Green Asymmetric Synthesis: β-Amino Alcohol-Catalyzed Direct Asymmetric Aldol Reactions in Aqueous Micelles

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ABSTRACT The ability of chiral β-amino alcohols to catalyze the direct asymmetric aldol reaction was evaluated for the first time in aqueous micellar media. A family of cheap and easily accessible β-amino alcohols, obtained in one step from naturally occurring amino acids, was shown to successfully catalyze the asymmetric aldol reaction between a series of ketones and aromatic aldehydes. These aldol reactions furnished the corresponding β-hydroxy ketones with up to 93% isolated yield and 89% ee. *(S)*-2-phenylglycinol and Triton X-100 proved to be the best organocatalyst and surfactant, respectively. *Chirality 25:119–125, 2013.*

KEY WORDS: organocatalysis; asymmetric synthesis; aldol reactions; β-amino alcohols; surfactants

INTRODUCTION

Over the last decade, the direct asymmetric aldol reaction has undergone a renaissance following the rebirth of organocatalysis.[1–6] In nature, Class I aldolase enzymes efficiently catalyze enantioselective aldol reactions in water via the formation of enamine intermediates.[7] These enzyme-catalyzed reactions occur in a hydrophobic active site, where contacts between bulk water and the reaction transition states can be substantially diminished.[8] From a green chemistry standpoint, the development of organocatalysts that can mimic the aldolase enamine mechanism, affording aldol products with high enantioselectivities in an aqueous environment, is of great importance.

In 2000, List and coworkers reported that *(S)*-proline efficiently catalyzes the intermolecular asymmetric aldol reaction under mild conditions, through the formation of enamine intermediates.[9] Since then, there have been a great number of reports on asymmetric aldol reactions catalyzed by proline and proline derivatives, affording enantiopure products in high yields.[10–21] The first reports used organic solvents, while, in most cases, the addition of water resulted in a significant decrease in both reactivity and enantioselectivity. More recently, however, a series of chiral proline-derived organocatalysts were developed for the aldol reaction in aqueous media. Some of these catalysts gave good yields and excellent enantioselectivities.[22–30] Only a small number of nonproline-derived chiral organocatalysts for aqueous aldol reactions have been reported to date.[31–36]

Although chiral primary β-amino alcohols are easily accessible from inexpensive α-amino acids,[37,38] there are only a handful of reports regarding their application in organocatalytic asymmetric aldol reactions thus far.[30,39–44] In most of these studies, the aldol reactions were performed in organic solvents.[39–43] In only two cases were chiral primary β-amino alcohols utilized to catalyze direct aldol reactions in aqueous media, affording poor-to-moderate results in terms of both reactivity and stereoselectivity.[30,44] Moreover, to the best of our knowledge, there are no reports on the catalytic efficiency of chiral primary β-amino alcohols in aldol reactions performed in micellar media. In this context, motivated by environmental and sustainable development concerns and also seeking to capitalize on the easily accessible chiral pool of amino acids, we decided to perform a detailed study on the catalytic efficiency of chiral primary β-amino alcohols in the aldol reaction of simple ketones with aromatic aldehydes in aqueous micelles (Scheme 1).

EXPERIMENTAL

General Remarks

Reagents and solvents were purchased from commercial suppliers and purified by standard techniques. For thin-layer chromatography (TLC), compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphor molybdic acid in ethanol followed by heating. Flash column chromatography was carried out on SiO_2 (silica gel 60, 70–230 mesh ASTM). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 500-MHz (125-MHz for ^{13}C) or a 250-MHz (62.5-MHz for ^{13}C) spectrometer at ambient temperature. Chiral high performance liquid chromatography (HPLC) analyses were carried out using Chiralpak AD-H, Lux Cellulose-2, Lux Cellulose-4, or Lux Amylose-2 columns. Optical rotation measurements were performed on a polarimeter and calculated from the equation $[\alpha]_D = (\alpha \text{ measured } 100)/c \times l$; where l is the path length of cell and c the concentration of the solution, which is given in g/100 ml. All reaction products were isolated as chromatographically pure materials. Amino acids were purchased from commercial suppliers and used without any further purification. Cyclopentanone, cyclohexanone, cycloheptanone, acetone, butan-2-one pentan-3-one, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, and 4-cyanobenzaldehyde are all commercially available and were used as received. β-Amino alcohol catalysts **4–9** were prepared according to the literature.[38]

Additional Supporting Information may be found in the online version of this article.

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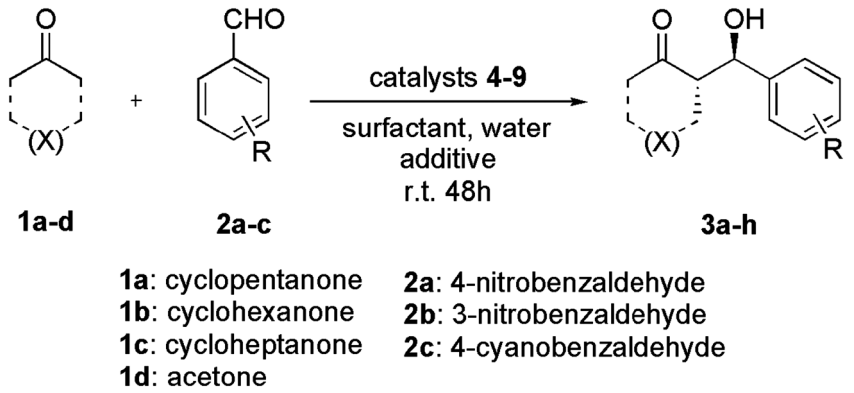


Scheme 1. Direct asymmetric aldol reaction between ketones and aromatic aldehydes catalyzed by β-amino alcohols in aqueous micellar media.

General Procedure for the Preparation of β-Amino Alcohol Catalysts 4–9[38]

In a three-necked, round-bottomed flask containing $NaBH_4$ (2.28 g, 60 mmol) and 30 ml distilled THF, 15 mmol of the appropriate α-amino acid were added and mechanically stirred under argon. The flask was immersed in an ice-water bath, cooled down to 0 °C and a solution of concentrated sulfuric acid (1.5 ml, 28.6 mmol) diluted in 5.0 ml diethyl ether was added in such a way that the reaction mixture temperature was maintained below 20 °C. The reaction mixture was then vigorously stirred at room temperature under an argon atmosphere for approximately 20 h. After the completion of the reaction, 10 ml of an aqueous hydrochloric acid solution (3 mole l^{-1}) was added and the reaction mixture was mechanically stirred vigorously for 2 h at room temperature. Subsequently, 15 ml of an aqueous sodium hydroxide solution (5.0 mole l^{-1}) were added and the reaction mixture was vigorously stirred for 3 h at room temperature. Note that the whole experimental procedure was performed inside a fume hood in order to safely vent dangerous emissions (H_2). The organic solvents of the mixture were evaporated under vacuum and the remaining aqueous solution was extracted with $CHCl_3$ (3×50 ml). After drying, the organic extracts over magnesium sulfate and evaporating the organic solvents, with the aid of a rotary evaporator, β-amino alcohols **4–9** were obtained in pure form after column chromatography ($CHCl_3$/MeOH: 5/1). The purity of all catalysts was verified by ^{1}H- and ^{13}C-NMR spectroscopy as well as by comparison of their optical rotation values with those published in the literature.[37,45–50]

General Procedure for the Preparation of the Chiral Aldol Products 3a–h[30]

To a mixture of a β-amino alcohol (1.0 mmol) in 10 ml of an aqueous micellar solution (2.0×10^{-2} mol l^{-1}), TFA (78.0 µl, 1.0 mmol) was added at room temperature. This reaction mixture was vigorously stirred for 10 min. The desired ketone (20.0 mmol) and aromatic aldehyde (5.0 mmol) were then added and the reaction mixture was stirred for 48 h. The product was extracted from the aqueous phase with diethyl ether (3×30 ml), dried over magnesium sulfate, and the organic solvents were evaporated under vacuum. Flash column chromatography purification (diethyl ether/petrol ether) gave the corresponding aldol products as colorless solids or viscous oils. The spectroscopic data of all aldol products were in agreement with those reported in the literature.[10,33,51] The *syn*/*anti* diastereoselectivity was determined by ^{1}H-NMR analysis of the crude aldol product or by HPLC analysis after column chromatography purification. The enantiomeric excess (ee) and the absolute configuration of the aldol products were determined by chiral HPLC analysis and comparison of the measured retention times with published data. The racemic products were obtained using the ammonium fluoride method described below.

General Procedure for the Preparation of the Racemic Aldol Products 3a–h[52]

A catalytic amount of NH_4F (44.4 mg, 1.2 mmol, 30 mol %) was added to a round-bottomed flask containing the desired aromatic aldehyde (4.0 mmol) and ketone (20.0 mmol) in 50 ml of distilled water. After vigorous stirring of the reaction mixture for 24 h at 60 °C, the racemic product was extracted with diethyl ether, dried over magnesium sulphate, and the organic solvents evaporated under vacuum. The crude racemic aldol products were purified by flash column chromatography (diethyl ether/petrol ether).

HPLC Data of Chiral and Racemic Aldol Products 3a–h

***Anti*-(*2S, 1'R*)-2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclopentanone (3a).**[10,33,52] HPLC (Lux Cellulose-4, n-hexane/isopropanol, 60:40, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 6.82 min (2.09), t_{R1}(*syn*) = 8.57 min (3.58), ee (*syn*-product) = 26%; t_{R2}(*anti*) = 11.54 min (166.30), t_{R2}(*anti*) = 14.89 min (59.73), ee (*anti*-product) = 47%; de = 94%.

***Anti*-(*2S, 1'R*)-2-[Hydroxy-(3-nitrophenyl)-methyl]-cyclopentanone (3b).**[33,52] HPLC (Lux Cellulose-2, n-hexane/isopropanol, 60:40, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 5.92 min (area 133.84), t_{R1}(*syn*) = 7.25 min (area 94.07) min, ee (*syn*-product) = 18%; t_{R2}(*anti*) = 8.91 min (area 128.42), t_{R2}(*anti*) = 11.47 min (area 45.88), ee (*anti*-product) = 48%; de = 14%.

***Anti*-(*2S, 1'R*)-2-[Hydroxy-(4-cyanophenyl)-methyl]-cyclopentanone (3c).**[52] HPLC (Lux Cellulose-4, n-hexane/isopropanol, 60:40, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 5.67 min (area 77.16), t_{R1}(*syn*) = 6.85 min (area 65.50), ee (*syn*-product) = 8%; t_{R2}(*anti*) = 9.60 min (area 241.33), t_{R2}(*anti*) = 14.06 min (area 92.33), ee (*anti*-product) = 44%; de = 40%.

***Anti*-(*2R, 1'S*)-2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone (3d).**[10,52] HPLC (Daicel CHIRALPAK AD-H, n-hexane/isopropanol = 90:10, flow rate: 1.0 ml/min, $\lambda = 254$ nm), t_{R1}(*syn*) = 18.62 min (area 345.60), t_{R1}(*syn*) = 21.80 min (area 121.92), ee (*syn*-product) = 48%; t_{R2}(*anti*) = 23.79 min (area 1198.48), t_{R2}(*anti*) = 31.81 min (area 116.24), ee (*anti*-product) = 82%; de = 48%.

***Anti*-(*2R, 1'S*)-2-[Hydroxy-(3-nitrophenyl)-methyl]-cyclohexanone (3e).**[10,33,52] HPLC (Lux Amylose-2, n-hexane/isopropanol, 70:30, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 8.68 min (area 10.47), t_{R1}(*syn*) = 9.95 (area 33.19) min, ee (*syn*-product) = 52%; t_{R2}(*anti*) = 12.79 min (area 10.60), t_{R2}(*anti*) = 15.52 min (area 180.4), ee (*anti*-product) = 89%; de = 62%.

***Anti*-(*2S, 1'R*)-2-[1-Hydroxy-1(4-cyanophenyl)-methyl]-cyclohexanone (3f).**[52] HPLC (Lux Cellulose-4, n-hexane/isopropanol, 60:40, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 7.39 min (area 26.45), t_{R1}(*syn*) = 9.00 (area 58.02) min, ee (*syn*-product) = 37%, t_{R2}(*anti*) = 10.35 min (area 224.17), t_{R2}(*anti*) = 16.22 min (area 22.26), ee (*anti*-product) = 82%; de = 50%.

***Anti*-(*2S, 1'R*)-2-[Hydroxy-(4-nitrophenyl)-methyl]-cycloheptanone (3g).**[33,52] HPLC (Lux Cellulose-4, n-hexane/isopropanol, 90:10, flow rate: 1.0 ml/min, $\lambda = 254$ nm): t_{R1}(*syn*) = 22.82 min (area 26.75), t_{R1}(*syn*) = 24.75 min (area 14.73), ee (*syn*-product) = 29%; t_{R2}(*anti*) = 27.18 min (area 94.94), t_{R2}(*anti*) = 32.93 min (area 71.45), ee (*anti*-product) = 14%; de = 60%.

(*4R*)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (3h).[10,33] HPLC (Lux Amylose-2, n-hexane/ isopropanol, 70:30, flow rate: 1.0 ml/min, λ = 254 nm): t_{R1} = 7.91 min *(S)*-isomer (area 74.04); t_{R1} = 8.56 min *(R)*-isomer (area 126.8), ee = 26%.

RESULTS AND DISCUSSION

To identify the most efficient micellar medium, we initially performed the direct aldol reaction between cyclohexanone (**1b**, Scheme 1) and 4-nitrobenzaldehyde (**2a**, Scheme 1), catalyzed by *(S)*-phenylglycinol (**4a**, Figure 1), employing a series of anionic, cationic, and non-ionic surfactants. The results from these optimization experiments are summarized in Table I. For comparison purposes, the same aldol reaction was also performed in DMSO and THF, in bulk water, as well as in neat conditions. When the reaction was carried out in organic solvents, it resulted in very low yields or no aldol product at all (entries 1–2, Table 1). Low yields were also observed when bulk water or neat conditions were employed; in this case, however, the isolated yields were satisfactory upon employing a large excess of cyclohexanone (entries 3–4, Table 1). The use of cationic surfactants cetyltrimethylammonium bromide (CTAB) and cetyltrimethylammonium chloride (CTAC) led to negligible yields too. On the other hand, the anionic surfactant sodium dodecyl sulphate (SDS) gave fairly good yields, though the enantioselectivity was not satisfactory. Additionally, the workup of the reaction proved to be a difficult task, mainly due to the surfactant's strong emulsifying properties. Utilization of nonionic surfactant Triton X-100 delivered the best results in terms of both isolated yield and stereoselectivity, in combination with a straightforward workup of the reaction mixture. During the course of our experiments, we also observed that the addition of a strong organic acid, such as trifluoroacetic acid (TFA), resulted in a significant acceleration of the reaction. Slightly inferior selectivities were obtained when TFA was replaced by other organic, inorganic, or Lewis acids such as boric acid, zinc chloride, or acetic acid (entry 8, Table 1; entry 7, Table 3). It is also important to note that while the organocatalytic aldol reactions between unmodified ketones and aldehydes are usually performed using a large excess of the ketone,[19,53] in the present work the utilization of only four molar equivalents of cyclohexanone, as well as the ketones that follow, was shown to be adequate.

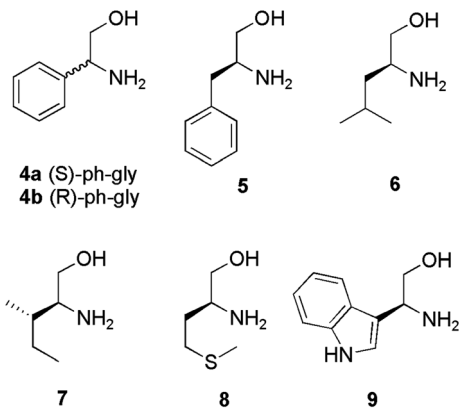


Fig. 1. Primary β-amino alcohol organocatalysts (synthesized in one step from α-amino acids) employed in this study.

With the optimum reaction medium and additive in hand, that is, Triton X-100 aqueous micellar solutions in the presence of TFA, we then evaluated the catalytic efficiency of a variety of chiral primary β-amino alcohols (**4–9**, Figure 1) in the aldol reaction between cyclohexanone (**1b**) and 4-nitrobenzaldehyde (**2a**). Note that all β-aminoalcohols utilized were prepared in one straightforward step from commercially available, inexpensive chiral α-amino acids.[37,38]

The results from these studies are summarized in Table 2. The best yield for the desired product **3d** (93%) was obtained when *(S)*-phenylalaninol (**5**) was used as catalyst (entry 3, Table 2); however, the corresponding diasteroeselectivity was very low. In terms of stereoselectivity, the best results (82% ee, 48% de) were obtained when *(S)*-phenylglycinol (**4a**) was utilized (entry 1, Table 2). *(S, S)*-isoleucinol (**7**) and *(S)*-methioninol (**8**) afforded similar diastereoselectivity, in relation to *(S)*-phenylglycinol, but their enantioselectivity (ee < 65%) was lower (entries 5 and 6, respectively, Table 2). In all cases the *anti* aldol product (**3d**) was produced in

TABLE 1. The direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde catalyzed by *(S)*-phenylglycinol (4a) in various solvents and aqueous micellar solutions[a]

Entry	Solvent/ Surfactant	Catalyst	Yield[b] [%]	*syn*:*anti*[c] [%]	ee (*syn*)/ ee (*anti*)[c] [%]
1	DMSO	**4a**	–	–	No reaction
2	THF	**4a**	22	50:50	64/29
3	No solvent[d]	**4a**	89	49:51	81/78
4	Water[d]	**4a**	97	49:51	52/65
5	CTAC	**4a**	Traces	Not determined	Not determined
6	SDS	**4a**	46	65:35	50/38
7	Triton X-100	**4a**	43	26:74	48/82
8	Triton X-100[e]	**4a**	48	31:69	39/81

[a]Reaction conditions: *(S)*-phenylglycinol (1.0 mmol), additive (1.0 mmol), **1b** (20.0 mmol), and **2a** (5.0 mmol) in 10-mL aqueous micellar media (2.0×10^{-2} mol L^{-1}).
[b]Isolated yields (48-h reaction time) after purification by flash column chromatography.
[c]Diastereoselectivities and enantioselectivities were determined by chiral HPLC. The configuration of aldol products has been assigned by comparison to literature data.[30]
[d]A 12-fold excess of cyclohexanone was employed.
[e]Boric acid instead of TFA was used as additive.

TABLE 2. Screening of β-amino alcohol catalysts in the asymmetric aldol reaction of cyclohexanone (1b) with 4-nitrobenzaldehyde (2a) affording 3d[a]

Entry	Catalyst	Yield[b] [%]	*syn*:*anti*[c] [%]	ee (*syn*)/ee (*anti*)[c] [%]
1	**4a**	43	26:74	48/82
2	**4b**	51	43:57	72/61
3	**5**	93	42:58	70/53
4	**6**	52	30:70	50/63
5	**7**	46	24:76	54/65
6	**8**	42	24:76	57/58
7	**9**	24	39:61	62/56

[a]Reaction conditions: β-amino alcohol catalyst (1.0 mmol), TFA (1.0 mmol), **1b** (20.0 mmol), and **2a** (5.0 mmol) in 10 mL aqueous Triton X-100 solution (2.0×10^{-2} mol L^{-1}).
[b]Isolated yields (48-h reaction time) after purification by flash column chromatography.
[c]Diastereoselectivities and enantioselectivities were determined by chiral HPLC. The configuration of aldol products has been assigned by comparison to literature data.[30]

excess, having the absolute configuration (*2S, 1'R*).[†] As expected, when *(R)*-phenylglycinol (**4b**) was used as catalyst, an excess of the *anti* aldol product (**3d**) with the (*2R, 1'S*) configuration was obtained.

Encouraged by these results, we then studied the scope and limitations of the *(S)*-phenylglycinol-catalyzed aldol reactions in Triton X-100 aqueous micellar solutions (Figure 2; Table 3). All reactions with cyclohexanone (**1b**) afforded the corresponding aldol products **3d–f** in good to high stereoselectivities (de = 44–62%, ee = 82–89%, entries 4–6, Table 3). Especially with regards to enantioselectivity, the reaction between cyclohexanone and 3-nitrobenzaldehyde gave the best results (89%, entry 5, Table 3). The reaction of cyclohexanone with 4-cyanobenzaldehyde (**2f**), in the presence of zinc chloride as an additive, resulted in significantly lower enantioselectivity for the major *anti* product (entry 7, Table 3). Aldol products **3a–c** and **3g**, obtained from cyclopentanone (**1a**) or cycloheptanone (**1c**), were isolated with low-to-moderate enantioselectivities for the major *anti* products (ee = 14–48%, entries 1–3 and 8, Table 3). Nevertheless, the reaction of cyclopentanone with 4-nitrobenzaldehyde gave the best results in terms of diastereoselectivity (94%, entry 1, Table 3). It is worth emphasizing that in almost all reactions the *anti* aldol products were obtained in excess, with only two exceptions: i) in the reaction of cyclopentanone (**1a**) with 3-nitrobenzaldehyde (**2b**) (entry 2, Table 3); and ii) when SDS was utilized as surfactant (entry 6, Table 1). Also note that all reactions recorded in Tables 1–3 were stopped after 48 h, since prolonged reaction times could lead to the racemization of the aldol products. Finally, it turned out that when aliphatic ketones, such as diethylketone, dipropylketone, acetophenone, propiophenone, and methylnaphthylketone, were employed as reagents, the corresponding isolated yields were very low (results not shown here), with the exception of acetone (**1d**) where isolated yields ranging between 33% and 36% were obtained.

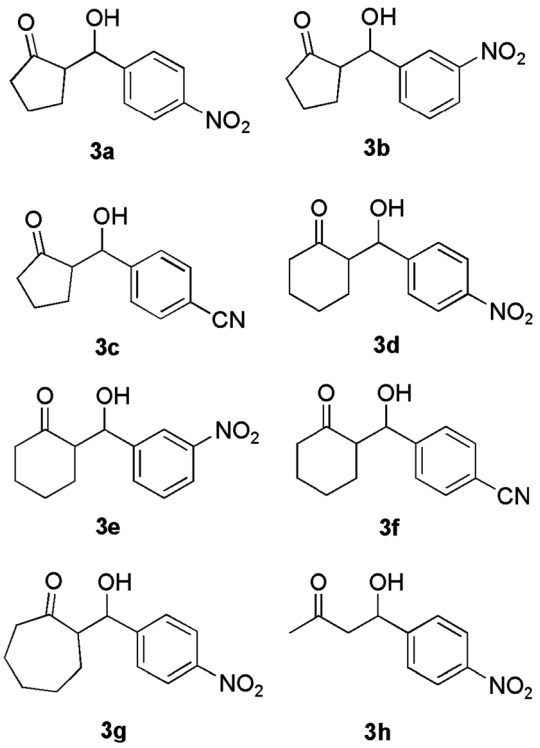


Fig. 2. Aldol products **3a–h**, obtained from *(S)*-phenylglycinol-catalyzed direct asymmetric aldol reactions of ketones **1a–d** with aromatic aldehydes **2a–c.**

TABLE 3. *(S)*-Phenylglycinol-catalyzed direct asymmetric aldol reactions of ketones 1a–d with aromatic aldehydes 2a–c affording aldol products 3a–h in aqueous Triton X-100 solutions[a]

Entry	Ketone/ aldehyde	Product	Yield[b] [%]	*syn*: *anti*[c] [%]	ee (*syn*)/ ee (*anti*)[c] [%]
1	**1a/2a**	**3a**	58	3:97	26/47
2	**1a/2b**	**3b**	36	57:43	18/48
3	**1a/2c**	**3c**	35	30:70	8/44
4	**1b/2a**	**3d**	43	26:74	48/82
5	**1b/2b**	**3e**	41	19:81	52/89
6	**1b/2c**	**3f**	56	25:75	37/82
7	**1b/2c**	**3f**[d]	37	28:72	32/41
8	**1c/2a**	**3g**	27	20:80	29/14
9	**1d/2a**	**3h**	36	–	26
10	**1d/2a**	**3h**[e]	33	–	27

[a]Reaction conditions: *(S)*-phenylglycinol (1.0 mmol), TFA (1.0 mmol), **1a–d** (20.0 mmol), and **2a–c** (5.0 mmol) in 10-mL aqueous Triton X-100 solution (2.0×10^{-2} mol L^{-1}).
[b]Isolated yields (48-h reaction time) after purification by flash column chromatography.
[c]Diastereoselectivities and enantioselectivities were determined by chiral HPLC. The configuration of aldol products has been assigned by comparison to literature data.[30,54]
[d]Zinc chloride was used as an additive.
[e]Myristic acid was used as an additive and surfactant.

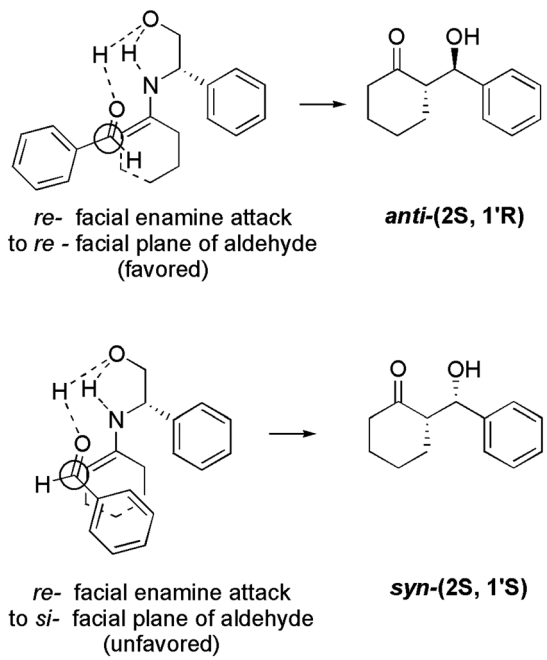
[†] The configuration of aldol products has been assigned by comparison to literature data. For example, the *anti* aldol product (*2S, 1'R*) produced in excess appears on the HPLC chromatogram at about 10.6 min, while the other *anti* enantiomer (*2R, 1'S*) appears at about 15.5 min (SI: Table 2, entry 4). The *syn* enantiomers appear at about 8.2 and 9.1 min, respectively. The diastereomeric excess was also determined by integrating the methine proton attached directly to the hydroxyl-carbon (CHOH) at about 5.20 and 4.82 ppm in the corresponding ^{1}H-NMR spectra, or the CHOH-carbon in the ^{13}C-NMR spectra at about 75 and 69 ppm for the *syn* and *anti* diastereomers, respectively.

A likely rationale for the materialization of asymmetric aldol reactions in aqueous micellar media is that the amino alcohol (the organocatalyst) and the acid (additive) self-assemble with the reactants in the micellar interior via hydrophobic interactions. The hydrophobic interior of these aqueous micelles excludes water molecules from the aldol reaction environment, resembling the enzyme-catalyzed aldol reactions occurring in the corresponding hydrophobic enzymatic active sites. In this concentrated micellar phase, the reaction proceeds efficiently to afford the desired aldol products with moderate-to-high enantioselectivity, which is most probably assisted by hydrogen bonds between the enamine, the β-amino alcohol, the acid, and the acceptor in the transition state (vide infra). In analogy, aldol reactions carried out in water by surfactant-like amphiphilic organocatalysts have been proposed to take place in an emulsion rather than a biphasic system.[30]

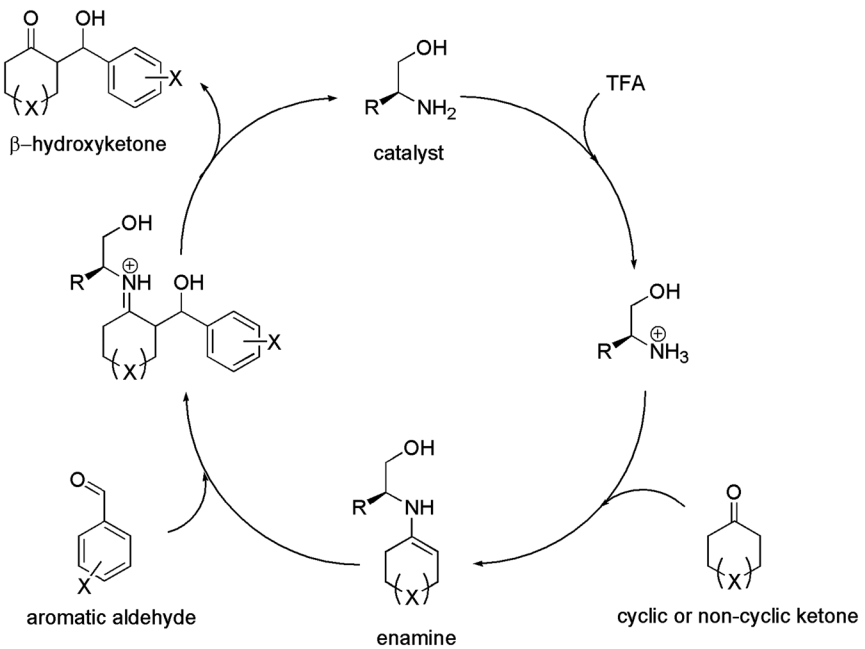
The proposed acid-assisted enamine mechanism for the β-amino alcohol-catalyzed asymmetric aldol reaction reported herein is shown in Scheme 2. The ketone initially reacts with the protonated β-amino alcohol resulting in the formation of an enamine, which, in the next step, reacts with the aromatic aldehyde to give, after hydrolysis, the enantiomerically enriched aldol products. The formation of *anti* product (*2S, 1'R*), when (*S*)-phenylglycinol is employed as a catalyst, is most probably favored by the minimization of the steric hindrance in the corresponding transition state. This diastereoselectivity originates from a *re-* facial attack of the ketone-enamine intermediate to the *re-* facial plane of the aldehyde (Scheme 3). As expected, a *si-* facial attack of the ketone-enamine intermediate to the *si-* facial plane of the aldehyde, leading to the *anti* products (*2R, 1'S*) that were indeed observed, is favored when (*R*)-phenylglycinol is utilized as a catalyst. These hypotheses are in accordance with previously proposed mechanistic rationalizations.[19,55] Finally, as visualized in Scheme 3, hydrogen bonds between the amine group of the catalyst and the carbonyl group of the aldehyde in the transition state are also presumed to play a key role in the observed stereoselectivity, given that they lead to a more rigid transition state.

CONCLUSIONS

In summary, we showed for the first time that chiral primary β-amino alcohols, prepared in one step from readily



Scheme 3. Simplified schematic representation of the two possible approaches of enamine-intermediates to aldehydes leading to *anti* (favored) and *syn* (nonfavored) aldol products.



Scheme 2. Proposed mechanism for the β-amino alcohol-catalyzed direct asymmetric aldol reaction of cyclic and non cyclic ketones with aromatic aldehydes.

available and inexpensive α-amino acids, efficiently catalyze the direct asymmetric aldol reaction of cyclic and noncyclic unmodified ketones with aromatic aldehydes in aqueous micellar solutions. The catalytic efficiency of these β-amino alcohols, especially *(S)*-phenylglycinol, is enhanced by the addition of TFA in catalytic amounts. This environmentally benign reaction affords a series of aldol products in moderate-to-high isolated yields and moderate-to-excellent diastereoselectivities and enantioselectivities. The enantioselectivity of the aldol products can be controlled through the selection of the appropriate chiral amino alcohol catalyst. Further studies focusing on the use of more complicated β-amino alcohol catalysts are currently underway and will be reported in due course.

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