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SHORT COMMUNICATION

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Electrostatic Repulsion and Hydrogen-Bonding Interactions in a Simple *N*-Aryl-L-valinamide Organocatalyst Control the Stereoselectivity in Asymmetric Aldol Reactions

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A novel stereocontrol method for asymmetric aldol reactions of aldehydes with ketones is described. The stereoselectivity of the products is controlled by the electrostatic repulsion and hydrogen-bonding interactions of an *N*-aryl-L-valinamide catalyst. The use of this catalyst in a cross-aldol reaction allows easy access to bioactive 3-cyclohexanone-3-hydroxy-2-oxindole with excellent diastereo- (*syn*/*anti* = >99:1) and enantioselectivity (>99 % *ee*).

Introduction

Organocatalytic asymmetric reactions performed with the use of chiral amines have received a great deal of attention in recent decades, and this area of organic chemistry has been rapidly growing.[1] Since List et al. reported the direct aldol reaction between acetone and a variety of aldehydes catalyzed by L-proline, which formed an enamine similar to the mechanism of class I aldolase,[2] asymmetric organocatalysts including L-proline derivatives have been extensively investigated.[3] However, most strategies for controlling the stereoselectivity of the products by using the organocatalysts reported thus far have been quite limited. Generally, hydrogen-bonding interactions and steric hindrance are crucial for achieving high stereoselectivity.[4–8] In addition, catalysts with more than two chiral centers have been used in some cases. Other excellent strategies such as the use of ion-pairing catalysts,[9] carbenes,[10] Lewis bases,[11,12] and other catalysts have also been reported, but most of these studies used large molecules to control stereoselectivity. New stereocontrol methods with the use of small molecules should open a new avenue in asymmetric organocatalysis.

We have developed a novel strategy for the stereocontrol of the asymmetric aldol reaction, which is one of the most important carbon–carbon bond-forming reactions in organic synthesis for obtaining pharmaceutically useful compounds.[13,14] Our strategy uses *N*-aryl-L-valinamide **1e**, which is a small, simple, and relatively inexpensive compound, as an organocatalyst (Figure 1). Of the amino acid derived catalysts, L-valine derivatives are used less often than proline derivatives, because the primary amine moiety in L-valine is flexible.[15] In addition, our preliminary experiment showed that the reaction with L-valine itself (see Table 1) did not proceed. Unlike the organocatalysts reported thus far, catalyst **1e** bears a 2,6-difluorophenyl group; electrostatic repulsion between one fluorine atom on the aromatic ring and the amide oxygen atom tilts the aromatic group,[16,17] and hydrogen bonding of the other fluorine atom with the amide hydrogen atom stabilizes this conformation.[18] As a result, the reaction proceeds preferentially from the less-hindered face of the enamine intermediate in the asymmetric aldol reaction. In addition, electrostatic repulsion between a catalyst fluorine atom and the aldehyde electrophile oxygen atom may also contribute to excellent stereoselectivity. Thus, our catalyst should expand the strategy in asymmetric organocatalysis. Herein, we report the development of an *N*-aryl-L-valinamide organocatalyst derived from L-valine for asymmetric aldol reactions.

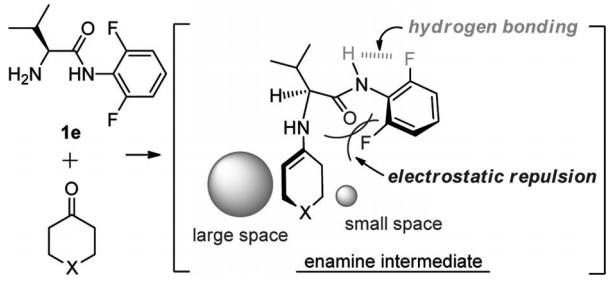

Figure 1. Stereocontrol strategy in the asymmetric aldol reaction.

Results and Discussion

Initially, we examined the aldol reaction of 4-nitrobenzaldehyde (**3a**) with cyclohexanone (**2a**) by using *N*-aryl-L-valinamides **1a**–**g** (25 mol-%) in brine at room temperature

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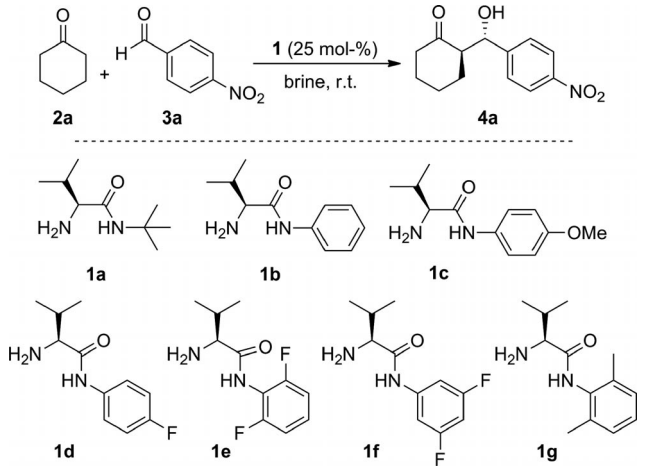
(Table 1). Catalyst **1a** with an alkyl amide afforded the product with 51% *ee* (Table 1, entry 1), whereas **1b**–**g** with an aryl group gave higher enantioselectivities (Table 1, entries 2–7). Catalyst **1c** achieved 83% *ee* but the yield was low (49%; Table 1, entry 3), because the electron-donating group on the aromatic ring led to undesired side reactions. Amongst the catalysts bearing an electron-withdrawing substituent (Table 1, entries 4–6), **1e** significantly improved the enantioselectivity and yield (*syn*/*anti* = 29:71, 96% *ee*; Table 1, entry 5). Unexpectedly, 2,6-dimethylphenyl derivative **1g** produced lower diastereo- and enantioselectivity (*syn*/*anti* = 50:50, 69% *ee*; Table 1, entry 7), indicating that the bulkiness of the aromatic substituent may not be important for high stereoselectivity. Furthermore, both **1c**, which has an electron-donating group, and **1d**, which has an electron-withdrawing group, gave higher enantioselectivity than **1b** (Table 1, entries 3 and 4 vs. entry 2). This suggests that catalyst **1** does not control the stereoselectivity through a hydrogen-bonding interaction between the acidic hydrogen atom on the amide group in **1** and the oxygen atom of **3a**.

Table 1. Asymmetric aldol reaction of aldehyde **3a** with cyclohexanone (**2a**) catalyzed by L-valinamides **1a**–**g**.[a]

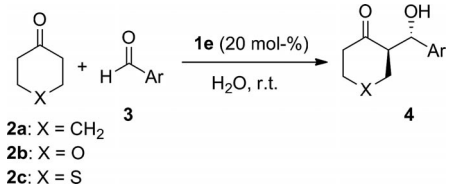


Entry	Catalyst	Time[b] [h]	Yield[c] [%]	*syn*/*anti*[d]	*ee*[e] [%]
1	**1a**	30	79	48:52	51
2	**1b**	24	72	38:62	64
3	**1c**	12	49	31:69	83
4	**1d**	24	70	27:73	81
5	**1e**	70	81	29:71	96
6	**1f**	48	82	24:76	85
7	**1g**	24	76	50:50	69

[a] All reactions were carried out with **2a** (5 equiv.) and **3a** (0.5 mmol) in brine (0.5 mL) in the presence of the catalyst (25 mol-%). [b] Monitored by TLC. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC on a chiral stationary phase for the *anti* product.

After optimizing the reaction conditions (see the Supporting Information), we investigated the generality of the reaction (Table 2). Aromatic aldehydes **3b**–**g** with different substitution patterns and electronic properties were evaluated, and they all afforded the corresponding aldol products in high stereoselectivities and yields (85–93% yield, 87 to >99% *ee*; Table 2, entries 1–6). Introducing a sterically demanding 2-nitrophenyl group (as in **3c**) or a 2,6-dichlorophenyl group (as in **3d**) also led to higher enantioselectivity (Table 2, entries 2 and 3). Furthermore, separate reactions with heterocyclic ketones **2b** and **2c** gave corresponding products **4h** (*syn*/*anti* = 16:84, 83% *ee*; Table 2, entry 7) and **4i** (*syn*/*anti* = 11:89, >99% *ee*; Table 2, entry 8), respectively.

Table 2. Asymmetric aldol reaction of aldehyde **3** with **2** catalyzed by L-valinamide **1e**.[a]



Entry	2	Ar	Time[b] [d]	4	Yield[c] [%]	*syn*/*anti*[d]	*ee*[e] [%]
1	**2a**	3-$NO_2C_6H_4$ (**3b**)	3	**4b**	93	16:84	92
2	**2a**	2-$NO_2C_6H_4$ (**3c**)	3	**4c**	89	19:81	>99
3	**2a**	2,6-$Cl_2C_6H_3$ (**3d**)	3	**4d**	92	1:>99	98
4	**2a**	4-ClC_6H_4 (**3e**)	7	**4e**	88	20:80	90
5	**2a**	Ph (**3f**)	11	**4f**	91	29:71	93
6	**2a**	4-$MeOC_6H_4$ (**3g**)	15	**4g**	85	12:88	87
7	**2b**	4-$NO_2C_6H_4$ (**3a**)	3	**4h**	90	16:84	83
8	**2c**	4-$NO_2C_6H_4$ (**3a**)	3	**4i**	92	11:89	>99

[a] All reactions were carried out with **2** (5 equiv.) and **3** (0.5 mmol) in H_2O (0.5 mL) in the presence of the catalyst (20 mol-%). [b] Monitored by TLC. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC on a chiral stationary phase for the *anti* product.

To elucidate the mechanism of stereoselectivity, our initial computational analysis focused on three enamine structures (Figure 2). All structures were fully optimized at the B3LYP/6-31G(d,p) level with Gaussian 09.[19] The 2,6-dimethylphenyl group of enamine **B** and the 2,6-difluorophenyl group of enamine **C** were inclined at –132.5 and –145.8° to the amide moiety, respectively, whereas the phenyl group was in the same plane as that in enamine **A**. Thus, the *Re* faces of enamines **B** and **C** were blocked by the 2,6-dimethylphenylamide and 2,6-difluorophenylamide, respectively. However, the diastereo- and enantioselectivity obtained with the use of **1e** were higher than those obtained with the use of **1g** (Table 1, entry 5 vs. 7), which suggests that the fluorine atoms are essential for stereocontrol: the 2,6-difluorophenyl group was inclined towards the amide group as a result of the electrostatic repulsion between the amide oxygen atom and a fluorine atom on the aromatic ring, and the hydrogen-bonding interaction between the amide hydrogen atom and the other fluorine atom on the aromatic ring stabilized the conformation.

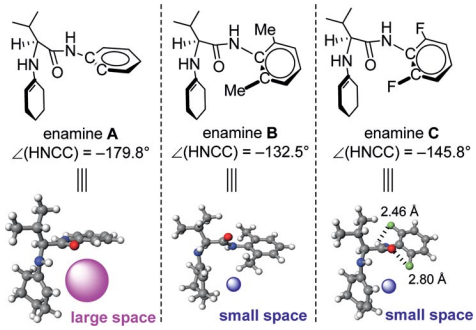


Figure 2. Enamine structures calculated at the B3LYP/6-31G(d,p) level.

The transition-state structures were also examined with DFT calculations (Figure 3, TS1 and TS2).[20] In TS1, which led to the major experimentally observed product, the steric hindrance and the electronic repulsion between the fluorine atom of **1e** and the benzaldehyde oxygen atom would preferentially lead to attack from the *Si* face of the enamine. The continuum solvation model was applied to estimate the barrier height for the aldol reactions, because water plays an important role in the high stereoselectivity.[21] Single-point energy calculations performed by using the geometry optimized at the B3LYP/6-31G(d,p) level with the self-consistent reaction field calculation based on the polarizable continuum model (ε = 78.39 for water) were conducted at the same level as that used for the geometry optimization. We found that the energy of TS1 was lower than that of TS2 by 4.5 kcal mol^{-1}, which was in good agreement with the experimental stereoselectivity results.

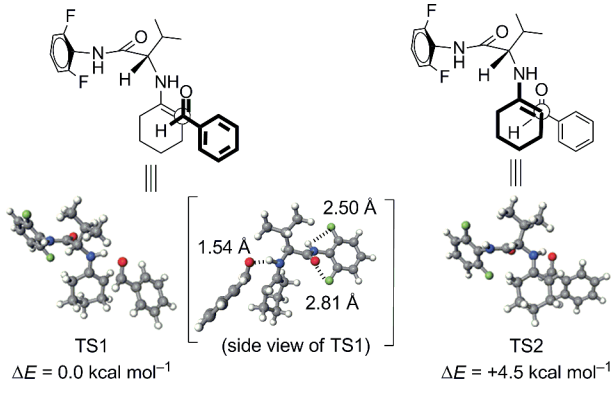
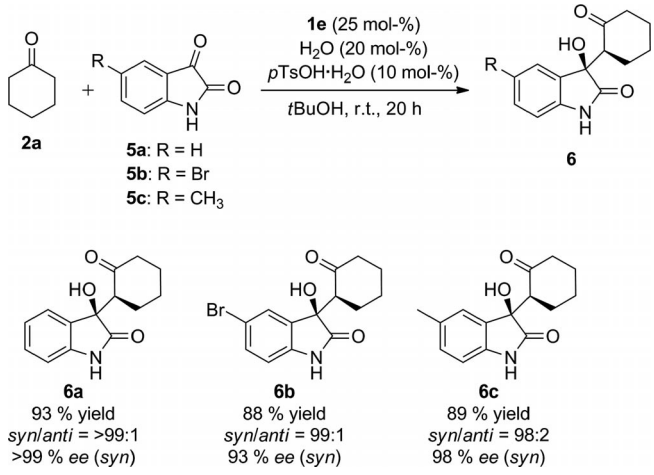


Figure 3. Calculated transition-state models for the asymmetric aldol reaction catalyzed by **1e**.

To demonstrate the utility of our catalyst, we prepared a series of 3-substituted-3-hydroxyindolin-2-ones (**6a**–**c**, Scheme 1), which are desirable targets because many related structural motifs are found in natural products and pharmaceutically active compounds.[22] In particular, cross-aldol product **6a** antagonizes maximal electroshock seizures (*anti*-MES).[23] Although the organocatalytic reactions of cyclohexanone with isatin (**5a**) or substituted isatins have been described,[24] only a few examples have been reported for a highly stereoselective reaction.[24b,24e] In addition, the synthesis of the (2′*S*,3*R*) isomer with excellent stereoselectivities has not been reported.[25] After optimizing the reaction conditions (see the Supporting Information), the reactions of **2a** with isatins **5a**–**c** proceeded smoothly in the presence of catalyst **1e** to afford corresponding aldol products **6a** [*syn*/*anti* = >99:1, >99% *ee* (*syn*)], **6b** [*syn*/*anti* = 99:1, 93% *ee* (*syn*)], and **6c** [*syn*/*anti* = 98:2, 98% *ee* (*syn*)], respectively. The absolute configuration of the products was unambiguously assigned by single-crystal X-ray analysis of **6b**.[26] Generally, the stereochemical courses of both aldol and cross-aldol reactions were the same with the use of the same catalyst. However, it is interesting to note that the aldol reaction with the use of our catalyst occurred on the less-hindered face of the enamine (*Si* face of enamine **C** in Figure 2), whereas the cross-aldol products were formed by *Re* face attack of the enamine. Because isatins bear two basic oxygen atoms, the hydrogen-bonding interaction between the oxygen atom in the isatin and the amide hydrogen atom in the catalyst could give the (2′*S*,3*R*) isomer in excellent stereoselectivity. We are currently conducting detailed mechanistic studies.



Scheme 1. Asymmetric cross-aldol reaction of isatins **5** with cyclohexanone (**2a**) catalyzed by **1e**. All reactions were carried out with **2a** (10 equiv.) and **5** (0.5 mmol) in *t*BuOH (1.0 mL) in the presence of **1e** (25 mol-%), H_2O (20 mol-%), and *p*TsOH·H_2O (10 mol-%, Ts = *para*-toluenesulfonyl).

Conclusions

In conclusion, we have developed a stereocontrol method by using catalyst **1e**, which contains a 2,6-difluorophenylamide group. Catalyst **1e** is inexpensive relative to L-proline derivatives and other organocatalysts and is easily prepared from L-valine. Catalytic asymmetric aldol and cross-aldol reactions by using catalyst **1e** gave the corresponding products in excellent stereoselectivity under mild, environmentally friendly conditions. We are currently conducting further mechanistic studies and exploring the application of the catalyst.

Experimental Section

General Procedure for the Asymmetric Aldol Reaction of Aromatic Aldehydes with Cyclic Ketones: To a stirred solution of the catalyst

(0.125 mmol, 25 mol-%) in H_2O (0.5 mL) was added cyclohexanone (5.0 mmol) and the aldehyde (0.5 mmol) at room temperature under an atmosphere of air. The reaction mixture was stirred at room temperature in a closed system for an appropriate time until the reaction was complete, as monitored by TLC. Then, the mixture was extracted with CH_2Cl_2 (3 × 2 mL), and the organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on SiO_2 (*n*-hexane/CH_3CO_2Et = 4:1) to afford the product.

General Procedure for the Asymmetric Cross-Aldol Reaction of Cyclohexanone with Isatins: To a stirred solution of the catalyst (0.125 mmol), H_2O (0.1 mmol), and *p*TsOH·H_2O (0.05 mmol) in *t*BuOH (1.0 mL) was added cyclohexanone (10.0 mmol) and the isatin (0.5 mmol) at room temperature under an atmosphere of air. The reaction mixture was stirred at room temperature in a closed system for an appropriate time until the reaction was complete, as monitored by TLC. Then, the mixture was extracted with CH_3CO_2Et (3 × 10 mL), and the organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on SiO_2 (*n*-hexane/CH_3CO_2Et = 1:4) to afford the product. The diastereomeric ratios and the enantiomeric excess values of the products were determined by HPLC on a chiral stationary phase.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data including ^1H NMR and ^{13}C NMR spectra of the catalysts and products, crystal structure of **6b**, and computational methods.

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[21] To examine the participation of water molecules in the transition state, we conducted the aldol reaction of 4-nitrobenzaldehyde (**3a**) with an imine prepared from cyclohexanone (**2a**) and catalyst **1e** under anhydrous conditions under an argon atmosphere. Notably, the diastereo- and enantioselectivity of the product were very low (*syn*/*anti* = 42:58, 53% *ee*), showing that water is important in stereocontrol.

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[25] During the course of our study, the preparation of the (2′*S*,3*R*) isomer was reported; however, the *ee* was 82% (*syn*/*anti* = 93:7), see: A. Kumar, S. S. Chimni, *Tetrahedron* **2013**, *69*, 5197.

[26] CCDC-941823 (for **6b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.

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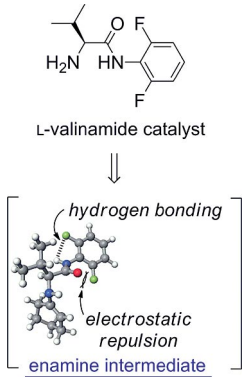
SHORT COMMUNICATION

Organocatalysis

Small, simple, and flexible *N*-(2,6-difluorophenyl)-L-valinamide controls the stereoselectivity in asymmetric aldol and cross-aldol reactions under environmentally friendly conditions. The use of this catalyst in a cross-aldol reaction allows easy access to bioactive 3-hydroxy-3-(2-oxocyclohexyl)indolin-2-one with excellent diastereo- and enantioselectivities.



Keywords: Synthetic methods / Organocatalysis / Asymmetric catalysis / Aldol reactions / Heterocycles

