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Prolinamides *versus* Prolinethioamides as Recyclable Catalysts in the Enantioselective Solvent-Free Inter- and Intramolecular Aldol Reactions

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Abstract: A solvent-free asymmetric and direct *anti*-aldol reaction of aliphatic ketones with aromatic aldehydes catalyzed by recyclable L-prolineamides and L-prolinethioamides **3** is studied. The L-prolinethioamide **3d** (5 mol%), derived from L-Pro and (*R*)-1-aminoindane, is the most efficient catalyst for this process affording the *anti*-aldol adducts in high yields with excellent diastereo- and enantioselectivities (up to >98/2 *dr*, up to 98% *ee*) at 0 °C or room temperature. Prolinethioamide **3d** is an effective organocatalyst for the first asymmetric, solvent-free, intramolecular Hajos–Parrish–Eder–Sauer–Wiechert reaction with comparable or higher levels of enantioselectivity (up to 88% *ee*) to reported catalysts in organic solvents. Moreover, organocatalyst **3d** can be easily recovered and reused by a simple acid/base extraction.

Keywords: aldol reaction; asymmetric catalysis; organocatalysis; prolinethioamides; solvent-free reactions

Asymmetric organocatalysis has definitively matured to become a recognized third discipline together with biocatalysis and metal complex catalysis, providing operationally simple, economic and environmentally friendly strategies to prepare enantioenriched compounds.[1] On the other hand, the necessity to further reduce any source of pollution has led to a growing interest in the development of organic reactions in aqueous media[2] and under solvent-free conditions.[3] Reactions under solvent-free conditions usually need shorter reaction times, simpler reactors and result in simple and efficient work-up procedures. For these reasons, organocatalyzed processes under solvent-free conditions have become a highly pursued goal in green chemistry.[4]

The aldol reaction is one of the most important carbon-carbon bond-forming processes[5] since generates β-hydroxy carbonyl compounds, derivatives which are found in many natural products and drugs. Very recently, great emphasis has been given to the design of new chiral organocatalysts for the aldol reaction.[6] Most of these studies have been performed in organic or aqueous solvents or using a large excess of nucleophile (5–138 equivalents) which allows it to act as reaction media as well. With respect to the solvent-free protocols, only a few catalytic systems have been shown to work satisfactorily when 3 or less equivalents of nucleophile donor are used (Figure 1).[7] L-Proline (10 mol%) has been used as organocatalyst for a fast aldol reaction (5–36 h) of symmetrical alkyl ketones (1.2 equiv.) with aromatic aldehydes using a ball-milling technique.[7a,b] The use of conventional magnetic stirring in the same solvent-free reactions afforded similar results but longer reaction times were required (1 to 4 days). Hayashi has

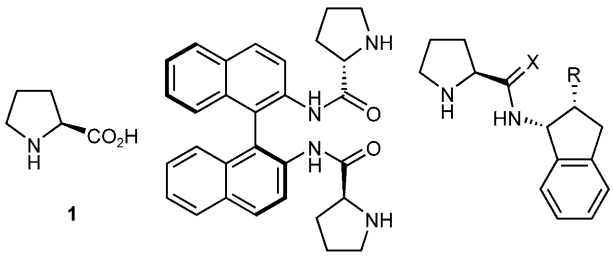


Figure 1. Organocatalysts for the direct solvent-free aldol reaction.

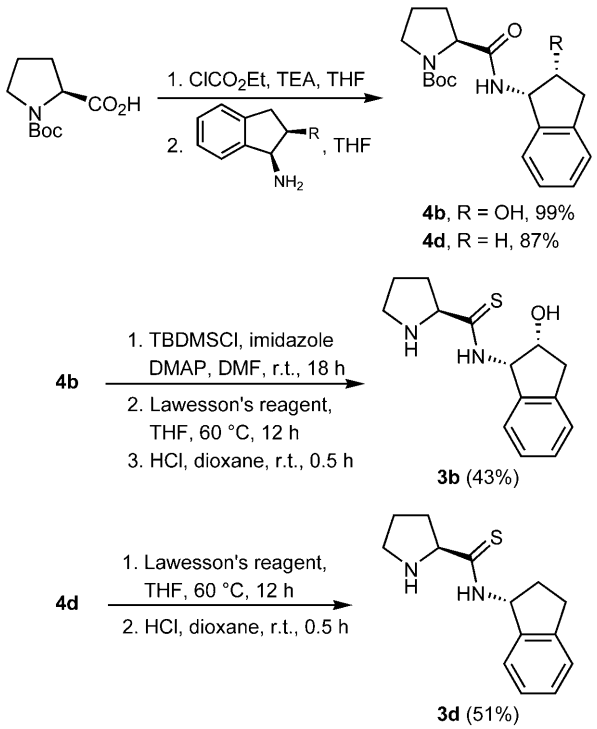
reported an isolated example of a L-proline-catalyzed (10 mol%) solvent-free aldol reaction between 2-chlorobenzaldehyde and propanal (3 equivs.) using conventional magnetic stirring.[7c] More recently, (S_a)-binam-L-prolinamide (**2**, 5 mol%) with benzoic acid as cocatalyst has been used in a solvent-free reaction of different ketones (2 equiv.) with aldehydes under conventional magnetic stirring.[7d]

We have recently shown[8] that prolinamide **3a**, derived from L-Pro and (1*S*,2*R*)-*cis*-1-aminoindan-2-ol (Figure 1), is an efficient and recyclable bifunctional organocatalyst for the conjugate addition[9] of ketones to β-nitrostyrenes with high levels of *syn*-diastereoselectivity (up to 94%) and good enantioselectivities (up to 80% *ee*). In this reaction the (1*S*,2*R*) configuration of the chiral 1-aminoindanol matched the (*S*)-configuration of the L-proline to enhance the stereochemical control.

On the other hand, L-prolinethioamides have been used as catalysts for the direct asymmetric aldol reaction of aromatic aldehydes with acetone or cyclic ketones in organic[10] or aqueous solvents,[11] respectively. In this communication, we report our findings in the solvent-free direct intra- and intermolecular aldol reactions catalyzed by recyclable 1-aminoindane- and 1-aminoindan-2-ol-derived prolinamides and L-prolinethioamides **3**.

Prolinamides **3a** and **3c** derived from (1*S*,2*R*)-*cis*-1-aminoindan-2-ol and (*R*)-1-aminoindane, respectively are known and were prepared as previously described from *N*-Cbz-L-Pro.[8] However, for the synthesis of **3b** and **3d** *N*-Boc-L-Pro was used as starting compound for the transformation into *N*-Boc-L-prolinamides **4b** and **4d** by reaction with commercially available (*R*)-1-aminoindane and (1*S*,2*R*)-*cis*-1-aminoindan-2-ol, respectively (Scheme 1). Prolinethioamide **3b** was synthesized from intermediate **4b** after protection of the hydroxyl function with TBDMSCl, thiation with Lawesson's reagent, and deprotection of the amine and hydroxyl functions with a saturated solution of hydrogen chloride in dioxane (Scheme 1). A similar procedure, except for the hydroxy protection, was followed to prepare prolinethioamide **3d** from intermediate **4d** in 51% yield. Catalysts **3b** and **3d** were prepared from *N*-Boc-L-Pro due to the Cbz hydrogenolysis problems associated with the presence of the thioamide moiety.

The efficacy of catalysts **3** was examined first in the solvent-free direct aldol reaction between cyclohexanone (2 equiv.) and 4-nitrobenzaldehyde (1 equiv.) in the presence of 20 mol% of catalyst and 4-nitrobenzoic acid (20 mol%) as cocatalyst under magnetic stirring conditions (Table 1). As depicted in entries 1–4, catalysts **3** exhibited high catalytic efficiency, especially prolinamide **3a** which provided a very fast cross-aldol reaction (10 min) although with moderate diastereo- and enantioselectivity (Table 1, entry 1). The highest diastereo- and enantioselectivity was observed



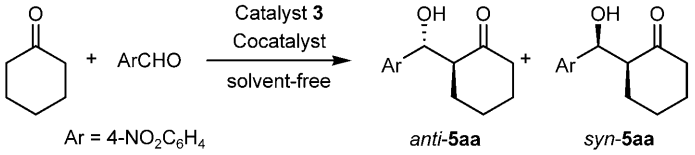
Scheme 1. Synthesis of prolinethioamides **3b** and **3d**.

with prolinethioamide **3d** (Table 1, entry 4) still under a very short reaction time [*anti*/*syn*: 89/11, 88% *ee* (*anti*), 1 h]. The efficacy of catalyst **3d** was not improved when the reaction was performed in a ball mill[7a,b] (Table 1, entry 5) or under conventional magnetic stirring with a pre-formed solution in THF and immediate evaporation of the solvent (Table 1, entry 6).[12] The diastereoselectivity of the process was slightly improved by working at 0 °C but not the enantioselectivity (Table 1, entry 7).

However, at the same temperature, reducing the catalyst loading to 5 mol% led to a dramatically improvement of the selectivity of the reaction (94/6 *dr*, 93% *ee*) the reaction time being also increased to 8 h (Table 1, entry 8). Notably, the presence of only 1 equiv of cyclohexanone at 0 °C (Table 1, entry 9) was sufficient to afford the reaction in high yield and selectivity, although 24 h were necessary for completion. Similar results were obtained when the process was carried out in the absence of cocatalyst employing two equiv. of nucleophile (Table 1, entry 10).

Finally, with respect to the recyclability of **3d** it is worthy to mention that this prolinethioamide had a similar behaviour to prolinamide **3a**[8] and could be easily recovered (91% recovery) from the reaction mixture (Table 1, entry 8) after extractive acid/base work-up (HCl/NaOH) and reused with similar results since no loss of optical activity was detected in the organocatalyst.

Table 1. Solvent-free *anti*-selective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **3**.[a]



Ar = 4-$NO_2C_6H_4$ *anti*-**5aa** *syn*-**5aa**

Entry	**3** (mol%)	Cocatalyst (mol%)	*T* [°C]	Time [h]	Conversion [%][b]	*anti*/*syn*[c]	*ee* (*anti*)[d]
1	**3a** (20)	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	10 min	99	79/21	64
2	**3b** (20)	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	3	97	82/18	71
3	**3c** (20)	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	3	99	70/30	58
4	**3d** (20)	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	1	99	89/11	88
5	**3d** (20)[e]	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	1	98	91/9	86
6	**3d** (20)[f]	4-$NO_2C_6H_4CO_2H$ (20)	r.t.	1	98	87/13	74
7	**3d** (20)	4-$NO_2C_6H_4CO_2H$ (20)	0	5	97	92/8	88
8	**3d** (5)	4-$NO_2C_6H_4CO_2H$ (5)	0	8	99	94/6	93
9	**3d** (5)[g]	4-$NO_2C_6H_4CO_2H$ (5)	0	24	95	98/2	93
10	**3d** (5)	–	0	24	99	98/2	96

[a] A mixture of the corresponding organocatalyst, cocatalyst and cyclohexanone (2 equiv.), were 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}H NMR on the crude reaction mixture.
[c] Determined by ^{1}H NMR over the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis over the crude reaction mixture.
[e] The reaction was performed in a ball mill at 400 rpm.
[f] **3d**, 4-nitrobenzoic acid and 4-nitrobenzaldehyde were first dissolved in THF, then the solvent was evaporated and cyclohexanone was added to the mixture, which was stirred for 1 h.
[g] 1 equiv. of ketone was used.

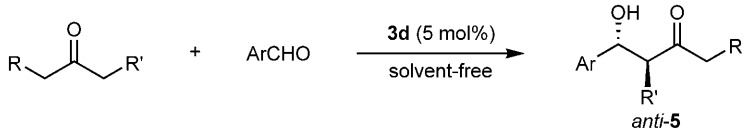
Considerations of stereoselectivity led us to focus our next study under the optimal reaction conditions as follows: ketone (2 equiv.), aldehyde (1 equiv.), and **3d** (5 mol%) at 0 °C or room temperature, although 4-nitrobenzoic acid (5 mol%) was added as cocatalyst in those cases where the reaction time was too long. Under these conditions, the solvent-free direct cross-aldol reaction of other several acceptor aromatic aldehydes with aliphatic donor ketones was examined in order to study the reaction scope (Table 2).

Reaction 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 (70–95%) with excellent diastereo- (95/5 to >98/2 *dr*) and enantioselectivities (88–98% *ee*) (Table 2, entries 1–6). The reaction also proceeded smoothly with non-activated aldehydes, such as benzaldehyde, 2-naphthaldehyde, and 4-methylbenzaldehyde although this required longer reaction times even employing 4-nitrobenzoic acid as cocatalyst to give the aldol products **5ah**, **5ai**, and **5aj**, respectively, in moderate yields, high diastereoselectivities and good enantioselectivities (Table 2, entries 7–9).

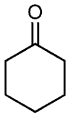
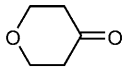
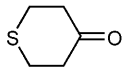
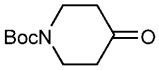
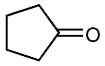
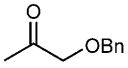
Heterocyclic cyclohexanones such as tetrahydro-4*H*-pyran-4-one, tetrahydro-4*H*-thiopyran-4-one, and *N*-Boc-4-piperidone reacted with 4-nitrobenzaldehyde leading to the corresponding *anti*-aldol adducts with high diastereo- and enantioselectivities (Table 2, entries 10–12). In the case of the reaction between 4-nitrobenzaldehyde and tetrahydro-4*H*-thiopyran-4-one or *N*-Boc-4-piperidone, the aldol reaction took place with purely solid reactants through an intermediate melt. 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.[13] As depicted in Figure 2 for the synthesis of **5ca**, the reaction worked even in the absence of stirring. On the other hand, when solid aldol products were 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 catalytic system also worked well for other cyclic ketones such as cyclopentanone. In this instance, the aldol process proceeded smoothly in high yield (85%), moderate diastereoselectivity and very high enantioselectivity for the *anti* isomer (92% *ee*) (Table 2, entry 13). Several acyclic alkyl ketones such as acetone and benzyloxyacetone were also tested as nucleophiles in the solvent-free aldol reaction with 4-nitrobenzaldehyde (Table 2, entries 14 and 15). When acetone was used as donor, the aldol product **5fa** was obtained after 48 h at room temperature in the absence of cocatalyst with good yield (80%) and 80%

Table 2. Solvent-free *anti*-aldol reactions of ketones with aromatic aldehydes.



anti-**5**

Entry	Ketone	Ar	*T* [°C]	Time [h]	No.	Yield [%][a]	*anti*/*syn*[b]	ee_{anti}[c]
1		2-ClC_6H_4	0	48	**5ab**	91	98/2	92
2		4-ClC_6H_4	0	48	**5ac**	70	97/3	94
3		2-$NO_2C_6H_4$	0	24[d]	**5ad**	82	96/4	96
4		3-$NO_2C_6H_4$	0	24[d]	**5ae**	92	96/4	95
5		4-CNC_6H_4	0	24[d]	**5af**	93	95/5	92
6		3,5-$Cl_2C_6H_3$	0	30	**5ag**	91	>98/2	98
7		Ph	0	72[d]	**5ah**	33	97/3	90
8		2-Naphthyl	0	72[d]	**5ai**	40	97/3	89
9		4-MeC_6H_4	0	6 d[d]	**5aj**	30	93/7	84
10		4-$NO_2C_6H_4$	0	24	**5ba**	99	>98/2	96
11		4-$NO_2C_6H_4$	r.t.	40	**5ca**	82	97/3	88
12		4-$NO_2C_6H_4$	r.t.	48[d]	**5da**	56[e]	>98/2	80
13		4-$NO_2C_6H_4$	0	24[d]	**5ea**	85	48/52	92[f]
14		4-$NO_2C_6H_4$	0	48	**5fa**	80[g]	–	80
15		4-$NO_2C_6H_4$	0	48[d]	**5ga**	90[h]	89/11	91[i]

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR on the crude reaction mixture.
[c] Determined by chiral HPLC analysis of the crude reaction mixture.
[d] Reaction carried out in the presence of 4-$NO_2C_6H_4CO_2H$.
[e] An 8% yield of dehydrated product was also obtained.
[f] *ee* (*syn*) = 43%.
[g] A 4% yield of diaddition product was also obtained.
[h] A 9% yield of *iso* addition product was also obtained.
[i] < 5% Conversion was observed after 2 d when L-Pro (5 mol%)/4-$NO_2C_6H_4CO_2H$ (5 mol%) was used as catalyst.

ee. Reaction with an α-oxyketone donor such as benzyloxyacetone provided with highly regioselective 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 yield (90%) and 91% *ee* (Table 2, entry 15). This result clearly showed the high activity of prolinethioamide **3d** for the solvent-free aldol reaction since L-Pro failed to promote this reaction after 2 days.

With respect to the HPLC *ee* determination, it is significant to mention that this analysis was performed over the crude reaction mixture. In general, the *ee* values after flash chromatography purification of aldol adducts **5** fit with the results observed before isolation with the exception of aldol **5da** which showed a marked tendency to racemize during the purification process.

Finally, organocatalysts **3** were also tested in the solvent-free intramolecular aldol condensation of triketones **6**. A preliminary catalyst study confirmed prolinethioamide **3d** as the most effective for the intramolecular reaction as well. Also, the absence of co-catalyst led to lower enantioselectivities. Therefore, as depicted in Scheme 2, the catalytic system **3d**/4-nitrobenzoic acid (5 mol%) provided a very efficient promoter for the intramolecular aldol condensation of **6a** affording, after 24 h at room temperature, compound

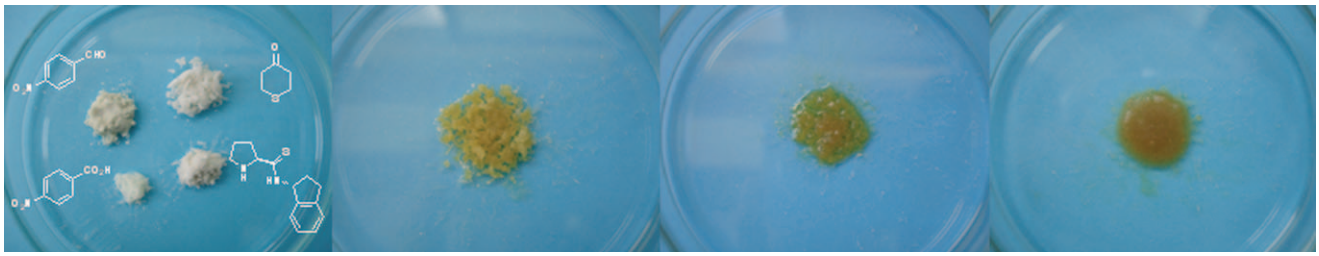


Figure 2. Aldol reaction of tetrahydro-4*H*-thiopyran-4-one with 4-nitrobenzaldehyde catalyzed by **3d** (30 mol%)/4-$NO_2C_6H_4CO_2H$ (30 mol%) after 1 h (*left center*), 2 h (*right center*), and 5 h (*right*) at room temperature without stirring.

7a in a 99% isolated yield and 86% *ee*. Under the same reaction conditions, 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 Scheme 2, bicyclic diketones **7b** and **7c** were obtained in high isolated yields and good enantioselectivities. The results obtained in this first intramolecular solvent-free version of the Hajos–Parrish–Eder–Sauer–Wiechert reaction clearly demonstrated the high activity of prolinethioamide **3d** since lower yields and enantioselectivities were obtained employing L-Pro as catalyst under the solvent-free reaction conditions for substrate **7a** (3d, 46% conversion, 61% *ee*).

In conclusion, although the organocatalyzed direct *anti*-aldol reaction between ketones and aldehydes is a well-established methodology in organic and aqueous solvents, the results from this investigation demonstrate that L-prolinethioamide **3d**, prepared from L-proline and (*R*)-1-aminoindane, is a robust, recyclable, and highly enantioselective catalyst for the solvent-free direct *anti*-aldol reaction between ketones and aromatic aldehydes under conventional magnetic stirring. Prolinethioamide **3d** has been also shown as a superior catalyst to L-Pro for the enantioselective solvent-free Hajos–Parrish–Eder–Sauer–Wiechert reaction. In all the cases studied, our investigations have clearly confirmed that L-prolinethioamides are more effective catalysts than the corresponding L-prolinamides in the solvent-free aldol reactions.

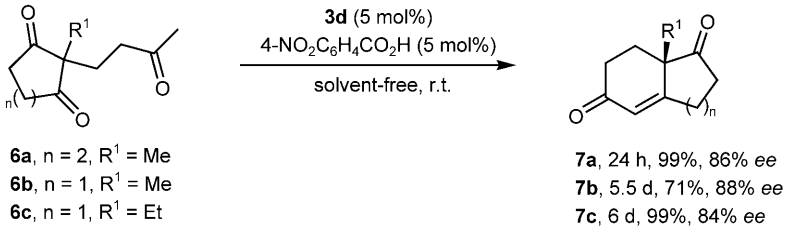
Experimental Section

Preparation of Prolinothioamide 3d

To a 0 °C solution of *N*-Boc-L-proline (1.72 g, 8.0 mmol) and TEA (1.12 mL, 8.0 mmol) in THF (30 mL) ethyl chloroformate (784 μL, 8.0 mmol) was added dropwise during 15 min. After the solution was stirred at 0 °C for 30 min more, (*R*)-1-aminoindane (1.1 g, 8.0 mmol) was added dropwise during 15 min. The resulting solution was stirred for 1 h at 0 °C and at room temperature for another 16 h, and finally refluxed for 3 h. After cooling down to room temperature, the solution was diluted with EtOAc. After filtration and removal of the solvent under reduced pressure, the corresponding *N*-Boc amide **4d** was obtained and used in the next step without further purification.

A mixture of compound **4d** (2.27 g, 6.87 mmol) and Lawesson's reagent (2.77 g, 6.87 mmol) in dry THF (30 mL) was stirred for 12 h at 60 °C under an argon atmosphere. After removal of the solvent under reduced pressure the resulting residue was purified by flash chromatography (hexane/EtOAc) to afford pure (*S*)-*tert*-butyl 2-[(*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamothioyl]pyrrolidine-1-carboxylate.

The obtained compound (1.4 g, 4.16 mmol) was then submitted to deprotection by stirring in a 4 M hydrogen chloride solution in dioxane (3.64 mL, 14.56 mmol) for 30 min. After this time EtOAc (25 mL) was added and the reaction mixture was extracted with water (3 × 25 mL). The aqueous phase was treated with 15% NaOH until pH 7–8 and then extracted with EtOAc (3 × 25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by recrystallization in hexane to give pure **3d**.



Scheme 2. Intramolecular solvent -free aldol reactions catalyzed by **3d**.

Typical Procedure for the Intermolecular Aldol Reaction and Recovery of the Catalyst 3d: Conventional Magnetic Stirring conditions (Table 1, entry 8)

A mixture of the catalyst **3d** (30 mg, 0.122 mmol), 4-nitrobenzoic acid (20.5 mg, 0.122 mmol) and cyclohexanone (508 μL, 4.88 mmol) was stirred for 20 min at 0 °C. Then, 4-nitrobenzaldehyde (368.4 mg, 2.44 mmol) was added and the reaction mixture was stirred at 0 °C. After 8 h water (20 mL), EtOAc (20 mL) and HCl 10% (127.14 μL, 0.366 mmol) were added to the reaction mixture. After separation, the organic layer was dried over anhydrous $MgSO_4$, filtered off and the solvent was evaporated under reduced pressure to give a crude that was purified by flash chromatography (silica gel, hexane/EtOAc: 1/6) to afford pure product *anti* **5aa**.

The aqueous layer was treated with NaOH 10% 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 off and the solvent was evaporated at low pressure to give a crude residue that was purified by recrystallization giving pure organocatalyst **3d**; yield: 27 mg (90%); $\{[\alpha]_D^{20}: +113$ (c 1.0, $CH_2Cl_2\}$.

Supporting Information

Additional experimental procedures, spectra data for new compounds and intermediates, as well as HPLC separation conditions and retention times for compounds **5** and **7** are available as Supporting Information.

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