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Dipeptide-catalyzed direct asymmetric aldol reactions in the presence of water

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Abstract—The L-proline-based dipeptide has been discovered and developed as an efficient catalyst for the direct asymmetric aldol reactions of unmodified ketones with various aldehydes including aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes in the presence of water at 0 °C. The resulted methodology and optimal conditions led to the corresponding aldol products with high yields (up to 94%) and good enantioselectivities (up to 97% ee).

1. Introduction

The aldol reaction is one of the most powerful methods for the formation of C–C bonds in organic synthesis.[1] In recent years, organocatalytic asymmetric direct aldol reactions have received great attention, and various organocatalysts have been developed in order to achieve high diastereomeric and enantiomeric selectivities.[2] However, these reactions were typically performed in organic solvents, such as DMSO, DMF, or chloroform.[3] Although addition of a small amount of water often accelerates reactions and/or improves enantioselectivities,[4] large amount of water or aqueous buffer typically resulted in low yield with low or no enantioselectivity.[5] Water as a preferred reaction solvent offers a series of advantages over organic solvents, such as safety, convenience, economy, and environmental benign, etc. Therefore, utilizing water as reaction solvent for the development of enantioselective aldol reactions is urgently needed, especially for the discovery of new small organic molecule catalysts to catalyze this critical reaction. Recently, while our research is in progress, Hayashi,[6] Barbas,[7] Zhao,[8] Pericas,[9] and Gong[10] reported the direct asymmetric aldol reactions catalyzed by some proline derivatives with high diastereomeric and enantioselectivities in the presence of water or in water. Therefore, we are prompted to disclose our discovery in this important area. Herein, we report a new dipeptide-based organocatalyst that efficiently catalyzed direct asymmetric aldol reaction in the presence of water with high yields (up to 94%) and good enantioselectivities (up to 97% ee).

2. Results and discussion

2.1. Design and preparation of catalysts

We have previously reported that a combination of Pro–Phe (**1**) with *N*-methyl morpholine (NMM) as a base and PEG400 as a surfactant (Pro–Phe/NMM/PEG400) efficiently catalyzed the asymmetric aldol reactions in DMSO.[11] Recently, Gong,[12] Kudo,[13] Tsogoeva,[14] Córdova,[15] and Lu[16]also examined the aldol reactions catalyzed by some amino acids and small dipeptides in different reactive systems including organic solvents, organic solvents/H_2O mixture or aqueous media. Though the catalysts used in these reports were easily synthesized, there were still no very successful examples on the use of this kind of catalysts in direct asymmetric aldol reactions for a broad scope of new substrates and desired results in water. Inspired by aldolase enzymes and antibodies catalyzed asymmetric biochemical aldol reactions in water[17] and based on our previous work,[11] we applied our catalytic system in the aldol reaction of cyclohexanone (**6a**) with 4-pyridinecarbaldehyde (**7a**) in the presence of water. It is interesting to find that the reaction proceeded very smoothly under emulsion conditions with good yield and enantioselectivity (Table 1, entry 1, 91%, 73% ee). We were encouraged by this result and four new dipeptides (Fig. 1, **2**–**5**) were designed by replacing the benzyl in Pro–Phe (**1**) with various

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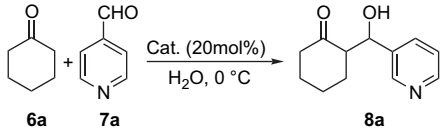
Table 1. Screening of reaction conditions in the direct asymmetric aldol reaction of cyclohexanone (**6a**) with 4-pyridinecarbaldehyde (**7a**) in the presence of water[a]



6a **7a** **8a**

Entry	Catalyst	Time (h)	*T* (°C)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[c] (%)
1	Pro–Phe (**1**)	3.5	0	91	72:28	73
2	Pro–Leu (**2**)	3.5	0	90	58:42	69
3	Pro–Ile (**3**)	3	0	92	67:33	75
4	Pro–Tyr (**4**)	2.5	0	94	68:32	77
5	Pro–Trp (**5**)	2.5	0	92	78:22	85
6	Pro–Trp (**5**)	2	10	93	69:31	78
7	Pro–Trp (**5**)	2	20	94	60:40	77
8[d]	Pro–Trp (**5**)	6	0	88	63:37	75
9[e]	Pro–Trp (**5**)	2.5	0	93	76:24	85

[a] Reaction was performed in a solution of 1 mmol scale of aldehyde and 6 equiv of ketone with 0.2 mmol catalyst, 0.2 mmol NMM, 0.05 mmol PEG400, and 1.5 mL water at 0 °C.
[b] Isolated yield of the corresponding product.
[c] Determined by chiral-phase HPLC.
[d] Donor **6a** (2 mmol, 2 equiv) was used.
[e] Donor **6a** (4 mmol, 4 equiv) was used.

larger side chains to further improve the diastereo- and enantioselectivities of the aldol reactions. The design of new catalysts was based on the following two principles: (1) keeping the proline unit and the hydrogen atom connected with the nitrogen of amide unit in the catalyst is necessary, which has been demonstrated in our previous work;[11] (2) a small organic catalyst with appropriate hydrophobic groups should assemble with hydrophobic reactants in water and sequester the transition state from water, which was hypothesized and demonstrated by Barbas.[8]

Dipeptides **1–5** were synthesized from the condensation of Boc-Pro-OH with the corresponding amino acid methyl ester hydrochlorides, following deprotection with NaOH and trifluoroacetic acid in sequence according to the general method for the preparation of dipeptides.[18]

2.2. Screening of catalysts and optimization of reaction conditions

The catalytic efficiency of dipeptides **1–5** was examined by the direct asymmetric aldol reaction of cyclohexanone with 4-pyridylaldehyde in the presence of water, and the results are listed in Table 1.

It can be seen from Table 1 that all the dipeptides utilized gave excellent yields (>90%), however, the enantioselectivities varied (range from 69% to 85% ee). Size of the side chains in dipeptides significantly influenced the catalytic efficiency. For example, the catalyst **5** containing the largest side chain gave the best result with 85% ee and 78:22 dr (entry 5), and the catalyst **2** containing the smallest side chain showed the lowest catalytic selectivity (entry 2, 69% ee and 58:42 dr). Raising the temperature slightly accelerated the reaction, but the ee and dr values decreased in some extent (entries 5–7). Entries 8 and 9 showed the effects of the ratios of donor **6a** to acceptor **7a** on the reaction rate and the selectivity. The decrease of their ratio from 4:1 to 2:1 led to slightly lower yield and selectivity (entry 8), and the increase of their ratio from 4:1 to 6:1 did not improve the yield and selectivity (entry 9). Therefore, the ratio of 4:1 was most suitable and adopted for further studies.

We further investigated the critical roles and effects of bases and surfactants on the asymmetric aldol reaction. In order to get more accurate results, 4-nitrobenzaldehyde (**7b**) was selected as the acceptor to react with **6a** in the presence of catalyst **5** due to its lower activity and longer reaction time than **7a**. As shown in Table 2, in the absence of both base and surfactant, only trace of product was detected by TLC even after 20 h (entry 1). However, when the base NMM or the surfactant polyethylene glycol 400 (PEG400) was used separately in the reaction, the aldol reaction products were obtained in yields of 90% and 60%, *anti*:*syn* ratios of 87:13 and 97:3, ee values of 77% and 90%, respectively (entries 2 and 3). Further, the yield and enantioselectivity are all excellent in the presence of both base and surfactant PEG400 (entry 4, yield of 92% and 92% ee). Therefore, the presence of base and surfactant is definitely essential for the success of this reaction. According to the phenomenon of the experiment, most of the catalyst was excluded from the reaction system as a form of solid in the absence of base (entry 3), and contrastively, the emulsion reaction system was formed in the presence of the base (entry 4), we presumed that the equivalent of catalyst and base might form the carboxylate of Pro–Trp under the reaction conditions. As a comparison, we also carried out the reaction in DMSO (entry 5) and obtained the aldol product in yield of 84% with 85% ee, which are obviously

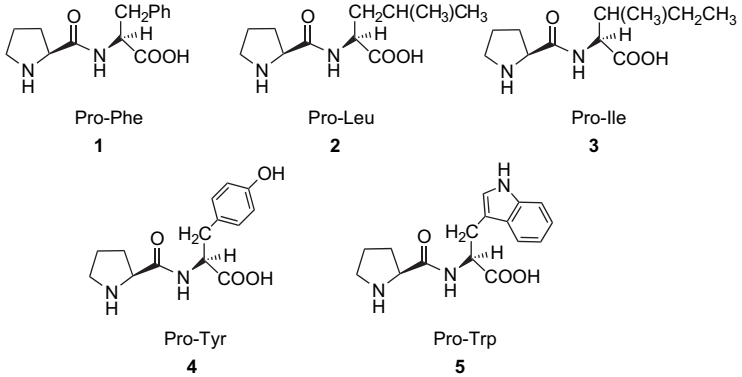


Figure 1. The structure of dipeptides **1–5**.