THF and immediate evaporation of the solvent, similar rate and lower diastereo- (*anti*/*syn*: 87/13) and enantioselectivity (74% *ee*) were observed (Table 1, entry 11). The effect of the temperature in the process was also studied. When the reaction was perfored at lower temperature (12 °C for Method A and 0 °C for Method B) no improvement of the enantioselectivity was detected (compare entries 7 and 8 with 12 and 13, respectively). Finally, we were pleased to observe an improvement of diastereo- and enantioselectivity for the both methodologies (Method A: 98/2 *anti*/*syn*, 94% *ee*; Method B: 94/6 *anti*/*syn*, 93% *ee*) when reducing the catalyst and cocatalyst loading to 5 mol% under low temperature conditions and longer reaction times (Table 1, entries 14 and 15). Notably, reducing the amount of nucleophile to 2 equivalents in the case of using water as solvent, and to 1 equivalent when working under solvent-free conditions (Table 1, entries 16 and 17) was sufficient to afford the reaction in high yield and selectivity, although 8 and 24 h were necessary for completion, respectively.[14]

The mechanism of the direct asymmetric aldol reaction catalyzed by L-prolinethioamides has been previously studied by ^{1}H NMR and electrospray-ionization mass spectrometry (ESI-MS) techniques revealing that the reaction proceeds through an enamine-iminium pathway.[15] This could be confirmed for the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by **1d**/4-$NO_2C_6H_4CO_2H$ in the pres-

Table 2. Match/mismatch effect of prolinethioamides.



2 equiv. 1 equiv. *anti*-**3aa**

Entry	Catalyst	Method	*T* [°C]	Time [h]	Conv.[%][a]	*anti*/*syn*[a]	*ee* [*anti*][b]
1		A	12	8	99	94/6	95
2		B	0	8	99	94/6	93
	1d						
3		A	12	8	96	98/2	92
4		B	0	12	95	91/9	94
	4						

[a] Determined by ^{1}H NMR over the crude reaction mixture.
[b] Determined by chiral-HPLC analysis over the crude reaction mixture.

ence of water (Method A) since the ESI-MS spectrum in positive ion mode clearly displayed (see Supporting Information) a peak at $m/z = 327$ probably corresponding to the iminium intermediate.

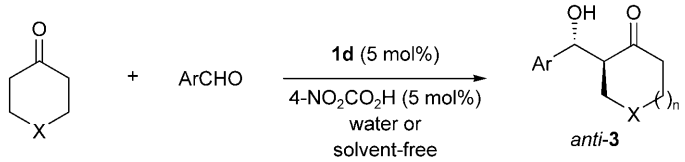
Diastereomeric catalyst **4**, prepared from L-Pro and (*S*)-1-aminoindane (see Supporting Information) was also tested as promoter of the reaction in order to test possible match/mismatch effects in the process (Table 2). It was found that, under optimized reaction conditions, there was not a significant match/mismatch effect in the reaction between cyclohexanone (2 equiv.) and 4-nitrobenzaldehyde (1 equiv.) (Table 2, entries 1–4) the enantioselectivity of the process being controlled by the proline moiety.

With respect to the recyclability of **1d**, it is worthy to mention that this organocatalyst could be easily recovered from the reaction mixture (Method A: 90% recovery; Method B: 91% recovery) after extractive acid/base work-up (HCl/NaOH) and reused with similar results since no loss of optical activity was detected in the organocatalyst (see Supporting Information).

Considerations of stereoselectivity and reaction time led us to focus our next study under the optimal reaction conditions for Methods A and B, as follows: Method A: ketone (2 equiv.), aldehyde (1 equiv.), **1d** (5 mol%), 4-nitrobenzoic acid (5 mol%), and H_2O (0.5 mL mmol^{-1} aldehyde) at 12 °C or room temperature; Method B: ketone (2 equiv.), aldehyde (1 equiv.), and **1d** (5 mol%) at 0 °C or room temperature, and 4-nitrobenzoic acid (5 mol%) in those cases where the reaction time was too long in its absence. Under these conditions, the direct cross-aldol reaction of other several acceptor aromatic aldehydes with aliphatic donor ketones was examined in order to study the reaction scope using water as solvent and under solvent-free conditions (Table 3). Reactions of cyclohexanone with a variety of electron-deficient aromatic aldehydes containing a variety of substitution patterns provided the desired *anti*-aldol products in high isolated yields (70–98%) with excellent diastereo- (95/5 to >98/2 *anti*/*syn*) and enantioselectivities (88–98% *ee*) (Table 3, entries 1–12). In general, under solvent-free conditions, slightly better stereoselectivities were obtained for all the studied reactions. The same trend was also observed for non-activated and deactivated aldehydes, such as benzaldehyde, 2-naphthaldehyde, and 4-methylbenzaldehyde. In those cases, the aldol reaction proceeded smoothly with longer reaction times even in the presence of 4-nitrobenzoic acid as cocatalyst to give the aldol products **3ah**, **3ai**, and **3aj**, respectively, in moderate yields, high diastereoselectivities and good enantioselectivities (Table 3, entries 13–18).

Heterocyclic cyclohexanones such as tetrahydro-4*H*-pyran-4-one, tetrahydro-4*H*-thiopyran-4-one, and *N*-Boc-4-piperidone reacted with 4-nitrobenzaldehyde leading to the corresponding *anti*-aldol adducts with high diastereo- and enantioselectivities (Table 3, entries 19–24). Good results were obtained in the presence of water and under solvent-free conditions in terms of yield and selectivity, though under the latter

Table 3. Aldol reactions of cycloalkanones with aldehydes catalyzed by **1d** in water (Method A) and under solvent-free conditions (Method B).



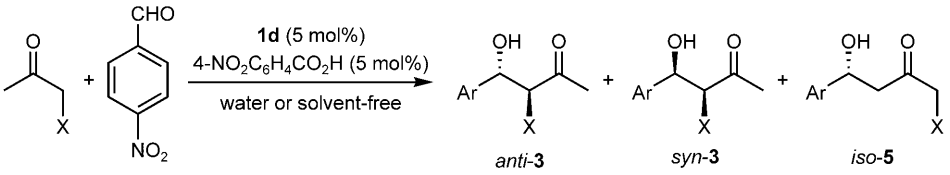
Entry	X	Ar	Method	T [°C]	Time [h]	No.	Yield [%][a]	*anti*/*syn*[b]	ee_{anti}[c]
1	CH_2	2-ClC_6H_4	A	12	36	**3ab**	82	95/5	88
2	CH_2	2-ClC_6H_4	B	0	48[d]	**3ab**	91	98/2	92
3	CH_2	4-ClC_6H_4	A	12	36	**3ac**	73	96/4	91
4	CH_2	4-ClC_6H_4	B	0	48[d]	**3ac**	70	97/3	94
5	CH_2	2-$NO_2C_6H_4$	A	12	24	**3ad**	90	96/4	91
6	CH_2	2-$NO_2C_6H_4$	B	0	24	**3ad**	82	96/4	96
7	CH_2	3-$NO_2C_6H_4$	A	12	24	**3ae**	95	97/3	91
8	CH_2	3-$NO_2C_6H_4$	B	0	24	**3ae**	92	96/4	95
9	CH_2	4-CNC_6H_4	A	12	24	**3af**	95	97/3	90
10	CH_2	4-CNC_6H_4	B	0	24	**3af**	93	95/5	92
11	CH_2	2,6-$Cl_2C_6H_3$	A	12	24	**3ag**	98	98/2	89
12	CH_2	2,6-$Cl_2C_6H_3$	B	0	30[d]	**3ag**	91	>98/2	98
13	CH_2	Ph	A	12	3 d	**3ah**	10	95/5	77
14	CH_2	Ph	B	0	72	**3ah**	33	97/3	90
15	CH_2	2-Naphthyl	A	r.t.	3 d	**3ai**	15	95/5	89
16	CH_2	2-Naphthyl	B	0	72	**3ai**	40	97/3	89
17	CH_2	4-MeC_6H_4	A	r.t.	3 d	**3aj**	10	98/2	86
18	CH_2	4-MeC_6H_4	B	0	6 d	**3aj**	30	93/7	84
19	O	4-$NO_2C_6H_4$	A	12	3 d	**3ba**	95	94/6	75
20	O	4-$NO_2C_6H_4$	B	0	24[d]	**3ba**	99	>98/2	96
21	S	4-$NO_2C_6H_4$	A	12	3 d	**3ca**	80[e]	97/3	88
22	S	4-$NO_2C_6H_4$	B	r.t.	40[d]	**3ca**	82	97/3	88
23	NBoc	4-$NO_2C_6H_4$	A	12	3 d	**3da**	50[f]	89/11	80
24	NBoc	4-$NO_2C_6H_4$	B	r.t.	48	**3da**	56[g]	>98/2	80
25	-	4-$NO_2C_6H_4$	A	r.t.	24	**3ea**	95	52/48	74[h]
26	-	4-$NO_2C_6H_4$	B	0	24	**3ea**	85	48/52	92[i]

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR over the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture.
[d] Reaction carried out in the absence of 4-$NO_2C_6H_4CO_2H$.
[e] A 19% yield of dehydrated product was also obtained.
[f] A 15% yield of dehydrated product was also obtained.
[g] An 8% yield of dehydrated product was also obtained.
[h] *ee* (*syn*) = 60%.
[i] *ee* (*syn*) = 43%.

conditions a minor or negligible impact of the aldol condensation reaction was observed. Aldol adduct **3da** (Table 3, entries 23 and 24) showed a marked tendency to racemize during the purification process. It is important to mention that the HPLC *ee* determination was performed over the crude reaction mixture for all the synthesized aldol adducts. In general, the *ee* values after flash chromatography purification of substrates **3** fitted with the results observed before isolation with the exception of the above-mentioned aldol **3da**.

Under solvent-free conditions, the reaction between 4-nitrobenzaldehyde and tetrahydro-4*H*-thiopyran-4-one or *N*-Boc-4-piperidone (Table 3, entries 22 and

Table 4. Aldol reactions of ketones with 4-nitrobenzaldehyde catalyzed by **1d** in water (Method A) and under solvent-free conditions (Method B).



Entry	X	Method	T [°C]	Time [d]	No.	Yield [%][a]	r[b]	ee_{iso}[d]	anti/syn[c]	ee_{anti}[d]
1	H	A	r.t.	4	**3fa**	64	-	-	-	56
2	H	B[e]	0	2	**3fa**	80[f]	-	-	-	80
3	Me	A	r.t.	6	**3ga**	20	72/28	58	89/11	89
4	Me	B	r.t.	3	**3ga**	86	37/63	60	83/17	80
5	MeO	A	r.t.	4	**3ha**	36	91/9	45	86/14	92
6	MeO	B	r.t.	3	**3ha**	87	98/2	65	80/20	87
7	BnO	A	r.t.	2	**3ia**	95	83/17	57	88/12	94
8	BnO	B	0	2	**3ia**	90	90/10	-	89/11	91

[a] Isolated yield after flash chromatography.
[b] Regioisomeric ratio (3/5) determined by 1HNMR over the crude reaction mixture.
[c] Determined by ^{1}H NMR over the crude reaction mixture.
[d] Determined by chiral HPLC analysis over the crude reaction mixture.
[e] Reaction carried out in the absence of 4-$NO_2C_6H_4CO_2H$.
[f] A 4% yield of diaddition product was also obtained.

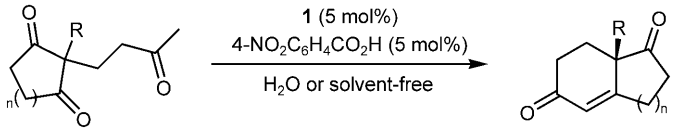
24) took place with purely solid reactants through an intermediate melt.[11] This implies the existence of a eutectic mixture with a fusion temperature below ambient temperature and over 0 °C since at this latter temperature the aldol reactions did not work.[16] On the other hand, when solid aldol products where formed from liquid ketones it was generally possible to see the evolution of the process since the initial heterogeneous mixture of the ketone, aldehyde, catalyst and cocatalyst evolved to a partially homogeneous honey-like reaction mixture where the aldol product was already formed.

The appearance of the reaction mixture when the **1d**-catalyzed aldol reactions were performed in the presence of water was rather different. Under Method A conditions, phase separation was normally observed, the enantioselective aldol reaction probably taking place in the formed organic phase.[7e]

Whereas cyclohexanone gave almost exclusively the *anti* adduct product in high *ee* in the presence of water and under solvent-free conditions (Table 1), only the latter (Method B) were suitable conditions for an enantioselective aldol reaction of cyclopentanone and 4-nitrobenzaldehyde (Table 3, entries 25 and 26) affording a 1:1 mixture of *anti*/*syn*-**3ea** isomers with a 92% *ee* for the *anti* isomer (entry 26).

The optimized catalytic system also worked out for acyclic alkyl ketones such as acetone, butanone, as well as other α-alkoxy ketone donors such as, benzyloxyacetone and methoxyacetone (Table 4). With the exception of acetone, using water as solvent (Method A) led to higher enantioselectivities than under solvent-free conditions (Method B) with the substrates studied. Thus, when acetone was used as donor (Table 4, entries 1 and 2), the aldol product **3fa** was obtained after 2 d at room temperature in the absence of cocatalyst with good yield (80%) and 80% *ee* under solvent-free conditions (entry 2). Prolinethioamide **1d** was a very enantioselective catalyst for the reaction with butanone under Method A and B reaction conditions (Table 4, entries 3 and 4). Using water as solvent, this challenging substrate provided aldol adduct **3ga** in only 20% yield and 89% *ee*. However, solvent-free conditions afforded **3ga** in 86% yield, 83/17 *anti*-favored *dr*, and 80% *ee* (Table 4, entry 4). The regioselectivity of the process was moderate since both Methods A and B led to large amounts of the *iso*-**5** regioisomer. Alkoxy ketone nucleophiles such as methoxy- and benzyloxyacetone were excellent substrates providing with high regioselectivity C–C bond formation at the alkoxy group-substituted α-position affording, as expected for a secondary amine-derived organocatalyst, the corresponding *anti*-aldol adduct in high enantioselectivities (Table 4, entries 5–8). Thus, methoxyacetone furnished aldol adduct **3ha** with a 87% yield, 80/20 *anti* favored *dr*, and 87% *ee* after 3 d at room temperature under solvent-free conditions (Table 4, entry 6), whereas higher *ee* (92%) was ob-

Table 5. Intramolecular aldol reaction catalyzed by **1** in the presence of water (Methd A) and under solvent-free conditions (Method B).



6 **7**

Entry	Cat.	Method	**6**	n	R	*T* [°C]	Time [d]	**7**	Conv. [%][a]	*ee*[b]
1	**1a**	B	**6a**	2	Me	r.t.	1	**7a**	98	66
2	**1b**	B	**6a**	2	Me	r.t.	1	**7a**	87	76
3	**1c**	B	**6a**	2	Me	r.t.	1	**7a**	100	74
4	**1d**	B	**6a**	2	Me	r.t.	1	**7a**	100 (99)	86
5	**1d**	B[c]	**6a**	2	Me	r.t.	1	**7a**	65	82
6	**1d**	A	**6a**	2	Me	r.t.	1	**7a**	86	80
7	**1d**	B	**6b**	1	Me	r.t.	5.5	**7b**	100 (71)	88
8	**1d**	B	**6c**	1	Et	r.t.	6	**7c**	100 (99)	84
9	**L-Pro**	B	**6a**	2	Me	r.t.	3	**7a**	46	61

[a] Reaction conversion determined by ^{1}H NMR over the crude reaction mixture. In brackets isolated yield after flash chromatography.
[b] Determined by chiral-phase HPLC analysis over the crude reaction mixture.
[c] Reaction performed in the absence of 4-$NO_2C_6H_4CO_2H$.

tained using water as solvent but in a very low 36% yield (entry 5). Reaction of benzyloxyacetone was even more efficient providing, both in the presence of water (95% yield, *anti*/*syn*: 88/12, 94% *ee* for *anti*-**3ia**) and under solvent-free conditions (90% yield, *anti*/*syn*: 89/11, 91% *ee* for *anti*-**3ia**), excellent yields and enantioselectivities (Table 4, entries 7 and 8).

Finally, organocatalysts **1** were also tested in the intramolecular aldol condensation of triketones **6** (Table 5). A preliminary catalyst study under solvent-free conditions (Method B, Table 5, entries 1–4) confirmed prolinethioamide **1d** as the most effective organocatalyst for the intramolecular reaction as well, affording after 24 h at room temperature, the Wieland–Miescher ketone **7a** in a 99% isolated yield and 86% *ee* (Table 5, entry 4). Catalyst **1d** was less efficient when the reaction was performed in the absence of cocatalyst (Table 5, entry 5) or in the presence of water (Method A, entry 6) affording ketone **7a** in a 65% conversion and 82% *ee* and 86% conversion and 80% *ee*, respectively, after 1 d at room temperature. Therefore, under solvent-free conditions and in the presence of 4-$NO_2C_6H_4CO_2H$, the intramolecular aldol reaction was applied to substrates **6b** and **6c** where the ring size and/or substitution in the 2 position of the cycloalkanedione were varied. As shown in entries 6 and 7, bicyclic diketones **7b** and **7c** were obtained in high isolated yields and good enantioselectivities. The results obtained in this study of the solvent-free version of the Hajos–Parrish–Eder–Sauer–Wiechert reaction clearly demonstrated the high activity of prolinethioamide **1d** under these conditions, since lower yields and enantioselectivities were obtained employing L-Pro as catalyst under the solvent-free reaction conditions for substrate **7a** (compare entries 4 and 9).

Conclusions

L-Prolinamide and thioamide derivatives **1** are excellent catalysts for the asymmetric direct aldol inter- and intramolecular reaction using water as solvent and under solvent-free conditions. These catalysts are easily prepared in a few high yielding steps, so they are easily accessible. In general, L-prolinethioamides **1c** and **1d** derived from L-Pro and (1*S*,2*R*)-*cis*-1-aminoindan-2-ol and (*R*)-1-aminoindane, respectively, are more efficient catalysts than the corresponding L-prolinamides **1a** and **1b** in the inter- and intramolecular aldol in the presence of water and under solvent-free conditions. In particular, L-prolinethioamide **1d**, prepared from L-proline and (*R*)-1-aminoindane, is a robust, recyclable, and highly enantioselective catalyst for the *anti*-aldol reaction between ketones and aromatic aldehydes in the presence of water and under solvent-free conditions. Generally, catalyst **1d** performed better under solvent-free conditions for the intermolecular aldol reaction between cyclic ketones and aromatic aldehydes affording the corresponding aldol adducts in higher yields and selectivities than in the presence of water. However, prolinethioamide **1d** was more selective in the presence of water for the aldol reaction of acyclic ketones and aromatic alde-

hydes. Prolinethioamide **1d** has been also shown as the most efficient catalyst for the enantioselective solvent-free Hajos–Parrish–Eder–Sauer–Wiechert reaction.

Experimental Section

Typical Procedure for the Enantioselective Aldol Reaction Catalyzed by 1d

A mixture of **1d** (30 mg, 0.122 mmol), 4-nitrobenzoic acid (20.5 mg, 0.122 mmol) and cyclohexanone (508 μL, 4.88 mmol) was stirred in water (1.22 mL) (Method A) or without solvent (Method B) for 20 min at 12 °C (Method A) or at 0 °C (Method B). Then, 4-nitrobenzaldehyde (368.4 mg, 2.44 mmol) was added and the reaction mixture was stirred at the above mentioned temperature for 8 h. Then, water (20 mL), EtOAc (20 mL) and 10% HCl (127.14 μL, 0.366 mmol) were added to the reaction mixture. After separation, the organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the crude reaction mixture that was purified by flash chromatography (silica gel, hexane/EtOAc: 1/6) to afford pure product *anti*-**3aa**.

The aqueous layer was treated with 10% NaOH solution (480 μL, 1.464 mmol) and then extracted with EtOAc (3× 20 mL). The resulting organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated at low pressure to give the corresponding crude that was purified by recrystallization affording pure organocatalyst **1d** $\{[\alpha]_D^{20}$: +113 (c 1.0, $CH_2Cl_2\}$.

Supporting Information

Synthesis of organocatalysts **1** and **4**, experimental procedures, spectral data for new compounds and intermediates, as well as ESI-MS experiments, HPLC separation conditions and retention times for compounds **3**, **5** and **7** are available as Supporting Information.

Acknowledgements

Financial support from the MEC (Projects CTQ2004-00808/BQU, CTQ2007–62771/BQU and Consolider INGENIO 2010 CSD2007-00006), from the Generalitat Valenciana (GRUPOS05/11, GV05/144, GV/2007/142) and the University of Alicante are acknowledged. D. A. thanks the EU and the Spanish MEC for a predoctoral fellowship.

References

[1] R. Mahrwald, *Modern Aldol Reactions*, Wiley-VCH, Weinheim, **2004**, Vols. 1 and 2.

[2] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267–9331; c) P. I. Dalko, *Enantioselective Organocatalysis, Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**; d) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413–5883; e) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; f) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; g) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.

[3] a) S. Doye, *Chem. Unserer Zeit* **2001**, *35*, 62–63; b) B. List, *Synlett* **2001**, 1675–1686; c) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545–548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529–532; d) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905; e) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569; f) E. J. Sorensen, G. M. Sammis, *Science* **2004**, *305*, 1725–1726; g) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579; h) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591; i) U. Kazmaier, *Angew. Chem.* **2005**, *117*, 2224–2226; *Angew. Chem. Int. Ed.* **2005**, *44*, 2186–2188; j) M. Limbach, *Chem. Biodiversity* **2005**, *2*, 825–836; k) B. List, *Chem. Commun.* **2006**, 819–824; l) G. Guillena, C. Nájera, D. J. Ramon, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.

[4] a) C. J. Li, T. H. Chan, *Organic Reaction in Aqueous Media*, John Wiley and Sons, New York, **1997**; b) P. A. Grieco, *Organic Synthesis in Water*; Blackie Academic and Professional, London, **1998**; c) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; d) C. J. Li, *Chem. Rev.* **2005**, *105* 3095–3196.

[5] a) J. O. Metzger, *Angew. Chem.* **1998**, *110*, 3145–3148; *Angew. Chem. Int. Ed.* **1998**, *37*, 2975–2978; b) G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun.* **2001**, 2159–2169; c) K. Tanaka, *Solvent-free Organic Synthesis* Wiley-VCH, Weinheim, **2003**.

[6] For pioneering aqueous aldol organocatalysis, see: a) J.-L. Reymond, Y. Chen, *J. Org. Chem.* **1995**, *60*, 6970–6979; b) T. J. Dickerson, K. D. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221.

[7] For recent examples of asymmetric aldol reactions in the presence of water, see: a) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735; b) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; c) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653–5655; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527–5529; d) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; e) S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246–10256; f) S. Guizzetti, M. Benaglia, L. Raimondi, G. Celentano, *Org. Lett.* **2007**, *9*, 1247–1250; g) S. Aratake, T. Itoh, T. Okano, T. Usui, M. Shoji, Y. Hayashi, *Chem. Commun.* **2007**, 2524–2526; h) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595; i) J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem.* **2007**, *119*, 9231–9235; *Angew. Chem. Int. Ed.* **2007**, *46*, 9073–9077; j) J.-F. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun, L.-Z. Gong, *Tetrahedron Lett.* **2008**, *49*, 3372–3375; k) D. Font, S.

Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337–340; l) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211–1214; m) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502–1511; n) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57.

[8] For recent discussions about the role of water in organocatalytic processes, see: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; b) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; c) D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem.* **2007**, *119*, 3872–3874; *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800.

[9] a) B. Rodriguez, T. Rantanen, C. Bolm, *Angew. Chem.* **2006**, *118*, 7078–7080; *Angew. Chem. Int. Ed.* **2006**, *45*, 6924–6926; b) B. Rodriguez, A. Bruckmann, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 4710–4722; c) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Commun.* **2007**, 957–958; d) G. Guillena, M. C. Hita, C. Nájera, S. F. Viózquez, *J. Org. Chem.* **2008**, *73*, 5933–5943; e) A. Bruckmann, A. Krebs, C. Bolm, *Green Chem.* **2008**, *10*, 1131–1141; f) G. Guillena, C. Nájera, S. F. Viózquez, *Synlett* **2008**, 3031–3035.

[10] a) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 2064–2068; b) D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, Y. Nagel, C. Nájera, *Eur. J. Org. Chem.* **2007**, 2328–2343.

[11] D. Almaşi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.* **2008**, *350*, 2467–2472.

[12] For the pioneering use of prolinethiomides in the aldol reaction in organic and aqueous solvents, see: a) D. Gryko, L. Radoslaw, *Eur. J. Org. Chem.* **2006**, 3864–3876; b) D. Gryko, W. J. Saletra, *Org. Biomol. Chem.* **2007**, *5*, 2148–2153.

[13] A. Orita, G. Uehara, K. Miwa, J. Otera, *Chem. Commun.* **2006**, 4729–4731.

[14] Following reviewers' suggestions, under the optimized reaction conditions, the efficiency of other acid cocatalysts such as CF_3CO_2H [$pK_a = 0.52$, 8 h, 5% conversion, *anti*/*syn*: nd, 92% *ee* (*anti*)] and Cl_2CHCO_2H [$pK_a = 1.35$, 8 h, 16% conversion, *anti*/*syn*: 98/2, 89% *ee* (*anti*)] was also checked affording high enantioselectivities but very low conversions. Thus, in terms of conversion and enantioselectivity, 4-$NO_2C_6H_4CO_2H$ [8 h, 99% conversion, *anti*/*syn*: 94/6, 95% *ee* (*anti*)] was definitively recognized as the best cocatalyst for the aldol reaction.

[15] D. Gryko, M. Zimnicka, R. Lipiński, *J. Org. Chem.* **2007**, *72*, 964–970.

[16] G. Rothenberg, A. P. Downie, C. L. Raston, J. L. Scott, *J. Am. Chem. Soc.* **2001**, *123*, 8701–8708.

