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Rationally designed organocatalyst for direct asymmetric aldol reaction in the presence of water

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Abstract—A rationally designed organocatalyst for direct asymmetric aldol reaction in the presence of water has been developed. High yield (up to 99%), diastereoselectivity (up to 99:1) and enantioselectivity (up to 97%) were obtained under optimal conditions.

The use of water as reaction media has attracted much attention because water is cheap, safe and environmentally benign.[1] Moreover, certain reactions can even be accelerated in dilute aqueous solutions.[2] Although it is generally assumed that solubility is essential for efficient reaction, Sharpless and co-workers found that substantial rate acceleration could be obtained when insoluble reactants were stirred in aqueous suspension, which they termed as 'on water' phenomena.[3] The organocatalytic direct asymmetric aldol reaction 'in the presence of' water was developed by Takabe, Barbas and Hayashi etc., which also proceeded in a heterogeneous way.[4] Though the origins of such 'on water' reactions are presently unclear, it is believed that hydrophobic effect is one of the key factors.[5]

The design of organocatalyst is of great current interest.[6] The enamine based organocatalysts such as proline and its derivates are proven to be very efficient in various reactions.[7] NOBIN **2** is an excellent ligand[8] with axis chirality and a scaffold similar to amino alcohol, which can provide double hydrogen bonding.[9] Since stronger acidity could provide stronger hydrogen bonding,[9] the very acidic hydrogens of NOBIN's $-NH_2$ and –OH groups may be better hydrogen bond donors than common amino alcohols'. Furthermore, the aromatic rings of NOBIN are hydrophobic. We envisioned that an appropriate combination of NOBIN moiety and pyrrolindine in a chiral scaffold might result in a potential bifunctional hydrophobic organocatalyst. Therefore, we designed two NOBIN–pyrrolindine based organocatalyst **3a** and **3b** as shown in Scheme 1 and found that both of them can catalyze the direct asymmetric aldol reaction of cyclohexanone and aldehydes in water efficiently. Here, we report the preliminary results.

The reaction of cyclohexanone and *p*-nitrobenzaldehyde was selected as a model. Initially, various conditions were examined at room temperature using **3a** as a catalyst. Without any additives, the reaction afforded moderate yield, enantioselectivity and good diastereoselectivity (entry 1) in the presence of water. The addition of a catalytic amount of TFA could increase dramatically both the yield and enantioselectivity (entry 2). Acetic acid can accelerate the reaction and slightly increase the dia- and enantioselectivity (entry 3). The reaction can proceed in brine affording moderate yield and good dia- and enantioselectivity (entry 4). The reaction can also proceed in THF using **3a**/TFA as catalyst, affording good results (entry 5). Interestingly, Catalyst **3b**/TFA gave slightly better diastereoselectivity and similar enantioselectivity and yield (entry 6).

The generality of the reaction was examined in detail using catalyst **3a**/TFA. The results were summarized in Table 2. In most cases, reactions afforded *anti*-aldol

Keywords: Asymmetric catalysis; Organocatalysis; Direct aldol reaction; NOBIN; Water.
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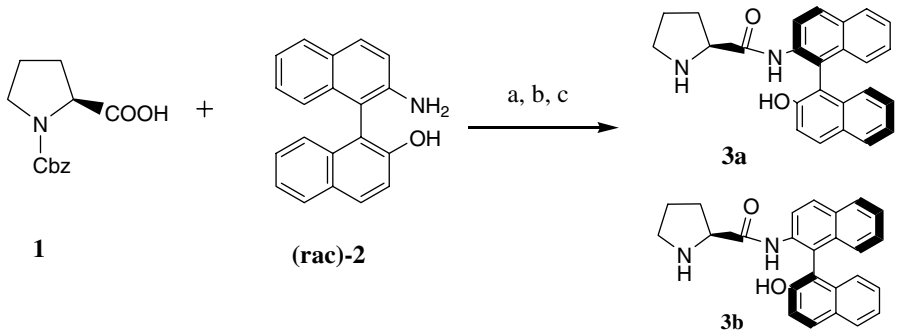
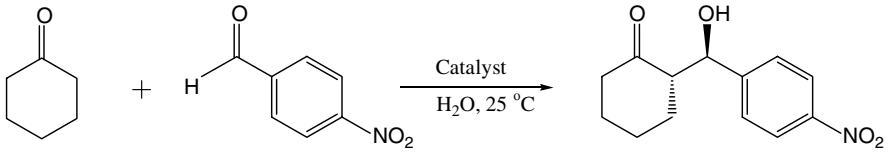


Scheme 1. The synthesis of the catalysts. Reagents: (a) ClCOOEt, NEt_3; (b) flash chromatography separation; (c) Pd/C, H_2.

Table 1. The effects of catalyst and additives on the reaction of cyclohexanone and *p*-nitrobenzaldehyde[a]



4 5 6

Entry	Catalyst	Additives	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	**3a**	None	24	41	81:19	63
2	**3a**	TFA	24	99	93:7	96
3	**3a**	CH_3COOH	24	95	83:17	73
4[e]	**3a**	TFA	24	56	94:6	91
5[f]	**3a**	TFA	24	83	93:7	92
6	**3b**	TFA	24	85	96:4	90

[a] The reactions were conducted with *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol) catalyst (0.05 mmol), TFA (0.05 mmol) and water (1 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis for *anti*-products.
[e] The reaction was carried out in brine.
[f] The reaction was carried out in THF.

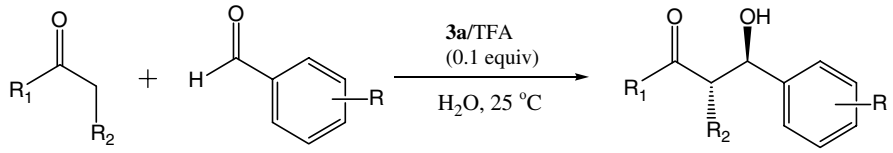
products in high yield with high enantioselectivity and excellent diastereoselectivity. For electron-poor aromatic aldehydes, the reaction could complete within 24 h (entries 1–4). Longer reaction time was required for less reactive aromatic aldehydes (entries 5–12). The ring size of the cyclic ketones was also examined-both cyclopentanone and cycloheptanone could be used as donors but giving poorer results than cyclohexanone (entries 13–14). The hydrophobic nature of the substrate seems to be crucial for this reaction system. All the water insoluble aldehydes and ketones formed an emulsion during the reaction. The limitation of this catalytic system is that it cannot extend to the simple acyclic ketones and aliphatic aldehyde. The reaction of acetone and *p*-nirobenzaldhyde in the presence of **3a**/TFA in THF could afford moderate yield and ee (entry 15), but no reaction was detected in water.

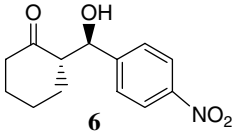
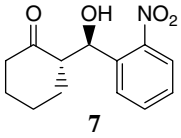
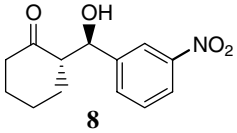
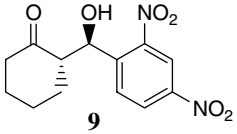
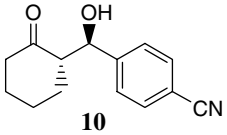
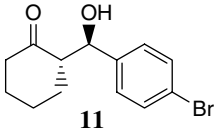
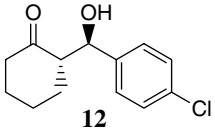
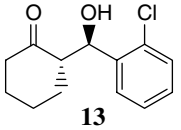
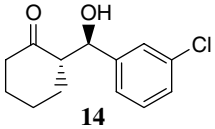
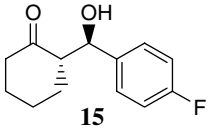
Catalyst **3a**/TFA gave similar results as **3b**/TFA (Table 1, entries 2 and 6). According to the X-ray crystal structure of **3a** (Fig. 1), it is difficult to form double hydrogen bond due to the distance between the hydroxyl group and amino group and the rigid structure of NOBIN scaffold. Hence, we reasoned that only one hydrogen bond between the amino group and the aldehyde was formed in the transition state. Our hypothesis was further proved by our experiments. We prepared catalyst **21** in which the hydroxyl group of the NOBIN scaffold was protected by $-CH_3$ (Fig. 2). The reaction of cyclohexanone and *p*-nitrobenzaldehyde catalyzed by 10 mol % of **21**/TFA afforded 98% yield, 97:3 *anti*:*syn* selectivity and 91% enantioselectivity in the presence of water in 24 h, which indicated that the hydroxyl group had little influence to the transition state.

The **3a**/TFA system was only applicable to aromatic aldehydes. And the reaction carried out in THF also afforded good results (Table 1, entry 5), which indicated that the hydrophobic effect might not serve as a key factor to the selectivity. We supposed that the pi–pi interaction between the aldehyde and the catalyst's aromatic rings in the transition state may play an important role in the selectivity. Based on the above analysis, we proposed a plausible transition state for the **3a**/TFA catalyzed aldol reaction as depicted in Scheme 2. The enamine attacks the aldehyde from the Re face, resulting in the formation of the major stereoisomer.

In summary, we have designed a new kind of organocatalysts that can catalyze the direct asymmetric aldol reac-

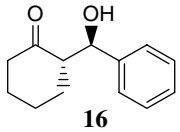
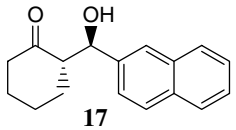
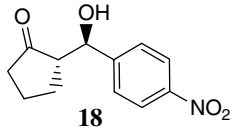
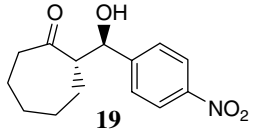
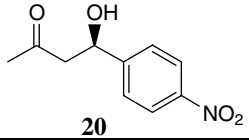
Table 2. **3a**/TFA catalyzed direct aldol reactions in water[a]



Entry	Product	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	 **6**	24	99	93:7	96
2	 **7**	24	99	94:6	97
3	 **8**	24	92	96:4	93
4	 **9**	6	99	94:6	88
5	 **10**	48	90	93:7	94
6	 **11**	72	95	92:8	93
7	 **12**	72	92	95:5	91
8	 **13**	72	90	99:1	86
9	 **14**	72	95	94:6	91
10	 **15**	72	55	92:8	84

(*continued on next page*)

Table 2 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
11	 **16**	72	50	90:10	81
12	 **17**	72	85	94:6	80
13	 **18**	24	90	70:30	83
14	 **19**	48	53	72:28	62
15[e]	 **20**	24	60	—	67

[a] The reactions were conducted with aldehyde (0.5 mmol), cyclohexanone (1 mmol) catalyst (0.05 mmol), TFA(0.05 mmol) and water (1 mL).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral-phase HPLC analysis for *anti*-products.
[e] THF was used as solvent.

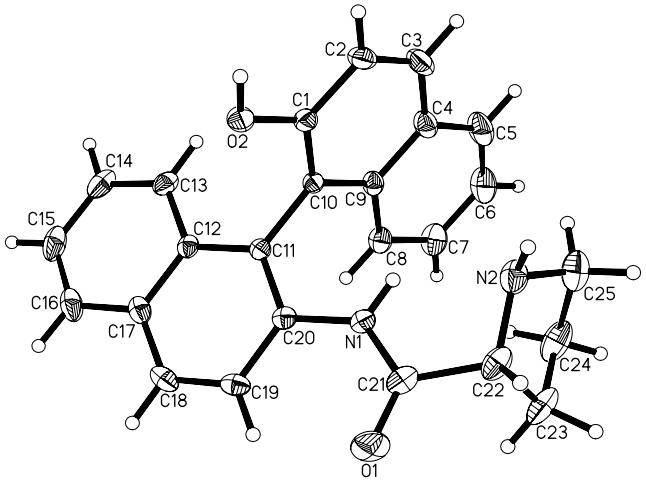
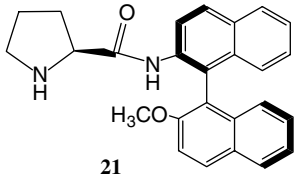
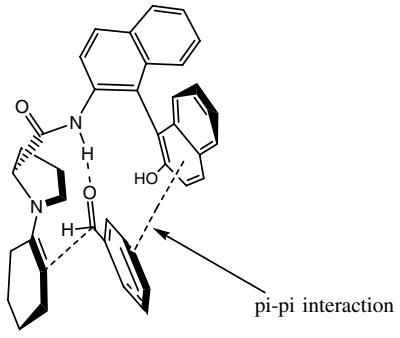


Figure 1. The X-ray crystal structure of **3a**.



21

Figure 2. The structure of protected catalyst **21**.



Scheme 2. Proposed transition state for the **3a**/TFA catalyzed direct asymmetric aldol reaction.

tion in the presence of water efficiently. The **3a**/TFA catalyst system demonstrated excellent reactivity, diastereoselectivity and enantioselectivity in the presence of water. The mechanism of the catalytic system was also studied. The hydrogen bonding and the pi–pi interaction might serve as key factors for the high selectivity.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2007.04.037. The crystal data are available at http://www.ccdc.cam.ac.uk. The CCDC number is 620413.

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