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Highly Enantioselective α-aminoxylation Reactions Catalyzed by Isosteviol-proline Conjugates in Buffered Aqueous Media

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Abstract Chiral amphiphilic conjugate catalysts were designed and synthesized by covalently connecting L-proline with an inexpensive natural product, isosteviol. These catalysts demonstrated remarkable efficiency in the asymmetric α-aminoxylation of aldehydes and ketones using nitrosobenzene in phosphate buffer solution, resulting in good to high yields and excellent enantioselectivities without using any additives. At pH 9.1, the amphiphilic catalysts showed a pH responsive ability in phosphate buffer solution, which facilitated the excellent *O*-selectivity reactions, illustrating a viable approach for the development of asymmetric supra-molecular catalysts.

Keywords Amphiphilic conjugate · Aminoxylation · Buffered media · pH responsibility

1 Introduction

Optically active α-hydroxy carbonyl and 1,2-diol moieties are frequently found in a large number of biologically active natural products [1–4], which motivated chemists finding the ways to explore highly effective catalytic systems for diastereoselective and enantioselective synthesis [5]. The asymmetric α-hydroxylation of enolates and enol derivatives utilizing transition metal complexes as catalysts is one of the simplest and most frequently used methods. Yamamoto [6] used catalyst (*R*)-BINAP·Pd(ClO_4)$_2$ for the catalytic enantioselective introduction of an oxy group at the α-position of ketone enolates using nitrosobenzene and the asymmetric synthesis of chiral *R*-hydroxy ketone in up to 97% ee.

Comparing with the corresponding transition metal catalysts, the organic catalysts showed more fine qualities: operational simplicity, availability, non-toxicity, high efficiency and selectivity. In 2003, the first organocatalyst was utilized to catalyze the direct α-aminoxylation of aldehydes with nitrosobenzene has reported by Zhong [7], MacMillan [8], and Hayashi [9] independently. The scope of the L-proline-catalyzed reaction was then extended to ketones by Hayashi [10] and Córdova [11, 12]. After this initial breakthrough in the organo-catalyst field, several modified L-proline catalysts have been developed to improve the enantioselectivity and reactivity, such as 4-siloxyproline [13], polymers-supported prolines [14], α,α-diphenylprolinol trimethylsilyl ether [15] and the substitution of the carboxylic acid moiety of L-proline with an amide [16–18] or tetrazole function [19]. However, most of the reported catalytic reactions were carried out in organic solvents such as DMSO, DMF, CH_3CN, $CHCl_3$, CH_2Cl_2, etc., and little work was done considering environmentally friendly reaction protocols.

Water is the least expensive and environmentally benign solvent. Therefore, it has been accepted as a convenient solvent in organo-catalysis reactions considering its great advantages as described below: (1) accelerates reaction and enhances selectivity; (2) facilitates the formation of intermolecular hydrogen bond in the transition state; (3) easily recycles the water-soluble catalysts

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after separation of the insoluble reaction products [20–24]. In 2009, Zhong and co-workers [25] reported the L-thiaproline-catalyzed α-aminoxylation of aldehydes in the presence of water and tetrabutylammonium bromide in good to high yields (74–88%) and with excellent enantioselectivities (93 to >99%). Wang and co-workers [26] reported that the addition of water could facilitate the hydrolysis of the iminium salt intermediate to α-aminoxyaldehyde, which regenerating the proline catalyst. Although initial enamine formation produced 1 equiv of water, it seemed that this was not sufficient to maintain a smooth catalytic cycle and additional amount of water might be required. In addition, L-proline has been shown to mechanistically mimic aldolase I with good enantioselectivity, and several examples of aldol reaction catalyzed under enzymatic conditions, i.e. buffered aqueous media, have also been reported [27–31]. Amino acid moieties covalently attached to long hydrocarbon chains are also reported for the preparation of pH-sensitive hydrogelators. Recently, Lin et al. [32] reported the formation of pH-responsive worm-like micelles in a mixture of cationic surfactants and hydrotropes with a carboxyl functional group. Herein, we present the first example of isosteviol-proline conjugate catalysts that promote α-aminoxylation of aldehydes or ketones with high efficiency and enantioselectivity in aqueous buffer (pH 9.1). In this catalyst system, amphiphilic amino acids are used as pH-responsive micelle through self-assembly in aqueous buffer, which facilitate the *O*-selective reactions and stereoselectivity. Moreover, the effects of non-covalent interactions between the catalysts and substrates in aqueous buffer are also discovered.

2 Experimental

2.1 General

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. All reported ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as an internal reference. IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro^{TM} instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined using a XT5A apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Enantiomeric excess was measured by chiral HPLC at room temperature using Labtech 2006 pump equipped with Labtech UV600 ultra detector with Chiralpak AD-H (4.6 mm × 250 mm).

2.2 Synthesis of Catalysts

2.2.1 *Synthesis of Catalyst* ***1a***

Isosteviol (6.36 g, 20 mmol) was dissolved in $SOCl_2$ (20 mL), and the mixture was stirred at room temperature for 1 h. After evaporating the solvent under vacuum, *trans*-4-hydroxy-L-proline (2.62 g, 20 mmol) and CF_3COOH (20 mL) were added. The resulted solution was stirred at room temperature for 2 h. Under cooling with an ice/water bath, Et_2O (40 mL) was added carefully to give a fine white precipitate that was vacuum-filtered, washed with Et_2O (5 mL × 2) and dried at room temperature for 2 h to give the hydrochloride as a fine white powder. The white powder was dissolved in 40 mL of warmed 95% EtOH, and propylene oxide (10 mL) was then added. Stirring was discontinued and the solution left for crystallization at room temperature for 7 h. The crystalline product was vacuum-filtered and dried at room temperature in vacuo to give product **1a** (7.16 g, 83%). m.p.:176–178 °C, $[\alpha]_D^{20} = -56.7$ (c 0.13, $CHCl_3$); IR (KBr, cm^{-1}): 3601, 3448, 2955, 2849, 1733, 1654, 1149, 1130; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.23 (s, 1H), 4.13 (s, 1H), 3.60 (s, 1H), 3.38 (s, 1H), 2.64–2.59 (d, $J = 20$ Hz, 1H), 2.20 (m, 3H), 1.85–1.78 (m, 2H), 1.66–1.38 (m, 10H), 1.18 (s, 3H), 1.12–1.09 (m, 2H), 0.95 (s, 3H), 0.98–0.88 (m, 2H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 222.5, 176.5, 173.1, 72.3, 59.7, 57.0, 54.5, 54.1, 49.8, 48.6, 48.4, 43.8, 41.4, 39.6, 39.4, 38.0, 37.5, 37.2, 35.4, 28.9, 21.5, 20.3, 19.8, 19.0, 13.8; HR-MS (ESI, *m/z*) calcd. for $C_{25}H_{37}NNaO_5$ $[M + Na]^+$ 454.2569, found: 454.2570.

2.2.2 *Synthesis of Catalyst* ***1b***

A solution of compound **1a** (8.62 g, 20 mmol) and sodium borohydride (1.71 g, 30 mmol) in dry ethanol (100 mL) was stirred at 0 °C for 2 h. The reaction mixture was then concentrated under vacuum, and treated with $CHCl_3$ and H_2O. The organic layer was separated and washed with saturated NaCl aqueous solution. Then the solvent was dried over anhydrous $MgSO_4$ and evaporated under vacuum to afford crude product. After methanol re-crystallized, the catalyst **1b** was obtained as a white powder(8.31 g, 96%). m.p.: 167–170 °C, $[\alpha]_{589}^{20} = -50.0$ (*c* 0.12, CH_3OH); IR (KBr, cm^{-1}): 3422, 2926, 2847, 1719, 1596, 1438, 1384, 1176, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.26 (s,1H), 4.20 (s, 1H), 3.81–3.80 (d, $J = 5.6$ Hz, 2H), 3.320–3.279 (d, $J = 16.4$ Hz, 1H), 2.394–2.308 (m, 2H), 2.16–2.12 (d, $J = 16.4$ Hz, 1H), 1.74–1.23 (m, 13H), 1.17 (s, 3H), 1.07–0.73 (m, 9H), 0.89 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 80.1, 72.7, 60.6, 57.0, 55.7, 55.0, 50.2, 43.8, 42.5, 42.0, 41.9, 41.6, 40.3, 39.7, 38.1, 37.7, 35.0, 33.7, 28.9,

24.9, 21.7, 20.4, 18.8, 13.8; HR-MS (ESI, *m/z*) calcd. for $C_{25}H_{39}NNaO_5$ $[M + Na]^+$ 456.2726, found: 456.2726.

2.3 General Procedure for the α-Aminoxylation of Aldehydes

PBS (phosphate buffered solutions, 0.20 mL) was added to a stirred mixture of corresponding aldehydes and catalyst at 0 °C, followed by nitrosobenzene. The reaction was stirred at room temperature until the green solution turned yellow which indicated complete consumption of the nitrosobenzene. The reaction mixture was then treated with $NaBH_4$ in EtOH at 0 °C. The excess $NaBH_4$ was quenched by the addition of water, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried with over anhydrous Na_2SO_4 and evaporated under vacuum. The crude oil was purified by thin layer chromatography on silica gel (petroleum ether/ethyl acetate).

2.4 General Procedure for the α-Aminoxylation of Cyclohexanone

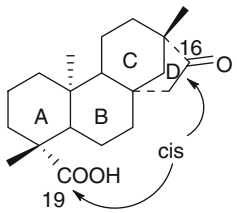
PBS (0.20 mL) was added to a stirred mixture of cyclohexanone and catalyst at 0 °C, and then the substitute nitrosobenzene was added. The reaction was stirred at room temperature until the green solution turned yellow which indicated complete consumption of the nitrosobenzene. The reaction mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude oil was purified by thin layer chromatography on silica gel (petroleum ether/ethyl acetate).

3 Results and Discussion

3.1 Synthesis of Catalysts

Based on our previous research [33, 34], the special features of isosleviol have been invoked our interest: hydrophobic polycyclic skeleton and chiral concave structure consist of the cis-junction of the 19-carboxyl group and D cyclopentane rings (Fig. 1). Recently, we [35] discovered that amphiphilic compound **1a** was an efficient organocatalyst in aldol reaction in a water system (Fig. 2), giving *β*-hydroxy carbonyl derivatives with virtually complete stereoselectivity. The hydrophobic effect of isosteviol subunit in the catalyst allows the proline moiety away from water phase, forming micelles on water surface, which facilitates the cluster of the catalyst with the lipophilic reactants. And the concave constructed by isosteviol and (2*S*, 4*R*)-4-hydroxyproline would facilitate the enantioselective formation of the transition states. In this context, it is delightful to find that this kind of amphiphilic isosteviol-proline conjugates is indeed a viable catalyst for the α-aminoxylation of carbonyl compounds in an aqueous buffer solution with good activities and excellent enantioselectivities.

Fig. 1 Structure of Isosteviol



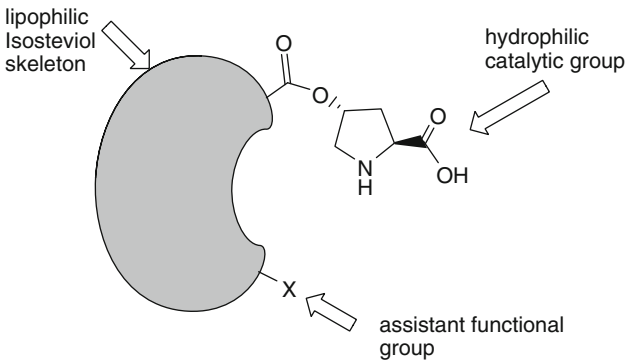


Fig. 2 Designed structure of catalyst with different functions

Amphiphilic conjugate **1a** was readily synthesized in high yield by the condensation of isosteviol with the *anti*-4-hydroxy-L-proline via a one-pot process as previously described (Scheme 1), and it can also be made on large-scale. In order to investigate the efficiency of the 16-functional group in the isosteviol skeleton, the catalyst **1b** was synthesized by the reduction of the 16-carbonyl group with $NaBH_4$ in C_2H_5OH. As previously reported, only 16-*R*-configuration product was obtained, which afforded a *cis* structure in account of the 16-hydroxyl and 19-carboxyl groups. The structures of these catalysts were fully characterized by IR, ^1H NMR, ^{13}C NMR, and HR-MS analyses.

3.2 The α-Aminoxylation Reaction of Carbonyl Compounds Catalyzed by Different Catalysts

With the L-proline derived chiral amphiphilic catalysts in hand, we proceeded to test their catalytic ability in asymmetric reaction of carbonyl compounds. It was reported that L-proline was efficient in catalyzing α-aminoxylation of aldehyde/ketone in ionic liquids or in the presence of water with phase-transfer catalyst as an additive. The amphiphilic L-proline derivatives **1a** and **1b** have the combined catalytic function of L-proline with the hydrophobic effect of the isosteviol subunit, which prompted us to evaluate their

Scheme 1 Synthetic route of catalysts **1a** and **1b**

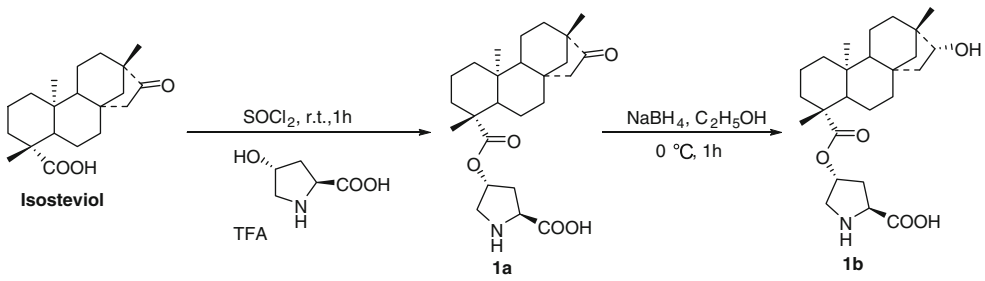
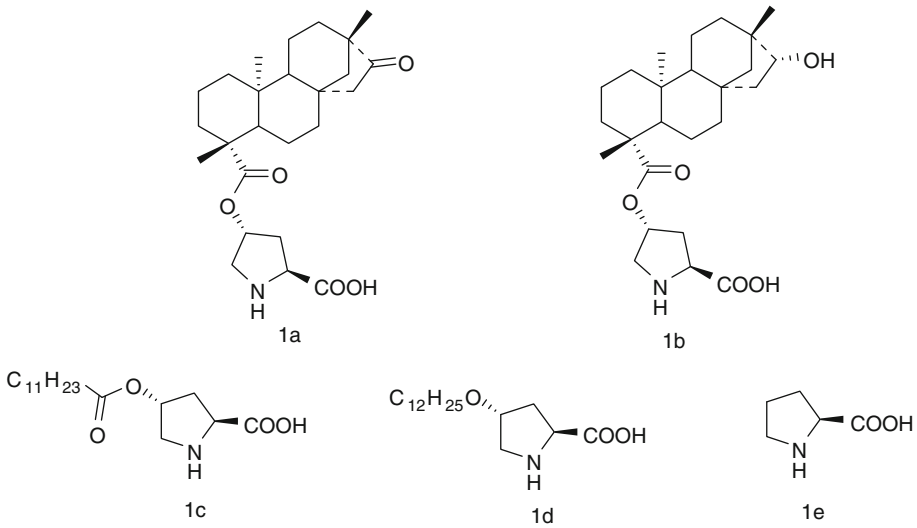


Fig. 3 Catalysts screened

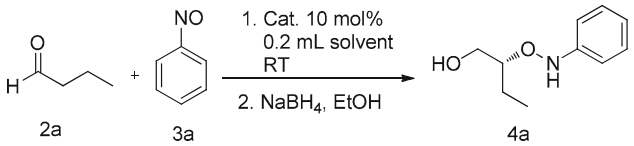


catalytic performance for the asymmetric α-aminoxylation reaction in aqueous media in the absence of any additive. To compare the catalytic behavior of different amphiphilic catalysts, the long-alkyl substituted proline derivatives **1c** [36] and **1d** [37], as well as L-proline **1e**, were also examined for the reactions (Fig. 3).

The catalytic activities and stereoselectivities of catalysts **1a**–**1e** were first investigated in aqueous media as well as in some organic solvents at room temperature by using the α-aminoxylation of nitrosobenzene and butanal as a model reaction (Table 1). After in situ conversion of the intermediate into the more stable 2-aminoxy alcohol, the corresponding *O*-regioselective addition product **4a** was isolated by silica gel chromatography. The absolute configuration of the major α-aminoxylation product was assigned as an ***R*** based on the optical rotation and HPLC analysis according to reported data [12]. Meanwhile, it is noteworthy that no apparent α-oxyamination by-products were observed under such conditions. The desired α-aminoxylation product was obtained with good yields and high enantioselectivities using the designed catalysts except L-proline (Table 1, entries 1–4 vs. 5). In all case, the amphiphilic isosteviol-proline conjugates **1a** and **1b** caused the reaction to completion in a short time with high catalytic activities and enantioselectivities (Table 1, entries 1 and 2). Then the screenings of various organic solvents revealed that THF and DMSO were not suitable for this reaction (Table 1, entries 6 and 8), and the enantioselectivities were improved when CH_3CN or $CHCl_3$ was used as solvent (Table 1, entries 7 and 9). The results revealed that the hydrophobic group containing amphiphilic proline catalysts, especially the isosteviol-proline conjugates **1b**, showed much higher catalytic activities for the α-aminoxylation reaction in aqueous media than other catalysts tested.

Though the reaction time was short in aqueous media, the enantioselectivity was barely satisfactory. The color of the reaction mixture changed from green to orange at the end of the reaction, which indicated the possible formation of azobenzene or azoxybenzene from nitrosobenzene according to IR and MS analyses of the reaction mixture. Therefore, if the transformation process to the azo-type by-products could be efficiently minimized, it would greatly facilitate the desired α-aminoxylation reaction. Recently, Hassan et al. [38] reported the pH-induced changes in the rheology, and microstructure in an aqueous mixture of polymer-like assemblies of a hydrophobic amino acid surfactant was studied by rheological measurements, small-angle neutron scattering (SANS) and light scattering. We were then inspired to perform the catalytic α-aminoxylation

Table 1 Catalyst screening



2a 3a 4a

Entry	Catalyst	Solvent	Time	Yield[a] (%)	ee[b] (%)
1	1a	H_2O	10 min	85	88
2	**1b**	**H_2O**	**4 min**	**86**	**89**
3	1c	H_2O	17 min	76	75
4	1d	H_2O	22 min	78	85
5	1e	H_2O	9 h 17 min	26	90
6	1b	THF	33 min	83	66
7	1b	$CHCl_3$	15 min	82	84
8	1b	DMSO	36 min	77	67
9	1b	CH_3CN	14 min	80	85

Conditions: Nitrosobenzene (0.5 mmol), butanal (10 equiv.), catalyst (10 mol%), and solvent (0.20 mL) was added at 0 °C and then warmed to RT

[a] Isolated yields

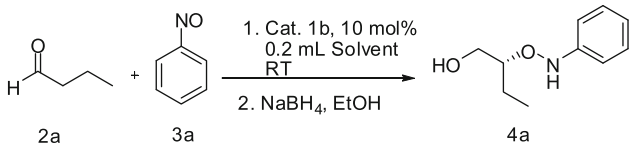
[b] The ee value was determined by chiral HPLC on a chiralcel AD-H column

Bold values indicate the best result in that reaction condition

reaction in buffered aqueous solution in order to facilitate the O-attack of the enamine intermediate on the nitrosobebzene in a special pH region and to increase the enantioselectivity. Therefore, the catalytic performances of catalyst **1b** were studied for the model reaction in different phosphate buffered solutions (PBS), and the pH-activity/stereoselectivity profiles were determined (Table 2). Firstly, when the reaction was process in pH <7, we only got poor ee value and low yield (Table 2, entries 3–5). Then the pH were extended to 9.1 (Table 2, entry 7), which was considered detrimental to *O*-regioselectivity because of its alkaline. Surprisingly, we only obtained the *O*-regioselectivity product with 96% yield and 97% ee value. The solution used here was pure alkalescent buffered aqueous media. No further improvements were observed when the reaction was done at the different temperature (entries 8 and 9), and lower catalyst loading (Table 2, entries 10 and 11) could obviously prolong the reaction time and give lower yields and poorer stereoselectivities. Then, when less amount of butanal was used, we got the same 97% ee value although the yield was slightly lower than entry 7. From all the results obtained such far, we chose the following as optimum conditions: 10 mol% catalyst **1b**, 0.2 mL of PBS (pH 9.1), and 5 eq of butanal.

The observed results suggest that the relationship of pH-activity/stereoselectivity plays a decisive role in controlling stereoselectivity. Compared with the inefficiency of the straight chain alkyl substituted prolines and L-proline itself (**1c**, **1d** and **1e**), catalysts **1a** and **1b** preferentially form

Table 2 Optimization of reaction conditions



2a 3a 4a

Entry	Solvent	pH (PBS)	Time	Yield[a] (%)	ee[b] (%)
1	H_2O	–	4 min	**86**	89
2	Brine	–	5 min	90	86
3	PBS	5.5	14 min	74	89
4	PBS	6.4	11 min	78	89
5	PBS	6.9	11 min	82	71
6	PBS	8.5	7 min	80	72
7	PBS	9.1	4 min	96	97
8[c]	PBS	9.1	15 min	93	95
9[d]	PBS	9.1	38 min	73	79
10[e]	PBS	9.1	21 min	91	89
11[f]	PBS	9.1	3 h 37 min	62	44
12 [g]	**PBS**	**9.1**	**4 min**	**89**	**97**

Conditions: Nitrosobenzene (0.5 mmol), butanal (10 equiv.), catalyst 1b (10 mol%), and solvent (0.20 mL) was added at 0 °C and then warmed to RT

[a] Isolated yields

[b] The ee value was determined by chiral HPLC on a chiralcel AD-H column

[c] 15 °C

[d] 0 °C

[e] 5 mol% catalyst loading

[f] 2 mol% catalyst loading

[g] 5 eq of butanal

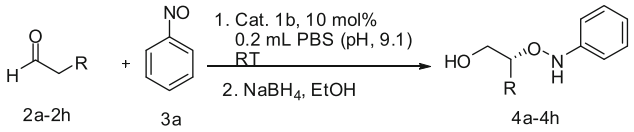
Bold values indicate the best result in that reaction condition

chiral micelle-like organo-microenvironments in the buffered aqueous solution, which could gather the hydrophobic reaction substrates into the small organic phase to accelerate the reaction and improve the stereoselectivity.

3.3 Substrate Scope

We subsequently extended the scope of the reaction to a variety of aldehydes, using the optimal reaction conditions established. The results are summarized in Table 3. The results indicated that the α-aminoxy alcohol products were obtained in high yields (79–95%) and excellent enantioselectivities (94–99%). It can also be seen that the reactions between nitrosobenzene and the straight chain aldehydes completed in only 4 min at room temperature with high yields and excellent ee values (Table 3, entries 1–8). Although the yields were lower than using 10 eq of aldehydes as reaction substrate, the ee values were remained (Table 3, entries 1 vs. 2, 3 vs. 4, 5 vs. 6). The enantioselectivity of the catalyzed reaction was improved

Table 3 Generality for α-aminoxylation in PBS



Entry	R	Products	Time	Yield[a] (%)	ee[b] (%)
1	Et	4a	4 min	89	97
2[c]	Et	4a	4 min	96	97
3	Me	4b	4 min	95	95
4[c]	Me	4b	4 min	98	95
5	Pr	4c	4 min	91	98
6[c]	Pr	4c	4 min	95	98
7	Bu	4d	4 min	90	>99
8	C_8H_{17}	4e	4 min	91	>99
9	Ph	4f	9 min	80	99
10	$PhCH_2$	4g	10 min	82	98
11[d]	Et	4h	9 min	79	94

Conditions: Nitrosobenzene (0.5 mmol), aldehyde (5 equiv.), catalyst 1b (10 mol %), and PBS (pH 9.1, 0.20 mL) was added at 0 °C and then warmed to RT

[a] Isolated yields

[b] The ee value was determined by chiral HPLC on a chiralcel AD-H column

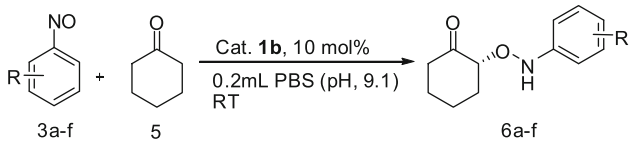
[c] 10 eq of butanal

[d] 4-Nitrosotoluene was used instead of nitrosobenzene

with increase of the length of carbon chain whereas the yields were decreased slightly (Table 3, entries 7 and 8). This phenomenon may be due to the different efficiency of the hydrophobic interaction between aldehydes and the amphiphilic catalysts in the buffered aqueous solution. When aldehydes containing an aromatic moiety, such as phenylacetaldehyde or 3-phenylpropanal, were used in the reaction (Table 3, entries 9 and 10), the reaction time was significantly protracted, which may be mainly due to the unmatched hydrophobic-hydrophobic interactions between aldehydes and catalysts. When 4-nitrosotoluene instead of nitrosobenzene was treated with butantal under the optimized conditions, the corresponding α-aminoxy alcohols were obtained in 79% yield with an enantioselecitivity of 94% (Table 3, entry 11), which is slightly lower than that from nitrosobenzene.

In addition, when ketones were used as the donor molecules in the α-aminoxylation reactions of carbonyl compounds, only cyclohexanone gave the corresponding α-aminoxylated product with >99% ee value and 87% yield in the PBS (pH, 9.1), but no reaction occurred in the case of both cyclopentanone and butanone. We then turned our attention to use the substituted nitrosobenzenes as acceptor molecules in α-aminoxylation reactions of cyclohexanone under the optimal reaction condition (Table 4). The results obtained showed that cyclohexanone performed high

Table 4 Reaction of α-aminoxylation with cyclohexanone in PBS



Entry	R	Products	Time	Yield[a] (%)	ee[b] (%)
1	H	6a	4 min	87	>99
2	**2-Me**	**6b**	**4 min**	**96**	**>99**
3	3-Me	6c	4 min	88	>99
4	4-Me	6d	5 min	83	>99
5	4-Cl	6e	3 min	67	>99
6	4-F	6f	4 min	57	>99

Conditions: Substitute nitrosobenzene (0.5 mmol), cyclohexanone (5 equiv.), catalyst 1b (10 mol %), and PBS (pH 9.1, 0.20 mL) was added at 0 °C and then warmed to RT

[a] Isolated yields

[b] The ee value was determined by chiral HPLC on a chiralcel AD-H column

Bold values indicate the best result in that reaction condition

activities and stereoselectivities in the α-aminoxylation with different substituted nitrosobenzenes as acceptors. It was noteworthy that the *o*-methyl nitrosobenzene showed the best activity (96% yield) and stereoselectivity (>99% ee), whereas the halogenated nitrosobenzene gave lower yields under the same reaction condition, but the enantioselectivity always maintained unchanged. These results indicate that the electron-donating substituents at the *ortho* position of nitrosobenzene are in favor of the activities of the α-aminoxylation reaction of cyclohexanone whereas the electron-withdrawing substituents are disadvantageous for this reaction (Table 4, entries 5 and 6).

4 Mechanistic Insights

To firmly establish the origin of the enantioselectivity in the present catalytic system, we postulated a possible transition state for the formation of the C–O bond in the reaction between aldehyde/ketone and nitrosobenzene, promoted by the amphiphilic catalyst **1b** in phosphate buffered solution. In the buffered aqueous media, the amphiphilic catalyst molecules may form some micelle-like asymmetric organic microenvironments with the assistance of hydrogen bonds, which could easily gather the lipophilic organic substrates around the catalyst. Therefore, the reaction was completed in a short time with high activity and stereoselectivity. In this case, amino acids are attractive molecules to the buffered solutions to create pH-responsive structures through self-assembly. In addition, the observed enantioselectivities of the catalytic α-aminoxylation of aldehydes and cyclohexanone can be

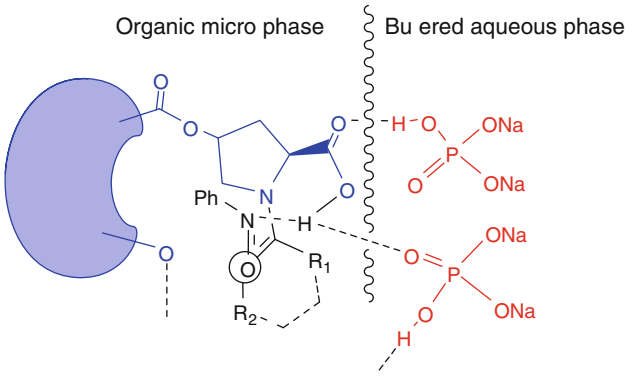


Fig. 4 Proposed transition state of the reaction

rationalized by invoking an enamine mechanism. The catalyst **1b** forms an (*E*)-*anti* enamine with aldehyde or cyclohexanone, which approaches the oxygen atom of the nitrosobenzene, providing a chiral α-aminoxyaldehyde with *R* configuration (Fig. 4). Meanwhile, the concave constructed by isosteviol and (2*S*, 4*R*)-4-hydroxyproline would facilitate the enantioselective formation of the transition states. This mechanism is in accord with the previously proposed models extremely well [6, 7, 25].

5 Conclusions

In conclusion, asymmetric amphiphilic catalysts have been evolved by covalently connecting L-proline with a naturally available isosteviol subunit, illustrating a viable approach for the development of asymmetric supramolecular catalysts. The amphiphilic isosteviol-L-proline conjugate **1b** was found to be a remarkable catalyst for the asymmetric α-aminoxylation of aldehydes/cyclohexanone in PBS (pH 9.1) with good to high yields and excellent enantioselectivities without any other additive. In a manner closely resembling enzymatic catalysis, the amphiphilic catalyst selectively binds and situates substrates in the asymmetric microenvironment by the synergistic action of a hydrophobic effect and non-covalent interactions on the surface of the aqueous phosphate buffer solution. Further investigations on the application of the amphiphilic isosteviol-proline conjugates in different asymmetric catalysis are in progress and will be reported in due course.

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