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Advances towards Highly Active and Stereoselective Simple and Cheap Proline-Based Organocatalysts

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Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

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Ten 4-acyloxy-L-prolines were screened as catalysts at loadings of 2–0.1 mol-% for the direct asymmetric aldol reaction in water by using variable amounts of water. Among them, a new catalyst, the L-proline carrying a *trans*-4-(2,2-diphenylacetoxy) group, and a catalyst previously synthesized by us, the L-proline carrying a *trans*-4-(4-phenylbutanoyloxy) group, were found to be excellent catalysts for the aldol reaction between cyclohexanone or cyclopentanone and substituted benzaldehydes when employed in only 1 and 0.5 mol-%, respectively, at room temperature without additives. For such catalysts, high turnover numbers were obtained, which are among the highest values obtained for enamine organocatalysis. Finally, these catalysts can be synthesized by direct *O*-acylation from inexpensive molecules and successfully used in scaled-up reactions.

Introduction

Organocatalysts are usually used at a loading of 5–30 mol-%, and in some cases higher catalytic loadings have been reported.[1] For synthetic purposes, it is of great interest to have highly active organic catalysts that display activity at a loading of less than 2 mol-%. Several examples of organocatalysts employed in low catalytic amount are present in the literature.[1] In the case of organocatalytic reactions occurring via an enamine, some catalysts have also been employed in low catalytic amount.[2] Concerning the direct asymmetric aldol reaction, several studies have been carried out where the organocatalysts were used in low loadings. For example, catalysts **1**–**6**[3–7] (Figure 1) were synthesized for such a purpose. Although these catalysts work at a loading of 0.5–2 mol-% to afford aldol products with high levels of stereoselectivity, they are expensive, synthetically demanding catalysts. These catalysts present additional chiral centers to that of proline and are used at low temperatures (from 0 to –25 °C)[3–6] or at room temperature.[7]

Organocatalysts that are even more complex were also reported for aldol reactions. A spiro diamine catalyst,[8] the tripeptide H-Pro-Pro-Asp-NH_2,[9] a biphenyl-based axially chiral amino acid,[10] and a very complex dendrimer catalyst[11] were employed in an amount of 1–0.5 mol-%.

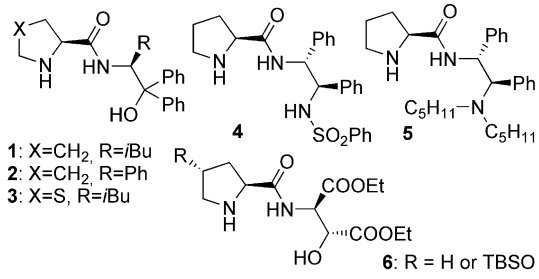

Figure 1. Catalysts **1**–**6**.

Catalysts **7**–**9** are simpler because they present only the chiral centers of hydroxy-L-proline or L-threonine (Figure 2). Catalysts **7** and **8** were used in 10 or 1 mol-%, although longer reaction times were needed, and 2 mol-%, respectively.[12] The ionic-tagged *cis*-4-hydroxy-L-proline **9** was employed in a lower amount, from 2 to 0.1 mol-%. The corresponding *trans*-4-hydroxy-L-proline was found to be less reactive. The authors ascribed the better performance of the former catalyst to the occurrence of a "*cis* effect".[13]

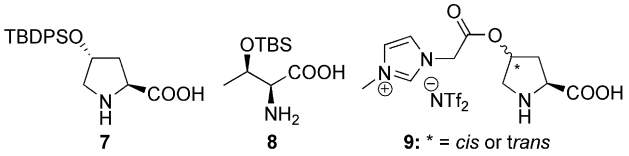

Figure 2. Catalysts **7**–**9**.

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Many of the reported reactions were carried out in water.[14] Indeed, it has been found that water is able to promote these reactions with high levels of enantio- and diastereoselectivity and in high yields. Usually, these reactions are carried out with an excess amount of the ketone, from 2 to 5 equiv. with respect to the aldehyde, and in the presence of variable amounts of water. Under such conditions the aqueous biphasic environment can simulate the hydrophobic pocket of class I aldolases. Therefore, hydrophobic aldehydes are forced into the hydrophobic region, resulting in increased activity and stereoselectivity of the catalyst. The hydrophobic region can be due to a hydrophobic substituent or to a hydrophobic support such as a polystyrene backbone.

Recently, we have been involved in research regarding the organocatalytic direct asymmetric aldol reaction by using both supported and nonsupported catalysts.[15] Supported organocatalysts are of great interest because their easy recovery allows the reuse of catalysts that are employed in high catalyst loading, or in the case of expensive organocatalysts.[16] The use of inexpensive highly active organocatalysts represents an important alternative approach.

Results and Discussion

The idea of this study was to find extremely simple and inexpensive organocatalysts that could be used in low loading (1–0.5 mol-%), working at room temperature without additives, and that could catalyze the aldol reaction between cyclic ketones and substituted benzaldehydes with high levels of stereoselectivity. To pursue this aim, we screened five new 4-substituted acyloxyproline derivatives **10a**–**e** and five known compounds **10f**–**i**[15b] and **10j**[12a] (Figure 3). The new proline derivatives were chosen to have very simple hydrophobic substituents. These molecules allow the set of known compounds to be expanded, which would make a deeper comparison with them possible. Such a comparison regarded the different hydrophobicities that substituents at the C-4 position give to the molecules. Compound **11** was prepared to investigate the role of the configuration at C-4. We show, for the first time, that low catalytic loading (down to 0.1 mol-%) and excellent enantio- and diastereoselectivities can be reached by using very simple and inexpensive *trans*-4-hydroxy-L-proline derivatives **10b** and **10f**.

4-Substituted acyloxyproline derivatives were easily prepared as previously reported (see the Experimental Section).[15b] More recently, a very short synthetic approach was also reported.[17] This new approach, which does not use chromatographic purification and which is easily scalable, makes our simple catalysts more appealing for their large use in organocatalysis.

To find the more active and stereoselective catalyst, we tested molecules in Figure 3 for the model aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. The screening was carried out by using 2, 1, or 0.5 mol-% of catalyst and an excess amount (175 μL, 19 equiv.) or

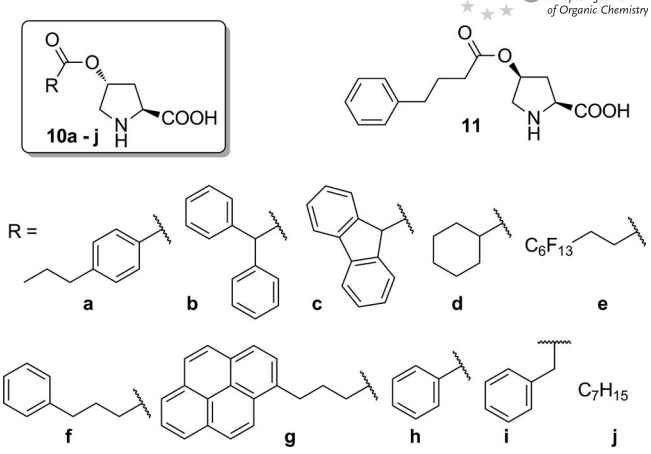


Figure 3. Catalysts **10a**–**j** and **11** used in this work.

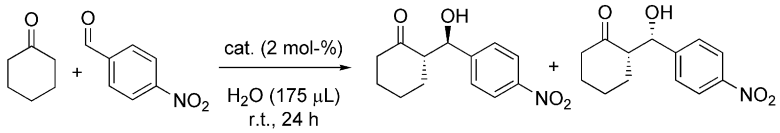
1.2 equiv. (11 μL) of water with the aim to see how the catalyst/water ratio influenced the reactions. We first carried out the reaction by using 2 mol-% of catalyst and an excess amount (175 μL) of water (Table 1). The increased hydrophobicity of **10b** compared to that of **10a** resulted in a moderate increase in stereoselectivity, whereas the higher rigidity offered by the fluorenone ring in catalyst **10c** afforded the aldol product in high stereoselectivity (Table 1, Entries 1–3). In each case, the yield was almost quantitative. When aliphatic chains were examined (**10d**,**e**), yields or stereoselectivities were lower. Cyclohexyl-substituted catalyst **10d** (Table 1, Entry 4) gave good stereoselectivity but not quantitative yield, showing an overall decreased efficiency compared to alkyl-substituted catalyst **10j** (yield 98%, 95:5 *dr*; 97% *ee*).[12a] Note that this compound has been previously synthesized by the Hansen group although it has never been employed as a catalyst for the aldol reaction.[17b] Simple fluorous proline derivative **10e** was much less reactive and stereoselective (Table 1, Entry 5). With the latter catalyst, two others solvents (MeOH and *i*PrOH) were employed, but again the results were disappointing (Table 1, Entries 6 and 7). This finding could be ascribed to its lower solubility (see the Experimental Section). Catalyst **11** was highly active and stereoselective. In comparison to its diastereoisomer **10f**,[15b] a slightly lower enantioselectivity was observed (Table 1, Entry 8).

A comparison between new and old data[15b] suggests that the best results are achieved when a rigid hydrophobic group (i.e., **10c**) or a long alkyl chain (i.e., **10j**)[12a] or, at least, a propyl chain bearing an additional hydrophobic group (i.e., **10f**,**g**, **11**) are present as the acyl substituent.

The main factors that play a role in activity and selectivity are, in addition to the nature of the acyl group, the amount of catalyst and the catalyst/water ratio.

After this preliminary test, we carried out further experiments by lowering the catalyst loading (1–0.1 mol-%) and by using an excess amount (175 μL) or 1.2 equiv. (11 μL) of water (Table 2). Different catalyst loadings and water/catalyst ratios caused different reaction outcomes in both the chemical yields and stereoselectivities. As an example, catalyst **10a** gave excellent enantioselectivity, high diastereo-

Table 1. Screening of catalysts **10a**–**e** and **11** (2 mol-%) in the direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of water.[a]

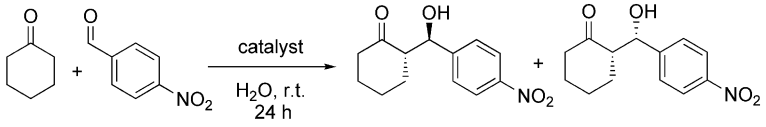


Entry	Catalyst	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	TON
1	**10a**	>99	99	87:13	86	50
2	**10b**	>99	98	91:9	91	49
3	**10c**	>99	>99	97:3	>98	50
4	**10d**	73	72	92:8	93	36
5	**10e**	18	16	83:17	11	8
6[e]	**10e**	98	95	62:38	28	47
7[f]	**10e**	48	45	78:22	94	23
8	**11**	>99	98	96:4	87	49

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst (0.01 mmol), H_2O (175 μL), room temperature, 24 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column. [e] Reaction was carried out in MeOH. [f] Reaction was carried out in *i*PrOH.

selectivity, and moderate yield when used in 1 mol-%. The enantioselectivity decreased when **10a** was used in 0.5 mol-%, whereas a lower amount of water caused a higher yield but a decreased diastereoselectivity (Table 2, Entries 1–3). A similar comparison can be done with the remaining catalysts (for example, see: Table 2, Entries 4–6 and 7–9). Among the new catalysts, the diphenyl and fluorenyl derivatives **10b**,**c** gave excellent results when employed in 1 mol-%

Table 2. Screening of catalysts **10a**–**j** and **11** in the direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of water.[a]



Entry	Catalyst	Cat. loading [mol-%]	Water [mL]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	TON
1	**10a**	1	175	57	54	96.5:3.5	>99	54
2[e]	**10a**	0.5	175	57	55	93:7	93	110
3[e]	**10a**	0.5	11	91	90	83.5:16.5	99	180
4	**10b**	1	175	>99	99	97:3	>99	99
5[f]	**10b**	0.5	175	74	72	96:4	97	144
6[f]	**10b**	0.5	11	>99	98	87:13	80	196
7	**10c**	1	175	>99	>99	97.5:2.5	99	100
8	**10c**	0.5	175	77	75	97:3	>99	150
9	**10c**	0.5	11	68	65	95:5	97	130
10	**10d**	1	175	29	29	93:7	96	29
11	**10d**	0.5	175	14	12	n.d.	99	24
12	**10d**	0.5	11	20	19	91:9	93	38
13	**10e**	0.5	175	–	–	–	–	–
14	**10f**	1	175	>99	99	96:4	98	99
15	**10f**	0.5	175	>99	98	96:4	98	196
16	**10f**	0.5	11	34	32	91:9	90	64
17[g]	**10g**	0.5	175	49	47	96.5:3.5	99	94
18	**10h**	0.5	175	21	20	96:4	>99	40
19	**10h**	0.5	11	39	36	96:4	>99	72
20[e]	**10j**	0.5	175	20	18	96:4	98	36
21[e]	**10j**	0.5	11	43	40	94:6	92	80
22[e]	**11**	1	175	70	69	96.5:3.5	97	69
23[e]	**11**	0.5	175	40	39	97.5:2.5	97	78
24[f]	**11**	0.5	11	95	93	93.5:6.5	80	186
25	**10f**	0.2	175	21	20	96:4	99	100
26[e]	**10f**	0.2	11	41	39	97:3	>99	195
27	**10f**	0.1	175	6	5	97:3	98	50

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst (0.1 mmol), H_2O, room temperature, 24 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column. [e] See ref.[18] [f] Hemiacetal in less than 5% (see ref.[18]). [g] See ref.[15b]

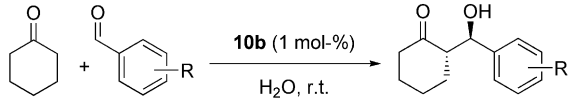
(Table 2, Entries 4 and 7). The latter catalysts were more active and stereoselective if compared to catalyst **7** when employed for the same reaction.[12a] Poor results were obtained with cyclohexyl derivative **10d** (Table 2, Entries 10–12). Fluorinated derivative **10e** was inactive (Table 2, Entry 13). Again, very promising results were observed with catalyst **10f** when used in 1 or 0.5 mol-% (Table 2, Entries 14 and 15), whereas a lower amount of water caused a lower conversion (Table 2, Entry 16). Other catalysts gave poorer results.

A comparison of the data obtained by using catalysts **11** and **10f** clearly indicated that catalyst **10f**, having a *trans* configuration, gave better results under the examined conditions. However, catalyst **11** was much less soluble (see the Experimental Section) than **10f**, and probably, the different solubility could make the comparison devoid of significance.

We further tested catalyst **10f** by decreasing its loading down to 0.1 mol-% (Table 2, Entries 25–27). In each case, the stereoselectivity was high. Particularly, an interesting turnover number (TON) of 195 was obtained by using only 0.2 mol-% of catalyst and 1.2 equiv. of water (11 μL).

After this deeper screening of catalysts **10a**–**f** we focused our attention on two of these compounds: known proline derivative **10f**, which nicely worked at 0.5 mol-% with an excess amount of water (Table 2, Entry 15), and new catalyst **10b**, which gave excellent results at 1 mol-% loading (Table 2, Entry 4). Under the same conditions, compound

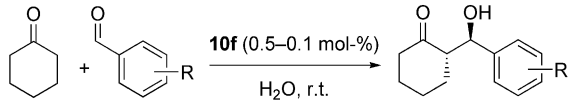
Table 3. Direct asymmetric aldol reaction between cyclohexanone and substituted benzaldehydes in the presence of water catalyzed by **10b**.[a]



Entry	R	*t* [h]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	TON
1	4-NO_2	24	>99	99	97:3	>99	100
2	4-CN	24	99	95	96.5:3.5	>99	95
3	2-NO_2	24	95	94	99:1	>99	94
4	4-Br	24	86	85	96:4	>99	85
5	4-Cl	24	87	81	95:5	>99	81
6	2,3,4,5,6-F_5	24	>99	>99	>99:1	98	100
7	H	24	75	69	93.5:6.5	97	69
8	4-CH_3	72	26	25	87:13	94	25
9	3-OCH_3	72	78	74	92:8	95	74
10	4-OCH_3	72	<5	–	–	–	–

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O (175 μL), room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column.

Table 4. Direct asymmetric aldol reaction between cyclohexanone and substituted benzaldehydes in the presence of water catalyzed by **10f**.[a]



Entry	Cat. loading [mol-%]	R	*t* [h]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	TON
1	0.5	4-NO_2	24	>99	99	96:4	99	198
2	0.5	4-Cl	24	48	46	96:4	>99	92
3	0.5	4-Br	24	27	24	95:5	>99	48
4	0.5	4-Br	48	50	47	94:6	99	94
5	0.5	4-CN	24	90	87	96.5:3.5	>99	176
6[e]	0.5	2-NO_2	24	47	45	99:1	>99	90
7[e]	0.5	2,3,4,5,6-F_5	24	99	97	>99:1	98	194
8[e]	0.2	2,3,4,5,6-F_5	24	75	75	>99:1	97	375
9[e]	0.1	2,3,4,5,6-F_5	24	40	39	>99:1	97	390
10[e]	0.5	3-NO_3	24	53	50	98:2	96	100
11	0.5	2-naphthyl	72	9	8	92:8	97	16
12	0.5	2-Cl	24	73	70	94:6	90	140
13	0.5	H	72	49	47	90.5:9.5	93	94
14	0.5	3-OCH_3	72	28	27	94:6	95	54

[a] Reaction conditions: cyclohexanone (260 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O (175 μL), room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column. [e] See ref.[18]

10c also furnished excellent results (Table 2, Entry 7). However, we decided to further investigate compound **10b** because this proline derivative is less expensive than **10c**.

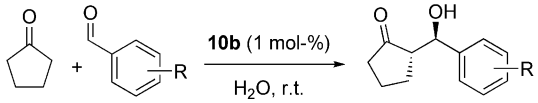
Then, using catalysts **10b** and **10f** under the optimized reaction conditions, we carried out several aldol reactions. The results obtained in the aldol reaction between cyclohexanone and several substituted benzaldehydes in the presence of catalysts **10b** and **10f** are reported in Tables 3 and 4, respectively. The use of catalyst **10b** gave aldol products in excellent optical purity (98 to >99%; Table 3, Entries 1–6), high diastereoselectivities, and high yields. Less-reactive aldehydes furnished products still with high *ee* values (94–97%; Table 3, Entries 7–9) and good yields. Only 4-tolualdehyde gave a moderate yield, whereas 4-methoxybenzaldehyde was unreactive.

Catalyst **10f** furnished aldol products with high (90–97%; Table 4, Entries 10–14) to excellent (98 to >99%; Table 4, Entries 1–7) optical purity. Diastereoselectivities ranged from high (90.5:9.5) to excellent (>99:1). In addition to these very interesting results concerning the stereochemical aspects, catalyst **10f** proved to be a very active catalyst, working well at a loading of only 0.5 mol-%. Good TONs were obtained, and in some cases, the values were over 190. In the case of highly reactive pentafluorobenzaldehyde, catalyst **10f** was used in only 0.1 mol-% and reached a TON as high as 390 (Table 4, Entry 9) while still maintaining high stereoselectivity.

Further experiments carried out by employing cyclopentanone confirmed the high performances of these catalysts. Catalyst **10b** gave aldol products with excellent *ee* values (96 to >99%), high diastereoselectivities (89:11 to 96:4), and very high yields (82 to >99%) even with less-reactive aldehydes (Table 5).

Reactions between cyclopentanone and substituted benzaldehydes were also carried out by using catalyst **10f** (Table 6). Again, compound **10f** was employed in 0.5 mol-%.

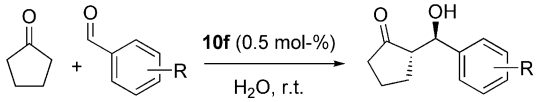
Table 5. Direct asymmetric aldol reaction between cyclopentanone and substituted benzaldehydes in the presence of water catalyzed by **10b**.[a]



Entry	R	*t* [h]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]	TON
1	4-NO_2	24	>99	>99	92:8	>99	100
2	4-CN	24	>99	99	91.5:8.5	>99	99
3	2-NO_2	24	>99	>99	96:4	>99	100
4	4-Cl	24	93	92	92:8	99	92
5	4-Br	24	96	96	92:8	99	96
7	H	24	87	86	92.5:7.5	98	86
8	4-CH_3	72	84	82	89:11	96	82
10	4-OCH_3	72	96	96	90:10	97	96

[a] Reaction conditions: cyclopentanone (220 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O (175 μL), room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column.

Table 6. Direct asymmetric aldol reaction between cyclopentanone and substituted benzaldehydes in the presence of water catalyzed by **10f**.[a]



Entry	Cat. loading [mol-%]	R	*t* [h]	Conv. [%]	Yield[b] [%]	*anti*/*syn*[c]	*ee* [d] [%]	TON
1	0.5	4-NO_2	24	63	60	93:7	>99	120
2	0.2	4-NO_2	24	36	35	95:5	98	175
3	0.5	4-CN	24	99	98	91:9	>99	196
4	0.5	4-Cl	48	86	86	92:8	>99	172
5	0.5	4-Br	48	86	84	91:9	>99	168
6	0.5	2-NO_2	24	63	61	98:2	>99	122
7	0.5	3-NO_3	24	87	86	92:8	>99	172
8	0.5	3-MeO	48	69	67	88:12	96	134
9	0.5	4-CH_3	72	49	49	87:13	96	98
10	0.5	H	24	81	80	87:13	96	160
11	0.5	2-Cl	24	73	72	89:11	96	144

[a] Reaction conditions: cyclopentanone (220 μL, 2.5 mmol), aldehyde (0.5 mmol), catalyst, H_2O (175 μL), room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic analysis of the crude product. [d] The *anti* diastereoisomer, determined by HPLC by using a chiral column.

In the case of 4-nitrobenzaldehyde, it was also tested in 0.2 mol-%, giving the aldol product with excellent stereoselectivity and enhanced TON (Table 6, Entry 2). Again, aldol products were obtained with excellent *ee* values and high diastereoselectivities. It is noteworthy that there are only few reports regarding aldol reactions between cyclopentanone and aromatic aldehydes furnishing aldols with high levels of enantio- and diastereoselectivity.[5,12a,19] In addition, as for cyclohexanone, also for these reactions good TON values were reached.

Finally, because of the excellent results obtained by using catalyst **10b**, we prepared it on a larger scale by using a slightly modified procedure than that reported by Hansen and co-workers.[17] Direct *O*-acylation, starting from *trans*-4-hydroxy-L-proline and diphenylacetic acid, gave catalyst **10b** in about 60% yield (not optimized), avoiding column chromatography purification and consequently large solvent wasting. Because of the very easy availability of the catalyst, we carried out the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde on a larger scale (20 mmol) in the presence of 1 mol-% of catalyst **10b**. The aldol product was obtained in >99% yield and 98:2 *dr* with an excellent optical purity of 99.8% *ee*.

Conclusions

In conclusion, the data reported represent an update regarding the use of cheap proline-based organocatalysts for the asymmetric aldol reaction in water. Deeper investigations showed the general and wide applicability of hydrophobic 4-acyloxyproline derivatives as catalysts for the direct asymmetric aldol reaction between cyclic ketones and substituted benzaldehydes. Particularly, here we presented the outstanding activity and stereoselectivity of *trans*-4-hydroxy-L-prolines bearing a simple 2,2-diphenylacetate (**10b**) and a 4-phenylbutanoate group (**10f**), which afforded aldol products with high to excellent enantio- and diastereoselectivities, even when cyclopentanone was employed, with as low as 1–0.5 mol-% catalytic loading. It is important to stress that simple catalysts such as **10b** and **10f** do not need the use of low temperature or additives, do not need new chiral centers in addition to those of inexpensive *trans*-4-hydroxy-L-proline, and can be very easily prepared by direct *O*-acylation starting from very inexpensive carboxylic acids.

Finally, the data reported in this work suggest that such catalytic molecules are organized at the ketone/water interface and their organization depends on the nature of the acyl group and on the catalyst/water ratio (see Tables 1 and 2). Further studies in this field may disclose new simple more active and stereoselective proline catalysts.

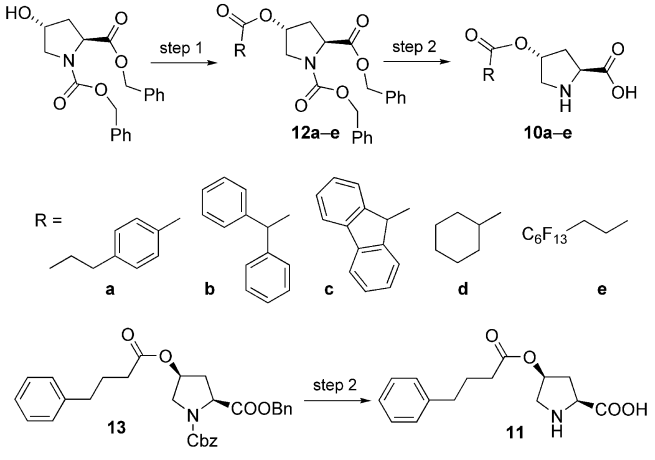
Experimental Section

General Methods: NMR spectra were recorded with a Bruker 300 MHz spectrometer by using $CDCl_3$ or [D_6]DMSO as solvent. Solid-state $^{13}C\{H\}$ CP-MAS NMR spectra was recorded with a Bruker AV 400, 400 MHz spectrometer with samples packed in zirconia rotors spinning at 15 kHz. FTIR spectra were registered with a Shimadzu FTIR 8300 infrared spectrophotometer. Carbon and nitrogen contents were determined by combustion analysis with a Fisons EA 1108 elemental analyzer. Optical rotations were measured with a Jasco P1010 polarimeter. Hydrogenation reactions were carried out by using a Parr apparatus. Flash chromatography was carried out by using Macherey–Nagel (0.04–0.063 mm) silica gel. Melting points were determined by using a Kofler hot plate. Chiral HPLC analyses were performed by using a Shimadzu LC-10AD apparatus equipped with an SPD-M10 A UV detector and Daicel columns (OD-H, AD-H, AS-H) by using hexane/2-propanol as the eluent. The aldol products are known compounds and showed spectroscopic and analytical data in agreement with their structures. The configurations of the products were assigned by comparison with literature data. *N*-Cbz-*trans*-4-hydroxy-L-proline was commercially available (Aldrich). (2*S*,4*R*)-Dibenzyl-4-hydroxypyrrolidine-1,2-dicarboxylate was prepared as reported in the literature.[20] Catalysts **10f**–**i**[15b] and **10j**[12a] are known compounds and showed spectroscopic and analytical data in agreement with their structures.

General Procedure for the Synthesis of Compounds 10 and 11

Step 1: To a solution of (2*S*,4*R*)-dibenzyl-4-hydroxypyrrolidine-1,2-dicarboxylate (562 mg, 1.58 mmol) in anhydrous dichloromethane (35 mL) the proper carboxylic acid (2.24 mmol) was added. The mixture was stirred for 10 min at 0 °C under an atmosphere of argon. Then, a solution of 1,3-dicyclohexylcarbodiimide (DCC; 2.24 mmol) and 4-(dimethylamino)pyridine (DMAP; 0.224 mmol) in dichloromethane (10 mL) was added, and the mixture was stirred at 0 °C for 15 min. The reaction mixture was stirred overnight at room temperature under an atmosphere of argon. After this period, the dichloromethane solution was washed with water (2 × 30 mL), and the organic phase was dried with $MgSO_4$ and concentrated under reduced pressure.

Step 2: To a solution of compounds **12a**–**e** or **13** (1.91 mmol) in methanol (65 mL) was added Pd(10%)/C (308 mg). The reaction mixture was stirred under an atmosphere of hydrogen in a Parr apparatus for 3 h. After this time, the reaction mixture was filtered through a short pad of Celite and then through a short pad of silica, washing with methanol. The organic phase was concentrated under reduced pressure to give compounds **10a**–**e** and compound **11** (see Scheme 1).



Scheme 1. Synthesis of catalysts **10a**–**e** and **11** used in this work.

(2*S*,4*R*)-Dibenzyl 4-(4-Propylbenzoyloxy)pyrrolidine-1,2-dicarboxylate (12a): The residue was purified by column chromatography (pe-

troleum ether/ethyl acetate, 5:1) to give compound **12a** as a pale-yellow oil. Yield: 92%. $[\alpha]_D^{29}$ = –33.0 (*c* = 0.84, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, CH_3), 1.57 (s, $^3J_{H,H}$ = 7.4 Hz, 2 H, CH_2), 2.25 (m, 1 H), 2.48 (m, 1 H), 2.56 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, CH_2), 3.80 (m, 2 H), 4.53 (m, 1 H), 4.93–5.20 (m, 4 H), 5.44 (br. s, 1 H), 7.14–7.28 (m, 12 H), 7.81 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C; two rotamers): δ = 172.0, 171.8, 165.9, 154.8, 154.2, 148.9, 148.8, 136.2, 136.2, 135.4, 135.6, 129.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1, 28.0, 127.9, 127.8, 126.9, 126.9, 72.9, 72.2, 67.3, 67.1, 67.0, 58.1, 57.8, 52.7, 52.4, 38.0, 36.8, 35.7, 30.9, 24.2, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 2959, 2931, 1749, 1715, 1609, 1353, 755, 698 cm^{-1}. $C_{30}H_{31}NO_6$ (501.57): calcd. C 71.84, H 6.23, N 2.79; found C 71.54, H 6.43, N 2.86.

(2*S*,4*R*)-4-(4-Propylbenzoyloxy)pyrrolidine-2-carboxylic Acid (10a): Pale-yellow, viscous liquid. Yield: 85%. $[\alpha]_D^{25}$ = –15.1 (*c* = 0.47, DMSO). ^1H NMR ([D_6]DMSO, 25 °C): δ = 0.79 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3), 1.50 (m, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH_2), 2.05 (m, 1 H), 2.42 (m, 1 H), 2.52 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH_2), 3.28 (br. s, 1 H), 3.49 (br. s, 1 H), 3.73 (br. s, 1 H), 5.28 (m, 1 H), 7.24 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H), 7.82 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6] DMSO, 25 °C): δ = 172.2, 165.0, 147.9, 129.2, 128.33 127.2, 127.0, 36.9, 35.9, 28.8, 24.2, 23.7, 23.5113, 13.2 ppm. $C_{15}H_{19}NO_4$ (277.32): calcd. C 64.97, H 6.91, N 5.05; found C 65.10, H 6.96, N 5.12.

(2*S*,4*R*)-Dibenzyl 4-(2,2-Diphenylacetoxy)pyrrolidine-1,2-dicarboxylate (12b): The residue was purified by column chromatography (petroleum ether/ethyl acetate, 4:1) to give compound **12b** as a pale-yellow oil. Yield: 98%. $[\alpha]_D^{29}$ = –29.8 (*c* = 0.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.20 (m, 1 H), 2.44 (m,1 H), 3.84 (m, 2 H), 4.47 (dt, 1 H), 5.05 (s, 2 H), 5.11 (s, 1 H), 5.23 (m, 2 H), 5.40 (br. s, 1 H), 7.36 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C; two rotamers): δ = 171.8, 171.7, 171.6, 154.5, 153.9, 137.9, 137.9, 137.8, 136.1, 136.0, 135.2, 135.0, 128.5,128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.7, 127.7, 127.3, 127.3, 73.1, 72.4, 69.3, 67.2, 67.1, 66.9, 66.8, 57.7, 56.6, 53.3, 52.2, 51.8, 36.2, 35.2, 31.6, 29.1 ppm. IR: $\tilde{\nu}$ = 1715, 1738, 1418, 1186, 1150, 768, 746 cm^{-1}. $C_{34}H_{31}NO_6$ (549.61): calcd. C 74.30, H 5.69, N 2.55; found C 74.55, H 5.88, N 2.60.

(2*S*,4*R*)-4-(2,2-Diphenylacetoxy)pyrrolidine-2-carboxylic Acid (10b): Pale-yellow solid; m.p. 102–105 °C. Yield: 93%. $[\alpha]_D^{29}$ = –2.5 (*c* = 0.62, methanol). ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.98 (br. s, 2 H), 2.95 (d, $^3J_{H,H}$ = 11.9 Hz, 1 H), 3.26 (m, 1 H), 3.37 (d, $^3J_{H,H}$ = 11.9 Hz, 1 H), 3.58 (br. s, 1 H), 5.17 (s, 1 H), 7.24 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 172.4, 139.6, 129.5, 129.2, 128.0, 75.6, 73.5, 60.6, 56.5, 50.8, 36.3 ppm. IR (nujol): $\tilde{\nu}$ = 2853, 2922, 1726, 1456, 1377, 1146 cm^{-1}. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.23, H 5.93, N 4.40.

(2*S*,4*R*)-Dibenzyl 4-(9*H*-Fluorene-9-carbonyloxy)pyrrolidine-1,2-dicarboxylate (12c): The residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give compound **12c** as a pale-yellow oil. Yield: 85%. $[\alpha]_D^{26}$ = –39.3 (*c* = 0.72, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.32 (m, 1 H), 2.51 (m, 1 H), 3.88 (m, 2 H), 4.63 (dt, 1 H), 4.90 (s, 1 H), 5.11 (s, 1 H), 5.18–5.31 (m, 3 H), 5.44 (br. s, 1 H), 7.32–7.49 (m, 14 H), 7.60 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H), 7.80 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C; two rotamers): δ = 171.6, 171.4, 169.8, 169.8, 154.46, 153.8, 141.1, 141.1, 139.8, 139.8, 136.0, 135.2, 135.0, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.6, 127.6, 127.2, 127.1, 125.2, 125.1, 125.0, 119.9, 73.3, 72.5, 67.1, 67.0, 66.8, 66.7, 57.7, 57.4, 52.8, 52.2, 51.9, 36.1, 35.1, 30.6 ppm. IR (neat): $\tilde{\nu}$ = 1748, 1715, 1418, 1167, 1353, 1190, 768, 746 cm^{-1}. $C_{34}H_{29}NO_6$ (547.60): calcd. C 74.57, H 5.34, N 2.56; found C 74.71. H, 5.30, N 2.61.

(2*S*,4*R*)-4-(9*H*-Fluorene-9-carbonyloxy)pyrrolidine-2-carboxylic Acid (10c): White solid; m.p. 129–131 °C. Yield: 90%. $[\alpha]_D^{26}$ = –17.8 (*c* = 0.40, MeOH). ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 2.36 (m, 1 H), 2.55 (m, 1 H), 3.48 (m, 1 H), 3.74 (m, 1 H), 4.27 (m, 1 H), 5.49 (m, 1 H), 7.37–7.48 (m, 4 H), 7.71–7.83 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C; two rotamers): δ = 171.5, 170.2; 141.2, 140.1, 127.9, 127.0, 125.1, 119.6, 74.2, 60.1, 50.2, 35.1 ppm. IR (nujol): $\tilde{\nu}$ = 1734, 1460, 1377, 1193, 721 cm^{-1}. $C_{19}H_{17}NO_4$ (323.34): calcd. C 70.58, H 5.30, N 4.33; found C 70.68, H 5.35, N 4.28.

(2*S*,4*R*)-Dibenzyl 4-(Cyclohexanecarbonyloxy)pyrrolidine-1,2-dicarboxylate (12d): The residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give compound **12d** as a pale-yellow oil. Yield: 97%. $[\alpha]_D^{26}$ = –39.9 (*c* = 0.90, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17–1.88 (m, 10 H), 2.16 (m, 2 H), 2.39 (m, 1 H), 3.62–3.79 (m, 2 H), 4.50 (dt, 1 H), 5.00 (s, 1 H), 5.06 (s, 1 H), 5.18 (m, 2 H), 5.28 (m, 1 H), 7.20 (s, 1 H), 7.28–7.34 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C; two rotamers): δ = 175.3, 175.3, 172.0, 171.8, 154.7, 154.1, 136.3, 136.2, 135.4, 135.2, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 72.1, 71.3, 67.3, 67.0, 66.9, 58.0, 57.7, 52.6, 52.2, 42.9, 36.7, 35.6, 32.7, 31.1, 29.9, 28.8, 28.8, 28.7, 25.6, 25.2 ppm. IR (neat): $\tilde{\nu}$ = 1709, 1418, 1167, 1130, 768, 754 cm^{-1}. $C_{27}H_{31}NO_6$ (465.54): calcd. C 69.66, H 6.71, N 3.01; found C 69.72, H 6.77, N 3.10.

(2*S*,4*R*)-4-(Cyclohexanecarbonyloxy)pyrrolidine-2-carboxylic Acid (10d): Analytical and spectroscopic data agree with those reported in the literature.[17b]

(2*S*,4*R*)-Dibenzyl 4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononanoyloxy)pyrrolidine-1,2-dicarboxylate (12e): The residue was purified by column chromatography (petroleum ether/ethyl acetate, 8:1) to give compound **12e** as a pale-yellow oil. Yield: 64%. $[\alpha]_D^{27}$ = –23.7 (*c* = 0.90, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.20 (m,1 H), 2.35 (m, 3 H), 2.54 (m,2 H), 3.55–3.75 (m, 3 H), 4.44 (dt, 1 H), 5.03 (m, 4 H), 5.25 (m, 1 H), 7.19 (m,10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.9, 171.6, 170.4, 170.4, 154.6, 154.1, 136.2, 136.1, 135.3, 135.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 120.4–103.8 (22 CF signals), 73.4, 72.7, 67.4, 67.4, 67.1, 67.0, 57.9, 57.6, 52.4, 52.0, 36.4, 35.4, 26.6, 26.3, 26.0, 25.5, 25.4, 25.4037 ppm. IR (nujol): $\tilde{\nu}$ = 1746, 1713, 1418, 1354, 1146, 1123, 737, 700 cm^{-1}. $C_{29}H_{24}F_{13}NO_6$ (729.48): calcd. C 47.75, H 3.32, N 1.92; found C 47.86, H 3.43, N 2.00.

(2*S*,4*R*)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononanoyloxy)pyrrolidine-2-carboxylic Acid (10e): White-gray powder; m.p. 130–135 °C. Yield: 92%. Because this compound is very poorly soluble, it was characterized in the solid state ^{13}C NMR (400 MHz, 25 °C; Figure 4): δ = 173.5, 170.8, 130–110 (CF signals), 73.7, 62.7, 51.9, 36.4, 25.8, 24.9 ppm. IR (nujol): $\tilde{\nu}$ = 2853, 1742, 1460, 1377 cm^{-1}. $C_{14}H_{12}F_{13}NO_4$ (505.23): calcd. C 33.28, H 2.39, N 2.77; found C 33.36, H 2.29, N 2.81.

(2*S*,4*S*)-Dibenzyl 4-(4-Phenylbutanoyloxy)pyrrolidine-1,2-dicarboxylate (13): The residue was purified by column chromatography (petroleum ether/ethyl acetate, 3:1) to give compound **13** as a pale-yellow oil. Yield: 70%. $[\alpha]_D^{28}$ = –41.5 (*c* = 0.73, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.17 (t, $^3J_{H,H}$ = 5.5 Hz, 1 H), 1.69 (m, 2 H), 1.96 (m, 2 H), 2.20 (dd, 1 H), 2.37 (m, 3 H), 3.45 (dd, $^3J_{H,H}$ = 5.0 Hz, 1 H), 3.64 (dd, $^3J_{H,H}$ = 5.0 MHz, 1 H), 4.45 (dd, $^3J_{H,H}$ = 9.4 MHz, 1 H), 5.02 (m, 5 H), 7.13 (m, 15 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 173.1, 171.81, 171.6, 155.3, 155.0, 141.6, 136.6, 136.0, 128.4, 128.3, 128.0, 127.7, 125.9, 73.3,

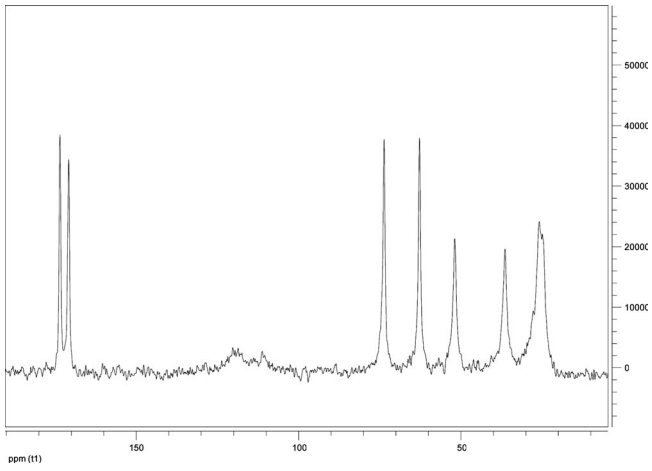


Figure 4. Solid-state ^{13}C NMR spectrum of compound **10e**.

72.3, 67.3, 66.8, 58.3, 58.1, 52.8, 52.5, 36.0, 35.1, 34.8, 33.1, 26.4 ppm. IR: $\tilde{\nu}$ = 3030, 2949, 1711, 1496, 1415, 1165, 1070, 1005 cm^{-1}. $C_{30}H_{29}NO_5$ (483.55): calcd. C 74.52, H 6.04, N 2.90; found C 74.66, H 6.20, N 2.99.

(2*S*,4*S*)-4-(4-Phenylbutanoyloxy)pyrrolidine-2-carboxylic Acid (11): White-gray powder; m.p. 163–167 °C. Yield: 95%. Because this compound is very poorly soluble, it was characterized in the solid state ^{13}C NMR: see Figure 5. IR (nujol): $\tilde{\nu}$ = 2924, 2852, 17430, 1597, 1460, 1377 cm^{-1}. $C_{15}H_{19}NO_4$ (277.32): calcd. C 64.97, H 6.91, N 5.05; found C 65.09, H 6.96, N 5.11.

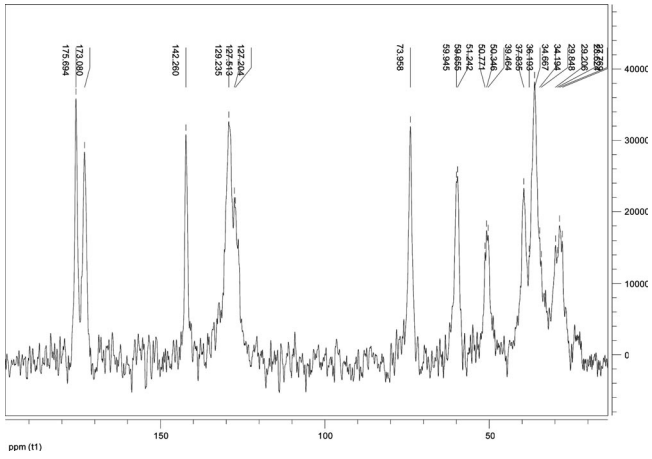


Figure 5. Solid-state ^{13}C NMR spectrum of compound **11**.

Typical Procedure for the Aldol Reactions: Catalysts were added to a mixture of the corresponding aldehyde (0.5 mmol) and ketone (2.5 mmol) in distilled water (0.175 mL), and the reaction mixture was stirred at room temperature. The reaction was quenched by adding ethyl acetate, and the organic phase was washed with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was checked by ^1H NMR spectroscopy and HPLC and was then purified by chromatography (petroleum ether/ethyl acetate). Enantiomeric excess values were determined by HPLC by using chiral columns (OD-H, AD-H, AS-H) and hexane/2-propanol as eluent.[2]

Direct Synthesis of (2*S*,4*R*)-4-(2,2-Diphenylacetoxy)pyrrolidine-2-carboxylic Acid (10b): A 25-mL round-bottomed flask was charged with diphenylacetic acid (4.29 g, 0.02 mol) and $SOCl_2$ (7.7 mL, 0.106 mol). The mixture was stirred for 30 min at room temperature and then at 50 °C for 1 h until a clear light-yellow solution was obtained. The excess amount of $SOCl_2$ was removed under reduced pressure to afford the diphenylacetic acid chloride as a light-yellow solid. In a 25-mL round-bottomed flask, *trans*-4-hydroxy-L-proline (1.31 g, 0.01 mol) was dissolved in trifluoroacetic acid (6.4 mL). This solution was added to the flask containing diphenylacetic acid chloride and additional TFA (4.6 mL) was added. A white precipitate was present, and the suspension was stirred at room temperature for 18 h. After this period, the solution was cooled and diethyl ether was carefully added whilst stirring. A white precipitate was present. The solution was decanted, and the liquid was removed. Another portion of diethyl ether was added, and the mixture was filtered under reduced pressure washing with diethyl ether several times. The white solid was poured in water and treated with an aqueous solution of $NaHCO_3$ (2 equiv.) until ca. pH 7 was reached. The solid was filtered under reduced pressure and dried (Yield: 1.92 g, ca. 60%).

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