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Asymmetric aldol reaction using a very simple primary amine catalyst: divergent stereoselectivity by using 2,6-difluorophenyl moiety

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ABSTRACT

Asymmetric aldol reactions of aliphatic ketones or aldehydes with aromatic aldehydes or isatins were catalyzed by a very simple and flexible *N*-(2,6-difluorophenyl)-L-valinamide. Interestingly, stereochemical course of the reaction of hydroxyacetones or α-branched aliphatic aldehydes as aldol donors was different from that of cycloalkanones.

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1. Introduction

Asymmetric reaction using organocatalysts has been rapidly developing in recent years because the methodology is metal-free, non-toxic, and environmentally friendly.[1] A great deal of efforts have been devoted to prepare various chiral organocatalysts, however, most strategies for the stereocontrol in the reaction rely on hydrogen bonding interaction and steric repulsion.[2] As a result, large molecules having many chiral centers, or secondary amines having a rigid structure, such as proline derivatives were thought to be necessary in the process of catalyst design. Although recent progress has been shown that primary amine catalysts have also been effective,[3] control of stereoselectivities with simple and flexible catalysts can be a challenge. In the course of our study, we have developed a very simple, small, and flexible *N*-(2,6-difluorophenyl)-L-valinamide **1a** as an organocatalyst, which was easily prepared from Boc-L-valine in two steps (Fig. 1).[4] The asymmetric aldol reaction[5] of aldehydes with cycloalkanones using the catalyst **1a** under environmentally friendly conditions gave the corresponding product in high yields with up to >99% ee. Unlike the organocatalysts reported thus far, the stereoselectivity of the products was controlled by using tilted 2,6-difluorophenylamide group of the catalyst **1a**.[6] As a result, the aldol reaction of aromatic aldehydes with cycloalkanones mainly proceeded by the attack of *Si*-face of the enamine on the *Si*-face of aromatic aldehyde due to the steric hindrance (Fig. 1). The novel approach encouraged us to explore the reaction of other aldol donors and acceptors for a wide variety of application. In this work, unexpectedly, stereochemical preference was different from that in the reaction of aromatic aldehyde with cycloalkanone.[7] Here we report the asymmetric aldol reactions of hydroxyacetones or aliphatic aldehydes with various aromatic aldehydes or isatins as aldol acceptors using our catalyst **1**.

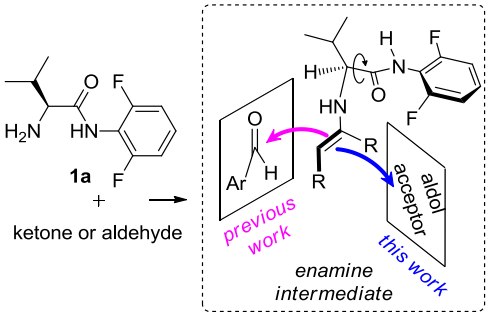

Fig. 1. A model for asymmetric aldol reaction catalyzed by **1a**.

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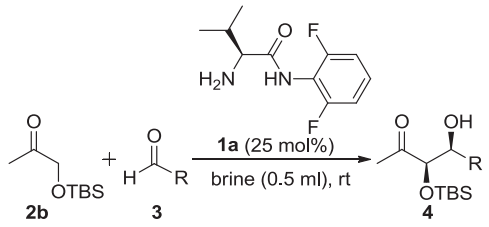
2. Results and discussion

1,2-Diols are found in many natural and biologically active compounds.[8] In spite of many reports on the reaction of hydroxyacetones, most of aldol reactions of hydroxyacetones use toxic additives, co-catalysts, or organic solvents.[9] To the best of our knowledge, only a few papers have been reported on the reaction under environmentally relevant conditions.[7,9e] In addition, stereoselective synthesis of (3*R*, 4*S*) isomers under environmentally benign conditions has not been reported yet. In our initial studies, aldol reaction of hydroxyacetone with 4-nitrobenzaldehyde **3a** using organocatalyst **1a** was examined, however, the reaction consistently resulted in moderate diastereo- and enantio-selectivities under various conditions (*syn*:*anti*=up to 75:25, up to 62% ee (*syn*)). Since the limited selectivity was thought owing to participation of the free hydroxyl group of hydroxyacetone, TBS-protected hydroxyacetone **2b** was used for the reaction (Table 1). After optimizing the reaction conditions, the scope of the reaction was explored. Reaction of various aromatic aldehydes proceeded with 67–94% ee (*syn*:*anti*=up to 85:15). Longer reaction time was necessary without electron-withdrawing group on the aromatic ring (entry 6). It should be noted that the reactions of both cycloalkanones[4] and hydroxyacetones proceeded using the catalyst **1a** with high stereoselectivities,[10] however, the stereochemistry of the products in Table 1 was different from that we expected in the reaction of cycloalkanones.

Table 1
Asymmetric aldol reactions of TBS-protected hydroxyacetone **2b** with various aromatic aldehydes **3**[a]



Entry	R (**3**)	Time (days)[b]	**4**	Yield (%)[c]	*syn*:*anti*[d]	% ee[e]
1	4-$NO_2C_6H_4$ (**3a**)	3	**4a**	94	83:17	85
2	2-$NO_2C_6H_4$ (**3b**)	4	**4b**	92	84:16	94
3	3-$NO_2C_6H_4$ (**3c**)	3	**4c**	94	85:15	80
4	4-$CF_3C_6H_4$ (**3d**)	3	**4d**	89	82:18	84
5	4-ClC_6H_4 (**3e**)	5	**4e**	79	78:22	79
6	C_6H_5 (**3f**)	7	**4f**	76	81:19	67

[a] All reactions were performed with 10 equiv of **2b** and 0.5 mmol of **3** in the presence of **1a** (25 mol %).
[b] Monitored by TLC.
[c] Isolated yield.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by chiral HPLC analysis of the *syn*-product.

With these results in hand, DFT calculations were performed for plausible transition state models (Fig. 2). First, enamine structures were fully optimized in the gas phase at the B3LYP/6-31G(d,p) level using Gaussian 09,[11] and the transition states for the reaction including the enamine were optimized at the same theory.[12] It was found that **TS2** giving (3*R*, 4*S*) isomer had the lowest, indicating that the aldol reaction catalyzed by **1a** might pass through **TS2**. Although it is necessary to consider the effect of brine, these models were in good agreement with experimental results. In addition, major isomer was the same even though various solvents were used (66% ee in dry CH_2Cl_2 and 82% ee in water). Unlike the reaction of aromatic aldehydes and cycloalkanones, three hydrogen bonding interactions between oxygen atom of silyloxy group and hydrogen of enamine, oxygen of benzaldehyde and enamine hydrogen, and benzaldehyde oxygen and amide hydrogen of 2,6-difloro phenylamide group would stabilize **TS2**. Additionally, hydrophobic interaction of TBS group of the enamine and phenyl group of benzaldehyde[7] might lead to different course of attack compared to that of cycloalkanones.

To demonstrate the utility of our organocatalyst **1**, the reaction of hydroxyacetone with isatins was investigated (Table 2) because the aldol adducts bearing a chiral 1,2-diol moiety[13] are desirable targets found in drug candidates, such as TMC-95A∼D.[14] Very recently, Hu et al. have reported the diastereoselective three-component reaction of α-diazo esters, water and isatin, and the corresponding products having a 1,2-diol unit were obtained in high diastereoselectivity (up to *syn*:*anti*=9:91),[15] however, the enantioselectivity of the products was not evaluated. Although the asymmetric aldol reactions of ketones with isatins have been described, the reaction of hydroxyacetone has not been reported yet because the reaction proceeded easily with weak bases, such as potassium carbonate. After optimizing the reaction conditions, we found that dry MTBE as a solvent was necessary for higher enantioselectivities. The reaction of **2a** with **5a** was completed within 24 h but with 55% ee (entry 1 in Table 2). The use of the catalyst **1b** derived from phenylalanine gave better ee (entry 3). Addition of

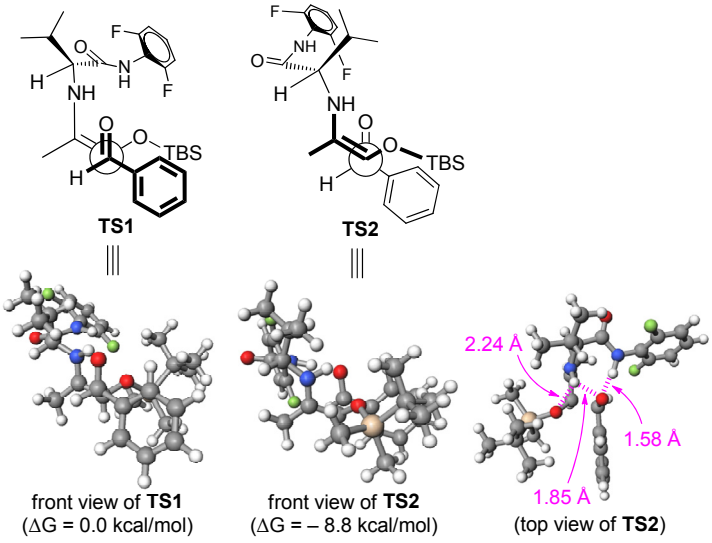


Fig. 2. Calculated 3D structures of **TS1** and **TS2**.

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