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Highly Diastereo- and Enantioselective Direct Aldol Reactions of Aldehydes and Ketones Catalyzed by Siloxyproline in the Presence of Water

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Abstract: Proline-based organocatalysts have been developed for a highly enantioselective, direct aldol reaction of aldehydes and ketones in the presence of water. While several surfactant–proline combined catalysts have proved effective, proline derivatives with a hydrophobic moiety such as *trans*-siloxy-L-proline and *cis*-siloxy-D-proline, both of which are easily prepared from the same commercially available 4-hydroxy-L-proline, have been found to be the most effective organocatalysts examined in this study, affording the aldol product with excellent diastereo- and enantioselectivities, these two catalysts generating opposite enantiomers. Water affects the selectivity, and poor results are obtained under neat reaction conditions or in dry organic solvents. More than three equivalents of water are required for the best diastereo- and enantioselectivities, while three equivalents is the recommended amount from a synthetic point of view. The reaction proceeds in the organic phase, and also proceeds in the presence of a large amount of water. The large-scale preparation of aldols with the minimal use of an organic solvent, including in the purification step, is described.

Keywords: aldol reaction · asymmetric synthesis · organocatalysis · proline · sustainable chemistry · water

Introduction

Processes using water as a reaction medium have recently attracted a great deal of attention,[1] because water possesses unique properties as a solvent. For example, Breslow et al. reported that the Diels–Alder reaction is accelerated in water under dilute conditions,[2] while Sharpless et al. reported that some organic reactions are accelerated under so-called "on water" conditions.[3]

The synthesis of enantiopure molecules is another important issue,[4] and the development of enantioselective reactions using water as a reaction medium is being intensively investigated,[5] although it was long thought that such reactions were mainly confined to the realm of enzymes. Successful catalytic versions of enantioselective reactions are mostly reliant upon transition metal complexes, and may require toxic, rare, and/or expensive metals, and suffer from possible metal contamination of the products. Organocatalysts,[6] in contrast, are free from these problems and, moreover, are inexpensive and stable to moisture and air. Thus, the development of small organic molecules capable of catalyzing enantioselective reactions using water as the reaction medium is currently a highly sought-after goal.

The aldol condensation is a key carbon–carbon bond-forming reaction, creating the β-hydroxy carbonyl structural unit found in many natural products and drugs.[7] In nature, type I and type II aldolases catalyze this reaction in an aqueous environment with perfect enantiocontrol by way of an enamine mechanism and by using a zinc cofactor, respectively.[8] The catalytic, direct asymmetric aldol reaction is an active research field, and excellent results have been reported in an organic solvent using organometallic catalysts,[9] while the development of this reaction using water as a solvent has also been intensively investigated. Chiral Lewis acids have been developed for the aqueous Mukaiyama aldol reaction, an indirect method using a silyl enol ether whereby water is used as a co-solvent with organic solvents.[10] Kobayashi reported the use of a chiral Lewis acid–surfactant combined catalyst in the Mukaiyama aldol reaction using water as the only solvent, in which a moderate enantioselectivity was attained.[11] A Zn-proline-catalyzed

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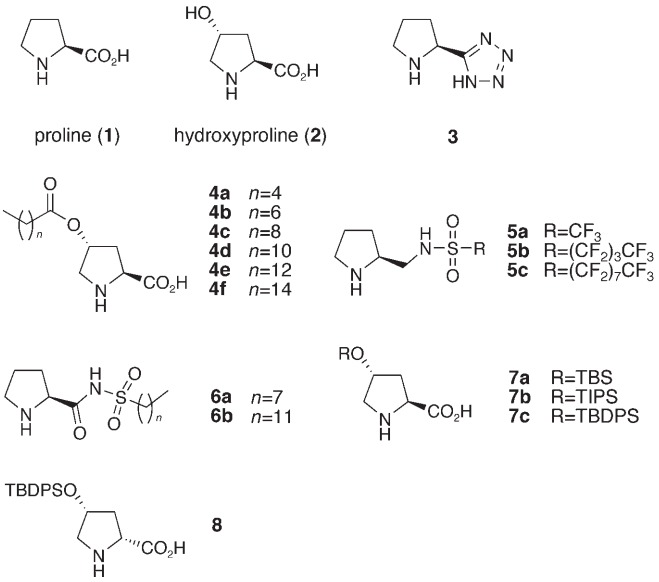
aldol reaction in aqueous media, in which a mixture of acetone and water was used as the solvent, proceeded with a moderate enantiomeric excess.[12] In this reaction, acetone acts not only as the nucleophile, but also as a co-solvent.

List, Lerner, and Barbas discovered the proline-mediated aldol reaction in 2000.[13] Since then, many organocatalysts have been developed for several asymmetric reactions.[6,14] Proline is capable of catalyzing the direct aldol reaction in polar organic solvents such as DMSO and DMF.[13,15,16] Recently, Bolm and co-workers reported that proline catalyzes a solvent-free asymmetric aldol reaction involving the use of a ball-mill.[17] When the reaction was performed in the presence of water or a buffer solution, a nearly racemic product was obtained.[18] Though several chiral organocatalysts have been developed for the aldol reaction, and some of them provide aldols enantioselectively in aqueous organic solvents,[19] they still require an organic co-solvent. It has been demonstrated by Janda's[20] and Barbas'[16] groups that the enamine, which had been considered to be easily hydrolyzed in the presence of water, is in fact generated and reacts with an electrophile to afford an aldol under aqueous conditions. However, it is very difficult to attain high enantioselectivity under aqueous conditions; Janda et al. used nornicotine as a catalyst with 10% DMSO, which afforded some asymmetric induction (≈20% *ee*).[20] Barbas et al. reported that the aldol reaction of acetone and *p*-nitrobenzaldehyde proceeds using proline in 20 vol% water, affording the aldol product with between 10 and 20% *ee*, while good enantioselectivity is obtained using DMSO as the solvent.[16] Pihko et al. reported a highly enantioselective aldol reaction in aqueous DMF, in which the reaction proceeds efficiently in the presence of a large excess of water.[19k] Though Chimni et al. reported that proline and its derivatives act as catalysts in the presence of water, the highest enantioselectivity achieved was just 62%.[21] As far as we are aware, only enzymes and antibodies of very high molecular weight have hitherto been shown to catalyze the direct aldol reaction with high enantioselectivity in purely aqueous media. Moreover, a rather high catalyst loading is usually required for these organocatalyst-mediated aldol reactions. At the same time as our preliminary publication on the asymmetric aldol reaction of aldehydes and ketones using siloxyproline in the presence of water,[22] Barbas and co-workers reported an asymmetric aldol reaction performed in the presence of water, in which the catalyst system used consisted of a combination of a diamine with a long alkyl chain and trifluoroacetic acid.[23] We also reported that a surfactant–proline combined catalyst is effective in the direct, enantioselective aldol reaction of two aldehydes, which proceeds in the presence of water.[24] Recently, we also reported that proline itself promotes the enantioselective aldol reaction without any organic solvent under neat conditions, and in the presence of three equivalents of water for aldehyde–aldehyde and aldehyde–ketone aldol reactions, respectively, when the reaction proceeds efficiently by virtue of reactive electrophilic aldehydes.[25] We also found that proline could catalyze the enantioselective aldol reaction even in the presence of a large amount of water, though the enantioselectivities were moderate.[25] Just recently, we found that proline amide acts effectively "in water", rather than "in the presence of water".[26] Since our first publication, a couple of asymmetric aldol reactions catalyzed by an organocatalyst and proceeding in the presence of water have appeared.[27]

As there is some confusion over the term "in water",[28,29] we would like to use it for reactions in which the participating reactants are homogeneously dissolved in water.[29] Throughout this paper, the term "in the presence of water" is used for a reaction that proceeds in a concentrated organic phase with water being present as the second phase, which influences the reaction in the organic phase.[29] Herein, we disclose full details of our enantioselective aldol reaction of ketones and aldehydes catalyzed by siloxyproline in the presence of water.

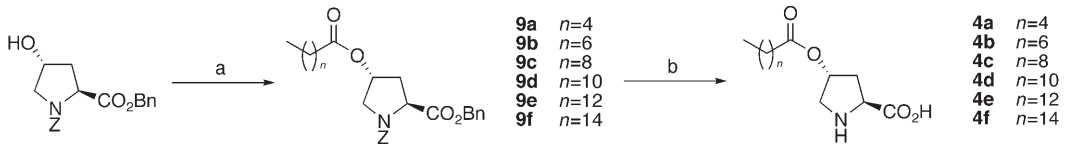
Results and Discussion

Catalyst preparation: The aldol reaction of cyclohexanone and benzaldehyde was selected as a model. The organocatalysts that have been investigated in this study are summarized in Scheme 1. The pyrrolidin-2-yl-1*H*-tetrazole catalyst



Scheme 1. Organocatalysts examined in this study. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

(**3**)[19a,30] and pyrrolidine sulfonamide catalysts **5**[31] were prepared according to the relevant literature procedures. The 4-acyloxyproline catalysts (**4a–f**) were prepared from the known benzyl ester of Z-4-hydroxyproline,[32] which is easily prepared from commercially available *trans*-4-hydroxy-L-proline; **4a–f** were prepared by first treating the benzyl ester with the appropriate acyl chlorides and pyridine to give **9a–f**, which were then subjected to hydrogenolytic debenzylation (Scheme 2). Pyrrolidines bearing an *N*-sulfonyl-



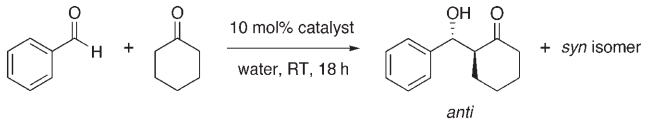
Scheme 2. Synthetic scheme for acyloxyprolines **4**: a) acyl chlorides, DMAP (cat.), pyridine, 0 °C to room temperature; b) H_2, $Pd(OH)_2$, EtOAc, room temperature

carboxyamide moiety **6** were synthesized by reaction of the 4-nitrophenyl ester of Z-proline **10** with the appropriate sulfonylamides to give **11**, followed by hydrogenolysis[33] (Scheme 3). The *trans*-siloxy-L-proline catalysts **7a–c** were prepared by first treating the benzyl ester of Z-4-hydroxyproline with the appropriate silyl chlorides and imidazole to give **12a–c**, followed by hydrogenolysis (Scheme 4). The *cis*-siloxy-D-proline **8** was prepared according to the literature procedure.[34]

Catalyst screening: The aldol reaction of benzaldehyde (1 equiv) and cyclohexanone (5 equiv) was performed using 10 mol% of the organocatalyst in the presence of water (18 equiv) for 18 h at room temperature. The results for the organocatalysts investigated are summarized in Table 1. Proline (**1**) was found not to promote the reaction, as was reported by Barbas and co-workers.[18] Neither did hydroxyproline (**2**) prove effective. The pyrrolidin-2-yl-1*H*-tetrazole catalyst (**3**), which has been reported to promote the aldol reaction of chloral under aqueous conditions[19a] and several other organic reactions,[30] does not catalyze the reaction under the present reaction conditions.

As Kobayashi and co-workers reported that surfactant-combined Lewis acids can be effective catalysts under aqueous conditions,[10p] we prepared several types of surfactant–proline combined organocatalysts. 4-Acyloxyprolines **4** with different side chains ranging from hexanoyloxy to hexadecanoyloxy were examined. It was found that these 4-acyloxyprolines catalyze the aldol reaction in the presence of water, and the aldol product was thereby obtained in moderate yield with excellent diastereo- and enantioselectivities. The length of the acyl side chain affected the yield, the best results being obtained when the organocatalyst **4a** bearing the hexanoyloxy moiety was employed.

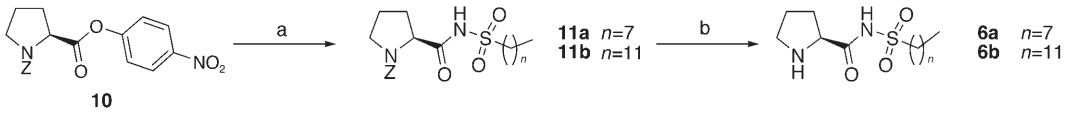
Table 1. The effect of catalyst on the reaction yield and selectivity.[a]



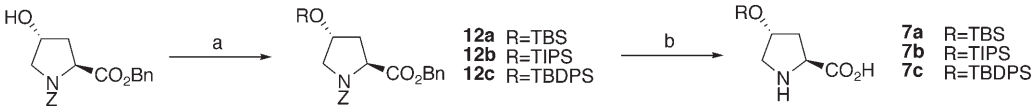
Entry	Catalyst	Yield [%][b]	*anti:syn*[c]	*ee* [%][d]
1	proline (**1**)	<5	N.D.[e]	N.D.[e]
2	hydroxyproline (**2**)	<5	N.D.[e]	N.D.[e]
3	**3**	<5	N.D.[e]	N.D.[e]
4	**4a**	53	20:1	99
5	**4b**	48	17:1	99
6	**4c**	37	15:1	98
7	**4d**	18	17:1	98
8	**4e**	30	10:1	97
9	**4f**	38	9:1	89
10	**5a**	65	2.3:1	82
11	**5b**	62	2.6:1	89
12	**5c**	20	3:1	87
13	**6a**	62	>20:1	98
14	**6b**	22	>20:1	97
15	**7a**	61	19:1	>99
16	**7b**	71	14:1	>99
17	**7c**	78	13:1	>99
18	**8**	70	>20:1	−98

[a] The reaction was performed by employing benzaldehyde (0.4 mmol), cyclohexanone (2.0 mmol), organocatalyst (0.04 mmol), and water (0.13 mL) at room temperature for 18 h. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^1H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase. [e] N.D. = not determined.

We also prepared some other types of surfactant–proline combined catalysts, including pyrrolidines bearing a sulfonamide moiety **5**. The pyrrolidine sulfonamide **5a** has been reported to be an effective catalyst in the Michael reaction of nitroalkenes.[31] We found that the enantioselective aldol



Scheme 3. Synthetic scheme for proline sulfonamides **6**: a) sulfonamides, NaH, DMF, room temperature; b) H_2, 10% Pd/C, MeOH, room temperature.



Scheme 4. Synthetic scheme for siloxyprolines **7**: a) R-Cl, DMAP (cat.), imidazole, DMF, 0 °C to room temperature, or R-OTf, 2,6-lutidine, 0 °C to room temperature; b) H_2, 10% Pd/C, MeOH, room temperature.

reaction was catalyzed by these catalysts in the presence of water, but that the diastereoselectivity was low and the enantioselectivity was less than 90%. The third type of surfactant–proline combined catalysts that we prepared were pyrrolidines bearing an *N*-sulfonylcarboxamide moiety **6**. The corresponding *N*-tosylcarboxamide has been reported to promote the aldol reaction of acetone with *p*-nitrobenzaldehyde in an organic solvent to afford the product with excellent enantioselectivity.[33] The length of the alkyl chain had a significant effect on the yield. The organocatalyst with an octylsulfonyl moiety, **6a**, produced a good yield with excellent diastereo- and enantioselectivities, while that with the dodecylsulfonyl moiety, **6b**, provided a low yield albeit with excellent selectivity.

In further screening of organocatalysts, we also investigated *trans*-siloxy-L-prolines **7**, which we found to be more reactive than proline in α-aminoxylations and three-component Mannich reactions.[35] To our surprise, though siloxyprolines **7** do not possess a long alkyl chain necessary for surfactant character, they efficiently promote the aldol reaction in a highly diastereo- and enantioselective manner. Not only the TBS-substituted proline **7a**, but also the TIPS- and TBDPS-substituted derivatives **7b** and **7c** proved to be effective. On increasing the hydrophobicity of the siloxy group the yield increased, and in the reaction catalyzed by the TBDPS-substituted proline **7c**, a good yield (78%) was obtained with excellent *anti*-selectivity and nearly perfect enantioselectivity.

Not only the *trans*-siloxy-L-prolines **7**, but also the *cis*-siloxy-D-proline **8** was found to be an effective organocatalyst, promoting the aldol reaction in good yield with the same excellent selectivity, while generating the opposite enantiomer of the product to *trans*-siloxy-L-proline **7c**. *cis*-Siloxy-D-proline **8** may be synthesized from *trans*-4-hydroxy-L-proline, the same starting material as for the synthesis of the *trans*-siloxy-L-proline, by routine published procedures.[34] While *trans*-4-hydroxy-L-proline is inexpensive, its enantiomer, *trans*-4-hydroxy-D-proline, is very expensive. Therefore, either enantiomer of the aldol product may be easily synthesized by judicious choice of either *trans*-siloxy-L-proline **7** or *cis*-siloxy-D-proline **8**, both of which are available from the same inexpensive starting material.

This is the first highly diastereoselective and enantioselective aldol reaction carried out in the presence of water without using any organic solvent.

Comparison of the reactions performed neat, in organic solvents, and in the presence of water: Excellent results were obtained in the presence of water using siloxyprolines **7** as catalysts. We have checked the solvent effect on this aldol reaction employing the TBS-substituted proline **7a** as catalyst; the results are summarized in Table 2. We first examined the reaction without any addition of water and found that a low diastereoselectivity and lower enantioselectivity were obtained, though the yield was moderate. This result indicates that water is indispensable for achieving excellent diastereo- and enantioselectivities. Next, we investigated the reaction in organic solvents. Due to its poor solubility in most such solvents, reactions mediated by proline itself are restricted to polar organic solvents such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*-methylpyrrolidone (NMP), while siloxyproline is more soluble than proline in organic solvents.[35] The reaction proceeded in the organic solvents examined, though the yield was dependent on the solvent used. In DMSO, a good yield was obtained but with poor diastereoselectivity and decreased enantioselectivity (80% *ee*). In CH_3CN, toluene, and hexane, the enantioselectivities were around 90% and the diastereoselectivity was low, though a moderate yield was obtained. In MeOH, which is a protic solvent like water, the reaction was slow, affording the aldol product in a low yield and with poor enantioselectivity (45% *ee*). This is in marked contrast to the result obtained in the presence of water, a protic solvent, in which case the aldol product was obtained with excellent diastereo- and enantioselectivities. The results summarized in Table 2 suggest that the reaction in the presence of water is different from that in its absence, and that compared to organic solvents water has a unique beneficial effect.

Table 2. The effect of solvent on the aldol reaction catalyzed by siloxyproline **7a**.[a]

Entry	Solvent	Yield [%][b]	*anti*:*syn*[c]	*ee* [%][d]
1	water	61	19:1	>99
2	none[e]	61	1.8:1	89
3	DMSO	66	1:1	80
4	CH_3CN	44	1.4:1	87
5	toluene	47	1.8:1	91
6	hexane	37	1.8:1	87
7	MeOH	26	2.8:1	45

[a] The reaction was performed by employing benzaldehyde (0.4 mmol), cyclohexanone (2.0 mmol), **7a** (0.04 mmol), and solvent (0.4 mL) at room temperature for 18 h. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase. [e] The reaction was performed without solvent.

Effect of the amount of water: Employing TBDPS-substituted siloxyproline **7c** as catalyst, the influence of the amount of water was investigated; the results are summarized in Table 3. In the presence of only one equivalent of water, the aldol product was obtained in a good yield with good diastereo- and excellent enantioselectivity. The diastereo- and enantioselectivities were further improved in the presence of three equivalents of water, and the same excellent diastereo- and enantioselectivities were attained with even greater amounts of water. From a synthetic point of view, it is desirable to use as little water as possible. Thus, three equivalents of water is the recommended amount. *It should be noted, however, that a large excess of water does not disturb the reaction at all*. The reaction proceeds smoothly even in the presence of 350 equivalents of water to provide the same excellent selectivity. This is in marked contrast to the observations of Barbas and co-workers, who found that an

Table 3. The effect of the amount of water present on the aldol reaction catalyzed by siloxyproline **7c**.[a]

Entry	Amount of water [equiv]	Yield [%][b]	*anti*:*syn*[c]	*ee* [%][d]
1	0	61	1.8:1	89
2	1	87	6:1	97
3	2	84	8:1	97
4	3	85	12:1	98
5	5	79	11:1	99
6	18	78	13:1	>99
7	50	88	12:1	>99
8	100	84	12:1	>99
9	350	77	16:1	>99

[a] The reaction was performed by employing benzaldehyde (0.4 mmol), cyclohexanone (2.0 mmol), **7c** (0.04 mmol), and various amounts of water at room temperature for 18 h. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase.

increase in the amount of water decreases the enantioselectivity of the aldol reaction of acetone and *p*-nitrobenzaldehyde catalyzed by proline.[16]

Effect of the amount of catalyst: Reducing the amount of catalyst was investigated, and the results are summarized in Table 4. In the presence of 5 mol% or 3 mol% of the catalyst **7c**, the reaction proceeded smoothly to afford the aldol product in good yield and with excellent selectivity. *Even in the presence of just 1 mol% of the catalyst, good yields and excellent diastereo- and enantioselectivities were obtained*, though the reaction proceeds slowly and a longer reaction time (49 h) is needed. For the proline-mediated aldol reaction, a sub-stoichiometric amount of proline (20–30 mol%) is usually necessary. As siloxyproline **7** is a reactive catalyst, the loading of the catalyst could be reduced to just 1 mol%. Recently, Gong and co-workers reported that the enantioselective aldol reaction of acetone and aldehydes was catalyzed by 2 mol% of proline amide derivatives.[36] In the present reaction catalyzed by siloxyproline in the presence of water, only 1 mol% of the siloxyproline **7c** is sufficient, and to the best of our knowledge this is the lowest organocatalyst loading for a highly enantioselective aldol reaction.

Table 4. The effect of the amounts of catalyst and ketone on the aldol reaction catalyzed by siloxyproline **7c**.

Entry	Amount of catalyst [mol%]	Amount of ketone [equiv]	Amount of water [equiv]	Time [h]	Yield [%][a]	*anti*:*syn*[b]	*ee* [%][c]
1[d]	10	5	18	18	78	13:1	>99
2[d]	5	5	18	25	85	11:1	99
3[d]	3	5	18	25	82	11:1	99
4[d]	1	5	18	48	76	10:1	99
5[e]	1	2	3	48	73	10:1	99
6[e]	1	1.2	3	60	32	9.3:1	93

[a] The combined isolated yield of the diastereomers. [b] The diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [c] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase. [d] The reaction was performed by employing benzaldehyde (0.4 mmol), cyclohexanone (2.0 mmol), various amounts of **7c**, and water (0.13 mL) at room temperature for the time indicated in the table. [e] The reaction was performed by employing benzaldehyde (2 mmol), cyclohexanone (4.0 or 2.4 mmol), **7c** (0.02 mmol), and water (0.108 mL).

Next, the amount of cyclohexanone was varied. Up to this point we had employed five equivalents of ketone when using 18 equivalents of water, but we found that the reaction proceeds even with only two equivalents of cyclohexanone in the presence of three equivalents of water, affording the aldol with the same excellent diastereo- and enantioselectivities, whereas a further reduction of the amount of ketone to 1.2 equivalents reduced the yield and enantioselectivity.

The effect of water: Of the siloxyprolines **7** employed, the TBDPS-substituted proline derivative **7c** gave the best results. The appearance of the reaction mixture was rather different for reactions using the other siloxyprolines **7a** and **7b**. In the presence of 18 equivalents of water, an emulsion was formed in the case of the TBS derivative **7a**, while the aqueous and organic phases were easily separated in the case of the reactions of the TIPS and TBDPS derivatives **7b** and **7c** (Figure 1). These results indicate that phase separation becomes easier as the hydrophobicity of the catalyst is increased.

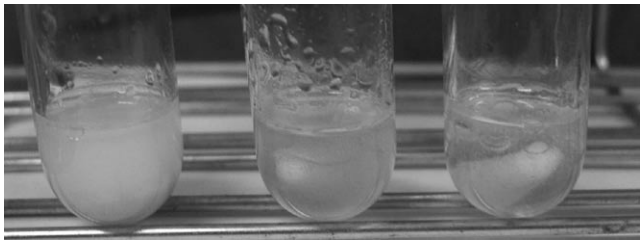


Figure 1. Reaction mixtures of *o*-chlorobenzaldehyde (1.2 mmol), cyclohexanone (6 mmol), and organocatalysts **7a**, **7b**, and **7c** (0.12 mmol) in the presence of 18 equivalents of water (0.389 mL) after stirring for 18 h, then standing for 5 min at room temperature. Left: catalyst **7a**. Middle: catalyst **7b**. Right: catalyst **7c**.

In the presence of a large amount of water, an emulsion was formed even in the case of the reaction of the TBDPS catalyst **7c**, in which case a good yield and excellent enantioselectivity were obtained (Table 3, entry 9). The solubility of cyclohexanone in water is 87 g L^{-1},[39] while that of benzaldehyde is 3 g L^{-1}.[40] Thus, cyclohexanone completely dissolves in the presence of 350 equivalents of water, whereas benzaldehyde does not. Regarding entry 9 of Table 3, it is surprising that the reaction proceeds smoothly even in the presence of 350 equivalents of water, because cyclohexanone should be completely dissolved in the water at this concentration. Moreover, we found that the reaction proceeds with the same efficiency when the reaction mixture is allowed to stand without stirring except for during the initial 5 min. To explain these unusual phenomena, the reaction in the presence of 350 equivalents of water was investigated in

detail (Figure 2). Siloxyproline **7c** (300 mg), which does not dissolve in water, was added to a clear solution of cyclohexanone (400 μL, 5 equiv) in water (4.86 mL, 100 equiv; Figure 2 left) forming a suspension. Benzaldehyde (78 μL)

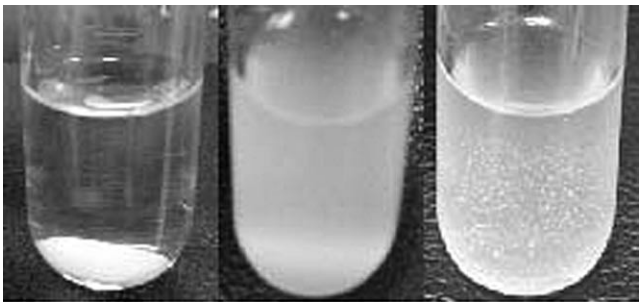
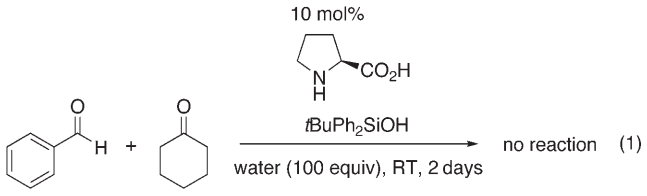


Figure 2. Reaction mixtures of a) cyclohexanone (5 equiv) in water (350 equiv) (left); b) mixture (a) + siloxyproline **7c** (10 mol%) + benzaldehyde (1 equiv), stirring for 5 min (middle); c) after stirring reaction mixture (b) for 5 min and then standing for 10 min (right); see text for details.

was then added to this suspension. As benzaldehyde partially dissolves in water, an emulsion was formed and the siloxyproline dissolved in the organic phase (Figure 2 center). After the reaction mixture had been left to stand for 10 min, the aqueous and oily phases were separated and the small oily particles were left attached to the reaction vessel (Figure 3 right). The oily particles were analyzed by ^{1}H NMR spectroscopy, which showed that they contained benzaldehyde and cyclohexanone in a ratio of 1:2.2. This indicates that benzaldehyde extracts some portion of the cyclohexanone from the aqueous phase. Even though cyclohexanone is hydrophilic, benzaldehyde, highly hydrophobic siloxyproline **7**, and cyclohexanone, which is extracted from the aqueous phase, form an organic phase, in which the enantioselective aldol reaction proceeds. The reaction does not proceed at the interface of the aqueous and organic phases, in spite of the formation of an emulsion in some cases. Thus, in this particular case, stirring is not necessary even in the presence of a large amount of water.

Next we examined whether it is necessary for the siloxy group and proline moiety to be combined in the same molecule for the reaction to proceed efficiently. We attempted to perform the aldol reaction of benzaldehyde and cyclohexanone in the presence of 100 equivalents of water using proline (10 mol%) and *tert*-butyldiphenylsilanol (10 mol%) [Eq. (1)]. Two phases were formed and no reaction proceeded within two days. Thus, it is essential that the siloxy and proline moieties be combined in the same molecule. It is known that proline can promote the aldol reaction in an aqueous polar organic solvent, in which case increasing the water content decreases the enantioselectivity.[16] Introduction of the hydrophobic siloxy moiety into the catalyst creates a hydrophobic organic phase even in the presence of a large amount of water, which is most probably the key to the excellent reactivity and stereoselectivity.



The rates of the reactions in the absence of water or in the presence of three and 100 equivalents of water were investigated (Table 5 and Figure 3). All reactions were found to proceed at a similar rate. Thus, water neither accelerates nor retards the reaction. When the reaction was performed without a solvent, low diastereoselectivity and good enantio-

Table 5. Effect of water on the diastereo- and enantioselectivities of the aldol reaction catalyzed by siloxyproline **7c**.[a]

Entry	Time [h]	Yield [%][b]	*anti*:*syn*[c]	*ee* [%][d]
		neat		
1	3	28	1.3:1	81
2	6	41	1.4:1	81
3	12	60	1.6:1	82
4	24	68	1.6:1	82
5	48	72	1.6:1	81
		3 equiv of water		
1	3	42	7.5:1	98
2	6	58	9.3:1	98
3	12	67	12:1	97
4	24	70	15:1	96
5	48	72	10:1	97
		100 equiv of water		
1	3	40	13:1	97
2	6	55	14:1	97
3	12	63	12:1	96
4	24	66	11:1	98
5	48	67	8:1	97

[a] The reaction was performed by employing benzaldehyde (2.4 mmol), cyclohexanone (4.8 mmol), and **7c** (0.24 mmol), under neat reaction conditions or in the presence of water (0.13 mL or 4.32 mL). [b] The combined isolated yield of diastereomers. [c] Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase.

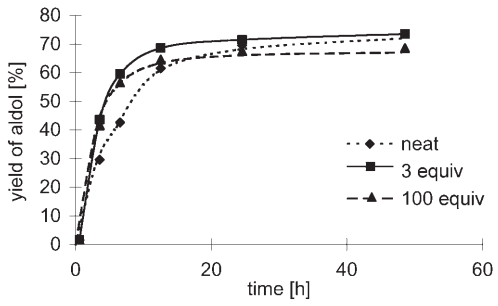


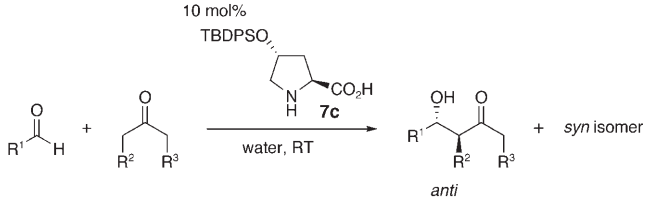
Figure 3. Effect of water on the rate of the aldol reaction catalyzed by siloxyproline **7c**.

selectivity were obtained from the beginning of the reaction, and these selectivities did not change during its course. In the presence of three equivalents of water, excellent enantioselectivity was observed from the beginning of the reaction. Though excellent diastereoselectivity was maintained throughout, the diastereoselectivity initially increased and then decreased from 24 h to 48 h. Thus, the retro-aldol reaction proceeds to some extent, as we have reported for the retro-aldol reaction of acetone and nitrobenzaldehyde catalyzed by proline.[41] The present results indicate that there is a degree of equilibrium between the starting materials and the aldol product via the retro-aldol reaction, and that the selectivity is mostly determined kinetically and not thermodynamically.

In the presence of water, the stereoselectivity was excellent compared to that obtained under neat reaction conditions (Table 2). The reaction proceeds in the organic phase in the presence of water, and these conditions are different from reaction conditions such as a "concentrated organic phase".[28,29] Benzaldehyde, cyclohexanone, and the hydrophobic siloxyproline catalyst **7** form a hydrophobic organic phase in which the enamine is generated, which then reacts with the aldehyde even in the presence of a large amount of water without any organic solvent. It is not clear at this stage how one or more water molecules can act to improve the stereoselectivity. We speculate that a small amount of water dissolved in the organic phase affects the transition state and that this improves the diastereo- and enantioselectivities. This effect is small in energy and appears to be effective in the reactions of cyclic ketones, such as cyclohexanone and cyclopentanone, but not in the reactions of acyclic ketones such as acetone or hydroxyacetone (vide infra).

Generality: The generality of the reaction was examined in detail using 1 mol% of siloxyproline **7c** and two equivalents of ketone in the presence of three equivalents of water, as well as under the conditions used in the previous paper, that is, 10 mol% of the catalyst and five equivalents of ketone in the presence of 18 equivalents of water (Table 6).[22] The reaction has broad applicability with respect to the aldehyde. Both excellent enantioselectivity (over 95% *ee*) and good *anti*-selectivity were obtained when cyclohexanone and cyclopentanone were employed. Not only reactive, electron-deficient aldehydes, but also aldehydes without an electron-

Table 6. Catalytic asymmetric aldol reactions in the presence of water catalyzed by siloxyproline **7c**.[a]



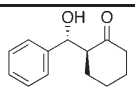
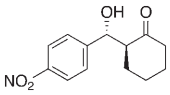
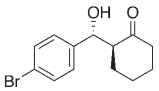
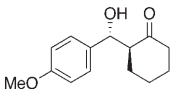
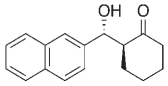
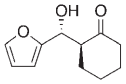
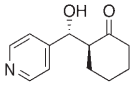
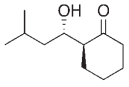
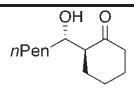
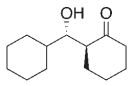
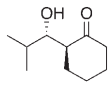
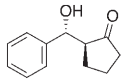
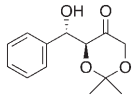
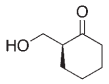
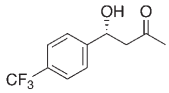
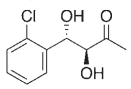
Entry	Product	Amount of catalyst [mol%]	Amount of ketone [equiv]	Amount of water [equiv]	Time [h]	Yield [%][b]	*anti*:*syn*[c]	Optical purity [% *ee*][d]
1		10	5	18	18	78	13:1	>99
2		1	2	3	48	73	10:1	99
3		10	5	18	5	86	20:1	>99
4		1	2	3	42	89	15:1	97
5		10	5	18	28	80	20:1	97
6		1	2	3	42	90	17:1	99
7		10	5	18	50	21	4.7:1	96
8		1	2	3	136	24	4.0:1	94
9		10	5	18	40	89	19:1	97
10		1	2	3	42	96	12:1	98
11[e]		10	5	18	28	79	4.7:1	97
12		10	2	3	36	73	4.9:1	95
13		1	2	3	62	35	4.2:1	82
14		10	5	18	2.5	92	12:1	95
15		1	2	3	7	85	8.0:1	98
16		10	5	18	20	54	>20:1	>99
17		1	2	3	132	81	>20:1	98

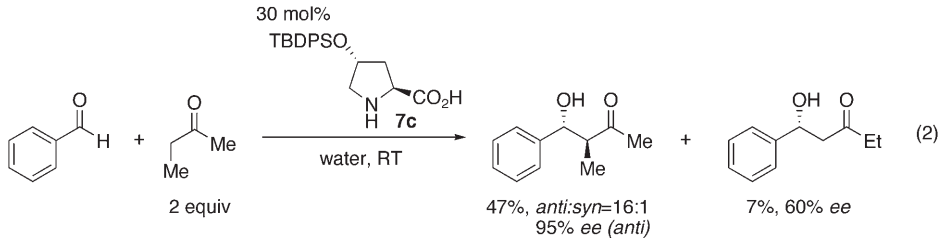
Table 6. (Continued)

Entry	Product	Amount of catalyst [mol%]	Amount of ketone [equiv]	Amount of water [equiv]	Time [h]	Yield [%][b]	*anti:syn*[c]	Optical purity [% *ee*][d]
18		10	2	3	84	21	>20:1	96
19		10	5	18	24	76	>20:1	>99
20		10	2	3	45	63	>20:1	99
21		1	2	3	152	40	>20:1	99
22		10	2	3	84	29	>20:1	99
23[e]		10	5	18	18	74	9.0:1	>99
24		1	2	3	42	76	10:1	96
25		10	5	18	18	48	>20:1	95
26		10	2	3	27	77	14:1	95
27		1	2	3	192	<10	>20:1	84
28[f]		10	5	18	90	37	–	96
29[g]		10	2	3	200	42	–	85
30[g]		1	2	3	200	15	–	95
31[h]		10	2	3	96	51	–	57
32		1	2	3	120	79	–	68
33		1	2	0	120	15	–	65
34		10	5	18	72	61	1:1	64, 61[i]
35		10	2	3	150	65	1:1.1	57
36		1	2	3	150	<5	–	–

[a] The reaction was performed by employing an aldehyde (0.4 mmol), ketone (2 mmol), **7c** (0.04 mmol), and water (0.13 mL) at room temperature, or the reaction was performed by employing an aldehyde (2 mmol), ketone (4 mmol), **7c** (0.02 mmol), and water (0.108 mL) at room temperature. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer, which was determined by HPLC analysis on a chiral phase. [e] Catalyst **7a** was used instead of **7c**. [f] Aqueous formalin (35%, 0.035 mL, 0.4 mmol) and NaCl (47 mg) were employed. [g] Aqueous formalin (35%, 0.17 mL, 2.0 mmol) and NaCl (235 mg) were employed. [h] Acetone (10.8 mmol) was employed. [i] Optical yield of the *syn* isomer.

withdrawing group proved to be excellent electrophilic partners in this reaction. In the case of electron-rich aldehydes, an excellent *ee* was obtained in spite of the low yield (Table 6, entries 7 and 8). Though both aromatic and aliphatic aldehydes could be employed, the yield was moderate or low with some of the aliphatic aldehydes, in which cases excellent enantioselectivities were realized (Table 6, entries 18 and 22). As regards heteroaromatic aldehydes, *p*-pyridinecarbaldehyde gave excellent results (Table 6, entries 14 and 15), but the reaction was slow in the case of furfural. In this case, however, good results were obtained by the use of 10 mol% of the catalyst (Table 6, entries 11–13). 2,2-Dimethyl-1,3-dioxan-5-one[37] can be successfully employed as the nucleophilic ketone, affording a polyoxy compound with excellent selectivity. Here, the recommended amount of catalyst is 10 mol% because the reaction is slow with just 1 mol% (Table 6, entries 25–27). A water-soluble aldehyde such as formaldehyde may be successfully employed, though the use of NaCl as an additive in order to aid extraction of formaldehyde into the organic phase and of five equivalents of ketone are recommended (Table 6, entries 28–30).[10i,j,g,19a,38] However, this method has its limitations. Though the aldol reactions of acetone and hydroxyacetone proceeded in the presence of water, the enantioselectivities were only moderate (Table 6, entries 31–36). Cycloheptanone and cyclooctanone gave low yields in their reactions with benzaldehyde under optimized conditions.

In the reaction of unsymmetrical ketones such as 2-butanone, the reaction occurs preferentially at the methylene carbon with good regiochemistry, affording the branched aldol product with excellent enantioselectivity [Eq. (2)]. This regioselectivity[27b,d,42] is opposite to that of the reaction performed in DMSO and catalyzed by proline.[16]



Large-scale preparation: Large-scale preparation of the aldol was investigated. As the present direct aldol reaction is atom-economical and does not generate by-products, and only three equivalents of water are used without any organic solvent, it should be possible to directly isolate the aldol product. We investigated direct distillation of the reaction mixture in cases when the aldol was liquid. If this were to be successful, a series of tedious, routine procedures, such as the addition of a quenching solution (e.g. buffer), extraction using an organic solvent, drying of this organic phase with a dehydrating reagent, then filtration and evaporation of the organic solvent, would be eliminated. Direct distillation of the reaction mixture, however, produced the aldol in 55% yield with low *anti*-selectivity and low enantioselectivity (89% *ee*). The yield and diastereo- and enantioselectivities were lower than those of the original reaction, in which the purification was performed by thin-layer chromatography. These unsatisfactory results are ascribed to side reactions such as the retro-aldol reaction, dehydration, and isomerization, which take place when the reaction mixture is subjected to high temperatures during distillation in the presence of the catalyst. We envisaged that these side reactions might be suppressed if the distillation were to be carried out in the absence of the catalyst. After some experimentation, the following experimental procedure was established (Figure 4). A reaction mixture of benzaldehyde (7.4 g, 1 equiv), cyclohexanone (13.7 g, 2 equiv), catalyst **7c** (259 mg, 1 mol%), and water (3.8 mL, 3.0 equiv) was stirred at room temperature for 2 days. Silica gel (2.5 g) was then added to the reaction mixture, subsequent filtration of which using ethyl acetate (60 mL) gave an ethyl acetate solution. Distillation of the filtrate produced the aldol product (10 g, 70%) with excellent diastereo- and enantioselectivities. Tedious procedures such as extraction and drying of the organic phase could thus be eliminated, and the total amount of organic solvent employed to synthesize 10 g of the aldol product was just 60 mL of ethyl acetate.

In the aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone, the product is solid and the following practical large-scale procedure was developed. After stirring the reaction mixture of *p*-nitrobenzaldehyde (10 g, 1 equiv), cyclohexanone (13.7 mL, 2 equiv), catalyst **7c** (245 mg, 1 mol%), and water (3.6 mL, 3 equiv) at room temperature for 42 h, a solid separated. This solid was collected by filtration using a small amount of hexane (5 mL), during which process excess cyclohexanone and the catalyst were removed because the catalyst dissolves in the excess cyclohexanone. The solid was obtained in 80% yield, and consisted of the pure aldol product as judged by ^{1}H NMR spectroscopy (400 MHz) with excellent diastereoselectivity (*anti*:*syn* $>$20:1) and enantioselectivity (97% *ee*). A single recrystallization from *i*PrOH (21.5 mL) gave the nearly diastereomerically and enantiomerically pure aldol in 72% yield (*anti*:*syn* $>$20:1, 99% *ee*). Only 26.5 mL of organic solvent was needed to obtain 16.5 g of aldol.

No organic solvent is used in the reaction and only a small amount is needed in the purification step. The required catalyst loading is 1 mol% and three equivalents of safe and inexpensive water is employed as an additive. Thus, these procedures constitute one of the most practical and environmentally benign, green methods for the synthesis of chiral aldol products. Reduction of the amount of ketone and catalyst loading would be a challenging problem. An ideal and even more environmentally benign process would be one that does not require any organic solvent, not only in the reaction but also in the purification steps. Recently, we have accomplished such an organic solvent-free process in the proline-catalyzed aldol reaction.[25]

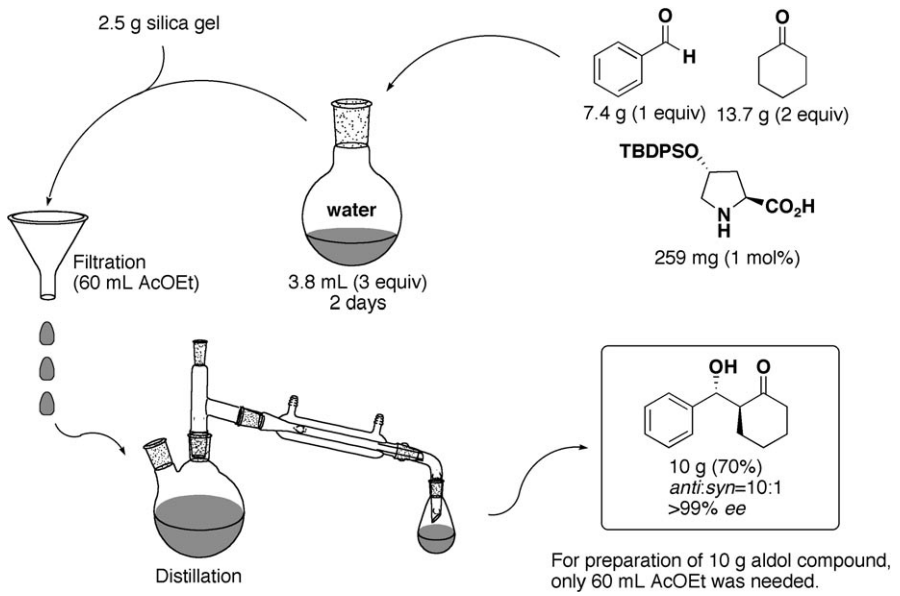


Figure 4. Large-scale performance of the aldol reaction of benzaldehyde and cyclohexanone catalyzed by 1 mol% of **7c**.

Conclusion

We have developed highly hydrophobic *trans*-siloxy-L-proline and *cis*-siloxy-D-proline catalysts, both of which promote the direct asymmetric aldol reaction of aldehydes and ketones with excellent diastereo- and enantioselectivities. The reaction proceeds in the organic phase, but water is essential for the high selectivities. As the reaction proceeds in the presence of three equivalents of water without any organic solvent, the large-scale preparation, including the purification steps, of chiral aldols with a minimal amount of organic waste becomes possible.

Even in the presence of a large amount of water, an organic phase is formed, and the enamine is generated and reacts with the aldehyde in this phase, affording the aldol product. As enamines are widely used in many kinds of organic reactions,[43] other enamine-based reactions might also be performed in the presence of a large amount of water.

Experimental Section

Typical procedure for the synthesis of (2*S*,1′*R*)-2-(hydroxyphenylmethyl)-cyclohexan-1-one (Table 1, entry 17)**:** Catalyst **7c** (14.8 mg, 0.04 mmol) was added to a mixture of benzaldehyde (0.041 mL, 0.4 mmol) and cyclohexanone (0.207 mL, 2.0 mmol) in water (0.13 mL) at room temperature. The reaction mixture was stirred for 18 h at this temperature, then the reaction was quenched by the addition of phosphate buffer (pH 7.0). The organic materials were extracted with three portions of ethyl acetate, and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ethyl acetate/hexane, 1:10→1:3) gave 2-(hydroxyphenylmethyl)cyclohexan-1-one (63.7 mg, 78%) as a clear oil: *anti*:*syn* = 13:1 (by ^{1}H NMR spectroscopy of the crude mixture), >99% *ee* (by HPLC on a Chiralcel OD-H column, $\lambda = 213$ nm, *i*PrOH/hexane, 1:100, 1.0 mL min^{-1}; $t_r = 19.4$ min (major), 25.9 min (minor)).

(2*S*,1′*R*)-2-(Hydroxyphenylmethyl)cyclohexan-1-one[30g]: This is a known compound. The absolute stereochemistry was determined by comparison with the literature data.[30g]

$[\alpha]_D^{24} = +27.7$ ($c = 0.85$, $CHCl_3$), >99% *ee*. Lit.: $[\alpha]_D^{24} = -24.2$ ($c = 1.03$, $CHCl_3$) (93% *ee*, (2*R*,1′*S*)-2-(hydroxyphenylmethyl)cyclohexanone).

Enantiomeric excess was determined by HPLC on a Chiralcel OD-H column, $\lambda = 213$ nm, *i*PrOH/hexane, 1:100, 1.0 mL min^{-1}; $t_r = 19.4$ min (major), $t_r = 25.9$ min (minor).

Large-scale preparation of (2*S*,1′*R*)-2-(hydroxyphenylmethyl)cyclohexan-1-one (used when the product is liquid): Catalyst **7c** (259 mg, 0.74 mmol) was added to a mixture of benzaldehyde (7.4 g, 74.4 mmol) and cyclohexanone (13.7 g, 149 mmol) in water (3.8 mL) at room temperature. The reaction mixture was stirred for 48 h, then silica gel (2.5 g) was added. The mixture was filtered through silica gel using ethyl acetate (60 mL), and the crude organic materials were purified by distillation to afford 2-(hydroxyphenylmethyl)cyclohexan-1-one (10.0 g, 70%) as a colorless oil: *anti*:*syn* = 10:1 (by ^{1}H NMR spectroscopy), >99% *ee* (by HPLC on a Chiralcel OD-H column, $\lambda = 213$ nm, *i*PrOH/hexane, 1:100, 1.0 mL min^{-1}; $t_r =$ 19.4 min (major), 25.9 min (minor)).

Large-scale preparation of (2*S*,1′*R*)-2-(hydroxy-*p*-nitrophenyl)methylcyclohexan-1-one (used when the product is solid): Cyclohexanone (13.7 mL, 132 mmol) was added to a mixture of *p*-nitrobenzaldehyde (10 g, 66.2 mmol), **7c** (244 mg, 0.66 mmol), and water (3.6 mL) at room temperature. After the reaction mixture had been stirred for 42 h at ambient temperature, a solid appeared and the mixture was filtered with hexane (5.0 mL). The filtrate was concentrated to dryness, and the residue was dried in vacuo and purified by recrystallization from isopropanol (21.5 mL), which gave (2*S*,1′*R*)-2-(hydroxy-*p*-nitrophenylmethyl)cyclohexan-1-one (11.9 g, 72%) as a colorless solid: *anti*:*syn* >20:1 (by ^{1}H NMR spectroscopy), 99% *ee* (by HPLC on a Chiralpak AS-H column, $\lambda = 254$ nm, *i*PrOH/hexane, 1:10, 1.0 mL min^{-1}; $t_r = 11.2$ min (major), 18.2 min (minor)).

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