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Asymmetric Organocatalytic Direct Aldol Reactions of Ketones with α-Keto Acids and Their Application to the Synthesis of 2-Hydroxy-γ-butyrolactones

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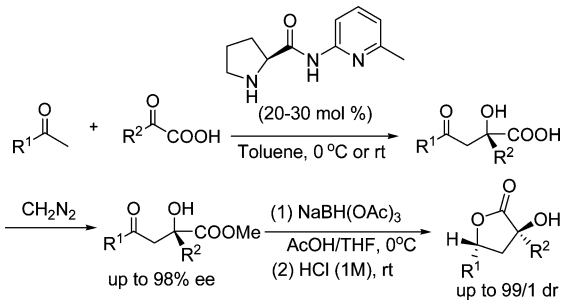

A variety of organocatalysts for the asymmetric direct aldol reactions of ketones with α-keto acids were designed on the basis of molecular recognition and prepared from proline and aminopyridines. The organic molecule **8e**, derived from proline and 6-methyl-2-amino pyridine, was the best catalyst, affording excellent enantioselectivities (up to 98% ee) for the direct aldol reactions of acetone or 2-butanone with a wide range of α-keto acids and for the reactions of various acyclic aliphatic ketones with 3-(2-nitrophenyl)-2-oxopropanoic acid. The aldol adducts could be converted to 2-hydroxy-γ-butyrolactones by reaction sequences of diastereoselective reduction and lactonization. Experimental and theoretical studies on the transition states revealed that the amide N−H and the pyridine N of the organocatalyst selectively form hydrogen bonds with the keto oxygen and the carboxylic acid hydroxy of the α-keto acid, respectively. These two hydrogen-bonding interactions are important for the reactivity and enantioselectivity of the direct asymmetric aldol condensation.

Introduction

The aldol reaction is one of the most important carbon−carbon bond-forming reactions in organic synthesis. Its utility in assembling natural products, in particular those with polyoxygenated subunits,[1] has promoted the rapid evolution of efficient chiral catalysts.[2] As a result, asymmetric catalytic aldol reactions of enol or enolate derivatives with aldehydes have been performed extensively.[2] In contrast to the well-documented aldol reactions with aldehyde acceptors, relatively few aldol reactions involving ketone acceptors have been reported. Copper complexes of C2-symmetric bis(oxazoline)[2f,3] and C1-symmetric sulfoximine ligands[4] have served as efficient and highly

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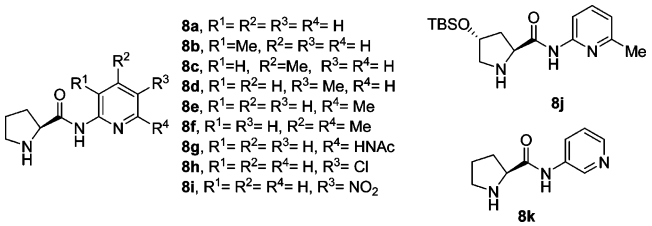
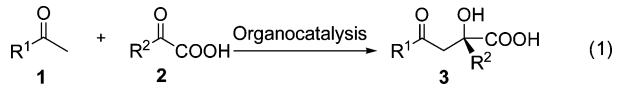


FIGURE 1. Organocatalysts used in this study.

enantioselective catalysts for Mukaiyama-type aldol reactions of pyruvate and glyoxylate esters with enolates. Very recently, a chiral amino acid-based ligand in combination with AgF_2 was reported to afford efficient and highly enantioselective catalysis of Mukaiyama aldol reactions of enolsilanes with α-keto esters.[5]

Because direct aldol reactions are atom-efficient alternatives of processes using enol or enolate derivatives as the aldol donor, asymmetric catalytic variants have attracted considerable attention. Accordingly, the highly enantioselective direct aldol reactions of aldehydes with ketones in the presence of catalytic amounts of bifunctional Lewis acids have been reported.[6] Since the seminal finding that L-proline could catalyze the direct aldol reaction,[7,8] many chiral organocatalysts have been discovered for direct aldol reactions.[9−21] Despite these successes, there have been few reports of direct aldol reactions with ketones as acceptors, which thus remain a great challenge for organic chemists. Recently, a proline-catalyzed direct aldol reaction of α-keto esters with aldehydes was reported.[22] In this case, only highly active α-keto esters, which contained two electron-withdrawing groups conjugated to a keto function, were investigated as acceptors. More recently, the proline-catalyzed asymmetric aldol reaction between cyclohexanone and phenylglyoxylate was used for the synthesis of a key intermediate in the preparation of (*S*)-oxybutynnin.[23] Direct aldol reactions between α-keto phosphonates and ketones in the presence of proline were also performed with high enantioselectivities.[24] However, with the exception of our previous work, there have been no reports of organocatalytic direct asymmetric aldol reaction of ketones with keto acids.[25] Herein, we report our further studies on the reaction of ketones with α-keto acids catalyzed by organic molecules. α-Hydroxy carboxylic acids with a tertiary stereogenic center were formed directly with high enantioselectivities (up to 98% ee) (eq 1), and 2-hydroxy-γ-butyrolactones were obtained with high yields from the aldol adducts.



(1)

Results and Discussion

Design of Organocatalysts for the Direct Aldol Reaction of Ketones with α-Keto Acids. Molecular recognition phenomena are critically important in the actions of enzymes on substrates. A large number of enzyme-mimetic systems such as crown ethers,[26] cryptands,[27] cyclodextrins,[28] and capsules[29] have been devised as artificial receptor sites to bind appropriate guest molecules or ions. Since the finding by Hamilton and coworkers that the acylaminopyridine function can form specific hydrogen bonds with a carboxyl group (**6**, Scheme 1),[30] organic

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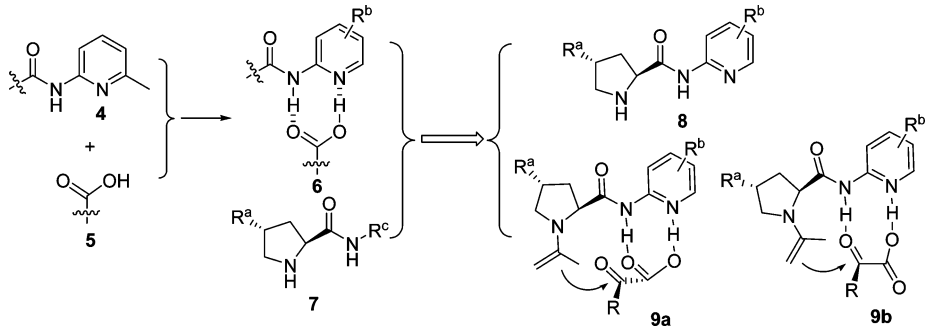
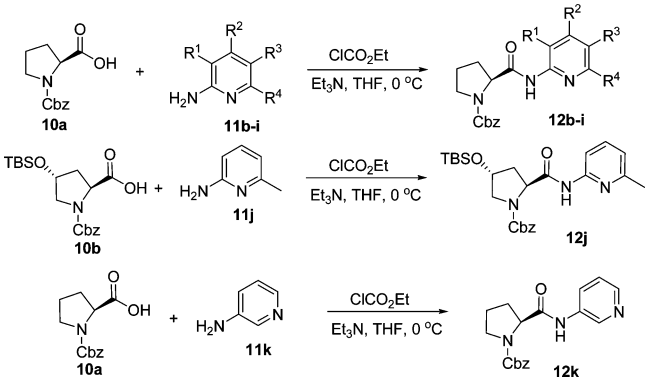
SCHEME 1. General Strategy for the Design of Organocatalysts



SCHEME 2. Preparation of *N*-Cbz-L-proline Amides 12b−k

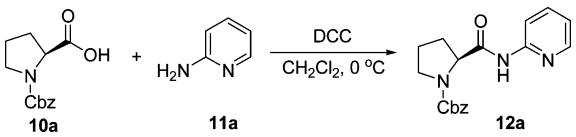


molecules containing the acylaminopyridine moiety have been developed for the self-assembly of supramolecular architectures[31] and for the molecular recognition of carboxylic acids.[32] The concept of molecular recognition has been employed to design organocatalysts for some asymmetric reactions.[33]

In our endeavors to design new, efficient, and highly enantioselective organocatalysts, we recently discovered that prolinamide derivatives **7** catalyzed the direct aldol reaction via an enamine intermediate with high stereoselectivity.[15] The previous successes in supramolecular chemistry with acylaminopyridine-based receptors and in prolinamide catalysis led us to hypothesize that the incorporation of pyrrolidine-2-carboxylic acid amide and aminopyridine in a single molecule would result in chiral organocatalysts **8**. According to the molecular recognition model of **6**, organocatalysts **8** would be able to catalyze the direct aldol reaction of ketones with α-keto acids via two possible transition states, **9a** and **9b** (Scheme 1). In principle, **9a** would be more stable than **9b** because dual hydrogen-bonded structures similar to **9a** have been commonly observed.[30] However, **9b** would undergo the aldol reaction more easily than **9a** because the keto group in **9b** is activated by a hydrogen bond.[15]

Preparation of Organocatalysts 8a−k. Organic molecules **8a−k** (Figure 1) were prepared starting with coupling reactions of *N*-Cbz-L-proline (**10a**) or *N*-Cbz-4-*tert*-butyldimethylsilyloxy-L-proline (**10b**) with 2-amino pyridines **11b−k** in the presence of stoichiometric amounts of ClCOOEt and triethylamine, affording the corresponding amides **12b−k** (Scheme 2).

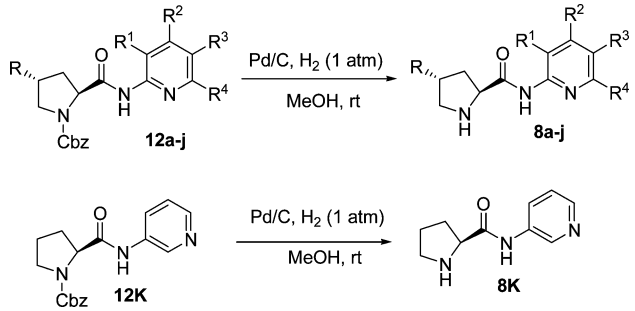
However, the condensation of *N*-Cbz-L-proline (**10a**) with amino pyridine (**11a**) failed to give the corresponding proline amide **12a**. Amide **12a** was obtained in 64% yield by coupling of *N*-Cbz-L-proline with the corresponding amino pyridine (**11a**) in the presence of DCC (eq 2).



(2)

The *N*-Cbz-L-proline amides **12a−k** were subjected to hydrogenolysis catalyzed by 5% Pd/C under 1 atm of hydrogen in methanol to give the desired organocatalysts **8a−k** in 43−81% yields (Scheme 3).

SCHEME 3. Hydrogenolysis of Compounds 12a−k



Optimization of Reaction Conditions and Screening of Organocatalysts 8. The direct aldol reaction of benzoylformic acid with neat acetone was first performed in the presence of 20 mol % of **8a** at room temperature. As anticipated, the reaction worked well to give the desired product **3a**, which was converted directly to **13a** by treatment of the reaction mixture with CH_2N_2 for the convenient measurement of enantiomeric excess. Compound **13a** was isolated in high yield (93%), albeit with modest enantioselectivity (51% ee, Table 1, entry 1). A survey of

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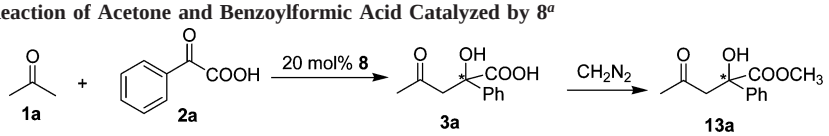
TABLE 1. Direct Aldol Reaction of Acetone and Benzoylformic Acid Catalyzed by 8[a]



entry	catalyst **8**	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**8a**	acetone	25	24	93	51
2	**8a**	toluene	25	24	92	53
3	**8a**	THF	25	24	86	36
4	**8a**	CH_2Cl_2	25	24	70	32
5	**8a**	DMSO	25	24	65	12
6	**8a**	toluene	10	48	95	75
7	**8a**	toluene	0	48	98	87
8	**8b**	toluene	0	48	86	79
9	**8c**	toluene	0	48	86	87
10	**8d**	toluene	0	48	90	90
11	**8e**	toluene	0	48	>99	92
12	**8f**	toluene	0	48	>99	90
13	**8g**	toluene	0	48	30	74
14	**8h**	toluene	0	48	94	78
15	**8i**	toluene	0	48	30	78
16	**8j**	toluene	0	48	70	90
17	**8k**	toluene	0	48	22	−9

[a] A mixture of benzoylformic acid **2a** (0.5 mmol), catalyst **8** (0.1 mmol), and acetone **1a** (1.0 mL) in toluene (2.0 mL) was stirred at 0 °C for 48 h. [b] Isolated yield of **13a**. [c] The ee value of **13a** determined by chiral HPLC.

solvents revealed that performance of the reaction in toluene gave the highest enantioselectivity (entries 1−5). Lowering the reaction temperature could substantially enhance the enantioselectivity. High enantioselectivity (87% ee) was observed when the reaction was carried out at 0 °C (entry 7).

Under the optimized conditions, prolinamides **8b**−**k** were evaluated for catalysis of the model direct aldol reaction of benzoylformic acid with acetone. As shown in Table 1, prolinamides **8b**−**k**, prepared from *N*-Cbz-L-proline and pyridine derivatives, were able to catalyze efficiently the direct aldol reaction of acetone with benzoylformic acid (Table 1, entries 8−17). Subtle variations in the substituent of the organocatalyst affected the performance of the reaction. Thus, organocatalysts **8b**−**e**, which contain an additional methyl group on the pyridine ring compared with **8a**, catalyzed the direct aldol reaction in high yields, with varying enantioselectivities that depended on the position of the methyl group (entries 8−11). In terms of yield and enantioselectivity, **8e** proved to be the best organocatalyst (entry 11). One more methyl group was introduced to the pyridine moiety, resulting in **8f**, which exhibited decreased enantioselectivity (entry 12). Organocatalyst **8g**, in which the methyl group was replaced with an acetylamino group, gave dramatically deteriorated yield and enantioselectivity, indicating that the introduction of an additional hydrogen bond donor negatively affected the catalytic performance (entry 13). Introducing either a chloro or nitro group to the pyridine moiety was substantially deleterious to the stereochemical outcome. Accordingly, the use of **8h** or **8i** as a catalyst afforded moderate enantioselectivity (entries 14 and 15). Organocatalyst **8j**, derived from 3-hydroxylproline and 6-methyl-2-aminopyridine, showed comparable enantioselectivity but slightly reduced catalytic activity compared with its analogue **8e** (entry 16). Interestingly, catalyst **8k** derived from 3-aminopyridine, which is theoretically unable to form double hydrogen bonds with the substrate, catalyzed the direct aldol reaction of acetone with benzoylformic acid with a very low yield (22%) and enantioselectivity (−9% ee) and with a reversed configuration (entry 17). This result demonstrates the importance of the double hydrogen bonds and suggests that the reaction proceeds via the transition state **9a** or **9b**.

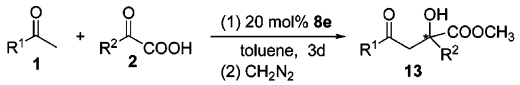
The protocol was then extended to direct aldol reactions of acetone or 2-butanone with a variety of α-keto acids including both aromatic and aliphatic acids (Table 2). The aldol reactions with acetone as a donor proceeded smoothly at 0 °C to afford aldol adducts with a tertiary center in high yields (up to >99%) and high enantioselectivities (up to 98% ee), regardless of the electronic and steric natures of the substituent of the keto acids (Table 2, entries 1−7). The absolute configuration of **13c** was determined to be *R* for the chiral carbon by X-ray crystallography.[25] However, 2-butanone was less reactive than acetone toward the keto acids probably because it forms a more sterically hindered enamine in comparison with acetone. Thus, the protocol that is optimal for the direct aldol reactions of acetone with keto acids failed to afford complete aldol reactions of butanone with keto acids, although the enantioselectivities were high (entries 8 and 10). Increasing the reaction temperature from 0 °C to room temperature for the aldol reactions involving 2-butanone resulted in high yields with enantioselectivities ranging from 81% to 96% ee (Table 2, entries 9 and 11−13).

The generality of the catalyst **8e** for ketone donors was also investigated. Aldol reactions of **2h** with several acyclic ketones were examined under the promotion of either 20 or 30 mol % of **8e** at room temperature in toluene (Table 3). In the presence of 20 mol % of **8e**, the reactions proceeded incompletely to give the linear aldol adducts in moderate yields (up to 65%), albeit with high enantioselectivities (87−96% ee). Increasing the catalyst loading from 20 to 30 mol % substantially enhanced the yields and, in general, slightly improved the enantioselectivities (88−97% ee).

2-Hydroxy-γ-butyrolactone and its structural analogues constitute an important class of chiral synthetic intermediates that have been used to assemble natural products and biologically active compounds.[34] New methods for the efficient production

(34) Wee, A. G. H.; Liu, B. S.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404.

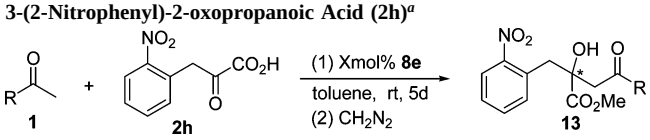
TABLE 2. Direct Aldol Reaction of Acetone or 2-Butanone with α-Keto Acids Catalyzed by 8e[a]



entry	product	R_1	R_2	temp. (°C)	yield (%)[b]	ee (%)[c]
1	**13b**	CH_3 (**1a**)	 (**2b**)	0	>99	93
2	**13c**	CH_3 (**1a**)	 (**2c**)	0	78	93
3	**13d**	CH_3 (**1a**)	$PhCH_2$ (**2d**)	0	75	98
4	**13e**	CH_3 (**1a**)	CH_3 (**2e**)	0	78	92
5	**13f**	CH_3 (**1a**)	CH_3CH_2 (**2f**)	0	85	95
6	**13g**	CH_3 (**1a**)	$(CH_3)_2CHCH_2$ (**2g**)	0	96	96
7	**13h**	CH_3 (**1a**)	$2\text{-}NO_2C_6H_4CH_2$ (**2h**)	0	93	96
8	**13i**	CH_3CH_2 (**1b**)	$2\text{-}NO_2C_6H_4CH_2$ (**2h**)	0	23	95
9	**13i**	CH_3CH_2 (**1b**)	$2\text{-}NO_2C_6H_4CH_2$ (**2h**)	25	83	96
10	**13j**	CH_3CH_2 (**1b**)	Ph (**2i**)	0	14	91
11	**13j**	CH_3CH_2 (**1b**)	Ph (**2i**)	25	52	81
12	**13k**	CH_3CH_2 (**1b**)	$(CH_3)_2CHCH_2$ (**2g**)	25	58	92
13	**13l**	CH_3CH_2 (**1b**)	$PhCH_2$ (**2d**)	25	64	93

[a] A mixture of benzoylformic acid **2** (0.5 mmol), catalyst **8e** (0.1 mmol), and ketone **1** (1.0 mL) in toluene (3.0 mL) was stirred for 72 h. [b] Isolated yield of **13**. [c] The ee value of **13** determined by chiral HPLC.

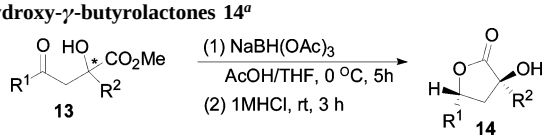
TABLE 3. Direct Aldol Reactions of Ketones with 3-(2-Nitrophenyl)-2-oxopropanoic Acid (2h)[a]



entry	product	R	mol % **8e**	yield (%)[b]	ee (%)[c]
1	**13i**	CH_3CH_2 (**1c**)	30	91	95
2	**13m**	$CH_3(CH_2)_2$	20 (30)	43 (63)	96 (97)
3	**13n**	$CH_3(CH_2)_3$	20 (30)	61 (74)	93 (95)
4	**13o**	$CH_3(CH_2)_4$	20 (30)	65 (80)	87 (93)
5	**13p**	$CH_3(CH_2)_5$	20 (30)	54 (67)	89 (92)
6	**13q**	$CH_3(CH_2)_6$	20 (30)	33 (56)	89 (91)
7	**13r**	$CH_3(CH_2)_7$	20 (30)	<20 (41)	ND (88)
8	**13s**	$Ph(CH_2)_2$	20 (30)	42 (55)	91 (93)
9	**13t**	CH_3SCH_2	20 (30)	43 (62)	91 (91)
10	**13u**		20 (30)	45 (59)	95 (95)

[a] A mixture of benzoylformic acid **2h** (0.5 mmol), catalyst **8e**, and ketone **1** (1.0 mL) in toluene (3.0 mL) was stirred for 120 h. [b] Isolated yield of **13**. [c] The ee value of **13** determined by chiral HPLC.

TABLE 4. Diastereoselective Reduction of 13 and Preparation of 2-Hydroxy-γ-butyrolactones 14[a]



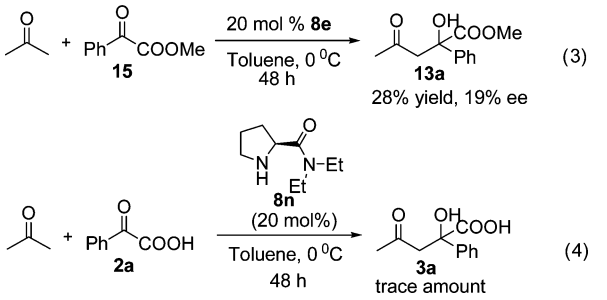
entry	**13**	R_1	R_2	**14**	dr (anti /syn)[b]	yield (%)[c]
1	**13a**	CH_3	Ph	**14a**	95/5	94
2	**13g**	CH_3	$(CH_3)_2CHCH_2$	**14b**	97/3	90
3	**13h**	CH_3	$2\text{-}NO_2C_6H_4CH_2$	**14c**	98/2	93
4	**13h**	CH_3	$2\text{-}NO_2C_6H_4CH_2$	**14c**	18/82	80[d]
5	**13i**	CH_3CH_2	$2\text{-}NO_2C_6H_4CH_2$	**14d**	96/4	95
6	**13m**	$CH_3(CH_2)_2$	$2\text{-}NO_2C_6H_4CH_2$	**14e**	99/1	95
7	**13n**	$CH_3(CH_2)_3$	$2\text{-}NO_2C_6H_4CH_2$	**14f**	95/5	95
8	**13o**	$CH_3(CH_2)_4$	$2\text{-}NO_2C_6H_4CH_2$	**14g**	94/6	93
9	**13p**	$CH_3(CH_2)_5$	$2\text{-}NO_2C_6H_4CH_2$	**14h**	96/4	81
10	**13t**	CH_3SCH_2	$2\text{-}NO_2C_6H_4CH_2$	**14i**	99/1	89

[a] The reaction was carried out at a 0.2-mmol scale. [b] Determined by ^1H NMR. [c] Isolated yield of **14**. [d] Reduced diastereoselectively by BH_3 in THF.

of structurally diverse, enantioenriched 2-hydroxy-γ-butyrolactones are desirable. Diastereoselective reduction of compounds **13** with $NaBH(OAc)_3$ in a solvent mixture of acetic acid and THF at 0 °C, followed by a one-pot lactonization with hydrochloric acid (1.0 M), gave rise to 2-hydroxy-γ-butyrolactones **14** in high yields (Table 4). This protocol favored the formation of *anti*-2-hydroxy-γ-butyrolactones, with excellent diastereomeric ratios (95/5−99/1) that slightly depended on the structures of compounds **13**. However, the reduction of **13h** with BH_3 in THF led to the favorable formation of *syn*-**14c** (entry 4), the structure of which was determined by X-ray crystallographic analysis (see the Supporting Information).

Studies of Transition States. To clarify which of the proposed transition state structures, **9a** or **9b**, governs the reaction pathway, aldol reactions of acetone with keto acid **2a** or its ester **15** were carried out in the presence of **8n** or **8e** as catalyst, respectively. In this way, the role of hydrogen bonding in controlling the reactivity and stereoselectivity of the reactions was explored. The aldolization of methyl benzoylformic ester (**15**) with acetone yielded **13a** in a 28% yield with poor enantioselectivity (eq 3), implying that the interaction between the carboxylic acid and pyridinyl group is important for the reaction, and a single hydrogen bond is insufficient to control the stereoselectivity.

The use of L-proline amide **8n**, which is unable to provide a proton from an amide N−H to form a hydrogen bond, to catalyze the aldol reaction of **2a** with acetone gave **3a** in a trace amount (eq 4). This result provides indirect evidence that the hydrogen bond formed between the keto and amide N−H exists



and plays a crucial role in promoting the reaction. Thus, this organocatalyzed reaction more likely proceeds via **9b** than **9a**.

To determine how many molecules of the catalyst participate in the reaction, the quantitative relationship between the optical purity of **8e** and that of the product **13a** was investigated. Plotting the enantiomeric excess of **13a** versus that of **8e** resulted in a perfect linear correlation (Figure 2). This result is consistent with the possible transition state **9b** (Scheme 1). Thus, a single molecule of **8e** participates in the reaction.

A set of relevant ab initio calculations on the mechanistic aspects of catalysis by proline and its derivatives indicated that the formation of enamine intermediates and/or C−C bonds is rate limiting. Furthermore, protonation of the carbonyl group of the aldehyde or ketone acceptor by hydrogen bonding with the enamine is crucial to activate the carbonyl carbon atom with improved electrophilicity and to simultaneously induce the stereoselectivity of the addition of the enamine olefin to the carbonyl carbon.[35]

To further understand the role of hydrogen bonds in controlling the reactivity and stereochemistry, theoretical calculations were performed on the direct asymmetric aldol reaction catalyzed by **8a** in toluene. By using different hydrogen-bonding models, we studied possible structures of the complex formed by the enamine intermediate generated from **8a**, acetone, and benzoylformic acid (**2a**). The corresponding transition states and subsequent intermediates were calculated with the Gaussian 03 program package.[36] To assess the influences of oxygen polarization and diffuse functions, the DFT variant hybrid density functional theory (B3LYP) was used in conjunction with the 6-31+G(d) basis set. The geometries of stationary points and first-order saddle points were identified by frequency analysis, and each transition structure was validated with one and only one imaginary frequency related to the formation of a C−C bond. The energy of each structure was evaluated and corrected by calculated zero-point energies and thermal effects from the frequency analysis by using the B3LYP/6-31+G(d) method. Solvent effects were not considered in these calculations because the toluene likely has little influence on reaction selectivity through affecting hydrogen bonding by its polarity, whereas the function of the ketone, a reagent present in excess amount, as a solvent is too subtle to be explored in detail in this reaction system. Thus, we carefully explored all possible conformers of the initially formed, energetically favorable complex structures and the corresponding transition states in the gas phase.

In the complexes formed from the enamine and benzoylformic acid, the hydroxy of the carboxylic group might contact either the carboxylic carbonyl or the keto group of benzoylformic acid, leading to the formation of five possible complex structures with relatively lower energies (Figure 3). Complex-**Ia** and complex-**III** were predicted to be much more stable than the other complexes due to the double H-bonds formed between the enamime and α-keto acid. Complex-**Ia** and complex-**III** differ in the orientation of the hydroxy of the carboxylic acid. Complex-**III** is more stable than complex-**Ia** by ∼2.5 kcal/mol due to the carboxylic acid predominantly adopting a *syn*-conformation[37] (dihedral angle O═C−O−H ≈ 0°) and to the stronger double H-bonds, which are slightly shorter than those of complex-**Ia**. In comparison with complexes **Ia** and **III**, which both possess double H-bonds, complexes **Ib**, **IIa**, and **IIb** are much less stable because they have single H-bonds. In addition, the binding interactions in complexes **Ib**, **IIa**, and **IIb,** with predicted binding enthalpy energies of 0−1 kcal/mol, are much weaker than those in complexes **Ia** and **III,** with predicted binding enthalpy energies of 6−9 kcal/mol (Table 5). These observations indicate that complex-**Ia** and complex-**III**, which reversibly interconvert, were predominantly formed and governed the reaction pathway.

We next studied the corresponding transition states (TS) of the located complexes **I**, **II**, and **III**. The located TS structures are shown in Figure 4, and the related energies are given in

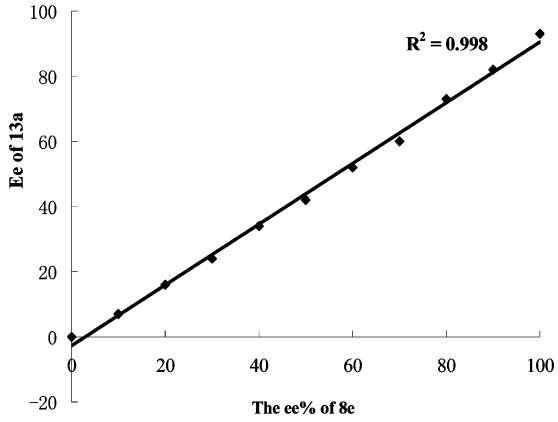


FIGURE 2. Linear relationship between enantiomeric excesses of product **13a** and catalyst **8e** in the direct aldol reaction of benzoylformic acid (**2a**) with acetone in toluene.

TABLE 5. Calculated Energies of Complexes of Enamine Intermediate with α-Keto Acid

entry	complexes	$\Delta H_{binding}$ (kcal/mol)	$\Delta H_{relative}$ (kcal/mol)	$\Delta G_{relative}$ (kcal/mol)
1	complex-**Ia**	−6.43	2.45	2.52
2	complex-**Ib**	−0.25	8.62	8.68
3	complex-**IIa**	−0.05	8.82	8.37
4	complex-**IIb**	−1.23	7.65	8.00
5	complex-**III**	−8.88	0.00	0.00

TABLE 6. Calculated Relative Energies of the TS and the Activation Energies

entry	transition state (TS)	ΔH_{active}	ΔG_{active}	$\Delta H_{relative}$	$\Delta G_{relative}$
1	TS-**Ia**	13.27	19.1	0.00	0.00
2	TS-**Ib**	10.41	17.3	3.31	2.53
3	TS-**IIa**	15.04	19.2	6.97	5.59

(35) (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911. (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (d) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 5155.

(36) Frisch, M. J.; et al. *Gaussian03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(37) Evanseck, J. D.; Houk, K. N.; Brigss, J. M.; Jorgensen, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 10630.

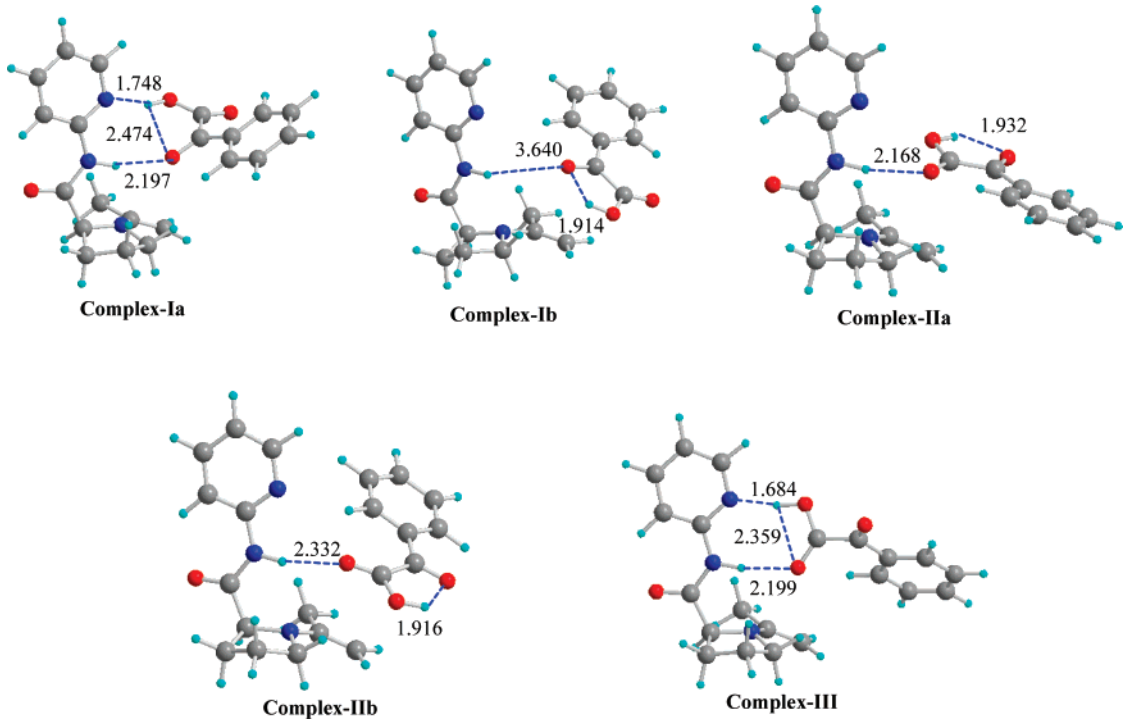


FIGURE 3. Calculated complex structures of enamine intermediate with α-keto acid.

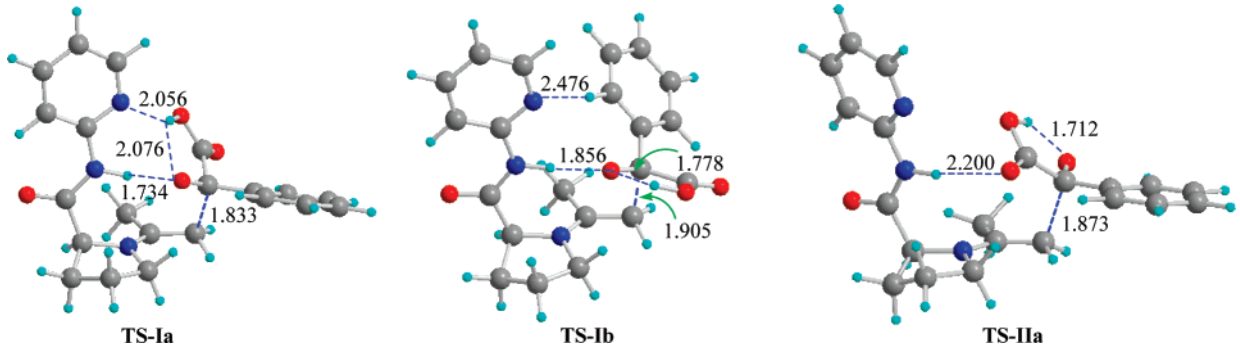


FIGURE 4. Calculated transition state structures from complexes **Ia**, **Ib**, and **IIa**.

Table 6. The most favorable transition state structure is TS-**Ia** located from complex-**Ia**, which yields the major product **3a**, because of the stabilization arising from the double H-bonds. TS-**Ib** located from complex-**Ib**, which gives the enantiomer of **3a**, is less stable than TS-**Ia** by ∼3.3 kcal/mol because only one H-bond is formed between the amide N−H and keto, and the acid group is distant from the pyridine ring. In both TS-**Ia** and TS-**Ib**, the keto carbonyl oxygen is protonated by two H-bonds to make the keto group more electrophilic. TS-**IIa** located from complex-**IIa**, which gives the same product as TS-**Ib**, is predicted to be less stable than TS-**Ia** by ∼7 kcal/mol due to its keto group being activated by only one H-bond. However, attempts to locate the TS structure from complex-**III**, in which the keto group is naked and not activated by any hydrogen bond such that the keto group is too inactive to react with the enamine, failed due to the highly unstable zwitterionic character of the forming TS structure. Zwitterionic transition structures are extremely disfavored[38] due to the poor electrophilicity of the keto carbonyl carbon without activation by an H-bond and to the high energetic penalty accrued by charge separation. To confirm the specific destabilization of the zwitterion, the intermediates resulting from related TS structures were studied further (Figure 5). Again, and not surprisingly, no stable zwitterion structure could be located from complex-**III**. On the basis of the intermediate structures from TS-**Ia** and TS-**Ib**, geometry optimization of the zwitterionic intermediate from complex-**III** with a fixed C−C bonding length of 1.685 Å was undertaken to estimate the relative stability of intermediate **III** versus TS-**Ia**, -**Ib**, and -**IIa**. The zwitterionic intermediate from complex-**III** was predicted to be less stable than TS-**Ia** by ∼21 kcal/mol (see the Supporting Information).

The free energy barrier to form TS-**Ia** is predicted to be 19.1 kcal/mol, ∼1.8 kcal/mol higher than the barrier to form TS-**Ib** but almost identical with the barrier to form TS-**IIa**. It seems that these calculations are in disagreement with the experimental major product from TS-**Ia**. However, as mentioned previously, TS-**Ia** is ∼3.3 kcal/mol more stable than TS-**Ib** and ∼7 kcal/mol more stable than TS-**IIa**. The extra barrier for the formation of TS-**Ia** comes from the much greater stability of complex-**Ia**, which is more favorable than both complex-**Ib** and complex-

(38) Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912.

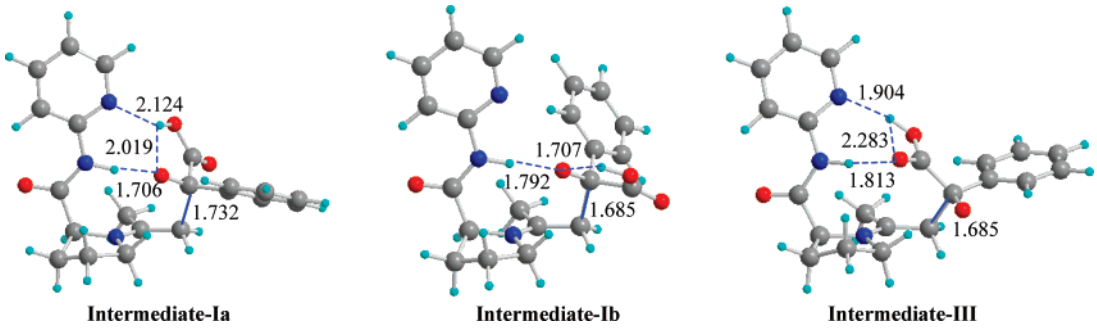


FIGURE 5. Calculated intermediate structures.

IIa by ~6 kcal/mol. Although the higher stability of complex-**Ia** slightly increases the activation energy of TS-**Ia**, the formation of complex-**Ia** is much more favorable and facilitates the aldol addition. On the other hand, although the most stable complex was predicted to be complex-**III**, the forming transition state with zwitterionic character is so unstable that the extremely high activation barrier inhibits the reaction. These results are highly consistent with the experimental observations of the reactions in toluene and substantiate the proposed transition state model **9b** (Scheme 1).

Conclusions

On the basis of the concept that an acylaminopyridine can form specific hydrogen bonds with a carboxyl group, we designed a variety of organocatalysts for catalyzing the asymmetric direct aldol reaction of ketones with α-keto acids. These organocatalysts were prepared from L-proline and aminopyridines. The organic molecule **8e**, derived from L-proline and 6-methyl-2-aminopyridine, was the best catalyst. Organocatalyst **8e** afforded excellent enantioselectivities (up to 98% ee) for the direct aldol reactions of acetone or 2-butanone with a wide range of α-keto acids, including both aromatic and aliphatic α-keto acids, and for the reactions of various acyclic aliphatic ketones with 3-(2-nitrophenyl)-2-oxopropanoic acid. The aldol adducts were effectively converted to 2-hydroxy-γ-butyrolactones by convenient reaction sequences of diastereoselective reduction and lactonization. A linear correlation of the enantiomeric excess of catalyst **8e** with that of the aldol product **13a** was observed, indicating that a single molecule of catalyst is involved in the reaction. Experimental studies showed that the double hydrogen bonds formed between the 2-aminopyridine of the organocatalyst and the keto and carboxyl groups of the α-keto acid are important for catalytic activity and enantioselectivity. Theoretical studies on the transition states revealed that the amide N−H and the pyridine N form hydrogen bonds selectively with the keto carbonyl oxygen and acid hydroxy, respectively. These specific H-bonding interactions act simultaneously to induce stereoselectivity, protonate the keto, and promote the formation of the precursor and transition state. The present studies have demonstrated the key roles of multihydrogen-bonding interactions in asymmetric catalytic aldol reactions and suggest a useful strategy for the design of organocatalysts for asymmetric organic reactions and related transformations.

Experimental Section

General Procedure for the Synthesis of 12. Compound **10a** or **10b** (2.0 g, 8.0 mmol) and TEA (0.81 g, 8.0 mmol) were dissolved in THF (30 mL). The solution was cooled to 0 °C. Then, ethylchloroformate (0.88 g, 8.0 mmol) was added dropwise to the solution for 15 min. After the solution was stirred for 30 min, one of the amino pyridines **11b**−**k** (8.0 mmol) was added for 15 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature for another 16 h, and then refluxed for 3 h. After being cooled to room temperature, the solution was diluted with ethyl acetate. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent, hexane/ethyl acetate = 2/1) to give **12b**−**k**.

Compounds **10a** (2.0 g, 8.0 mmol) and **11a** (8.0 mmol) were dissolved in dichloromethane (40 mL). The solution was cooled to 0 °C, and then DCC (3.2 g, 16.0 mmol) was added. The solution was stirred at 0 °C for 2 h and at room temperature for another 12 h. Then the solution was placed in the refrigerator for 2 h, and the white solid was filtered. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent, hexane/ethyl acetate = 4/1; then dichloromethane/ethyl acetate = 4/1) to give **12a**.

Typical Procedure for the Synthesis of 8h. Compounds **12h** (1.0 g), 5% Pd/C (0.1 g), and methanol (30 mL) were mixed in a two-necked flask (100 mL). After stirring under hydrogen (1 atm) for 1 h, the solution was filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent, hexane/ethyl acetate = 2/1) to give **8h** in 52% yield. **Pyrrolidine-2-carboxylic acid (5-chloropyridin-2-yl)-amide (8h):** Yield: 52%; mp 92−94 °C; ^{1}HNMR (400M Hz, $CDCl_3$) δ (ppm) 1.77 (m, 2H), 2.04 (m, 2H), 2.22 (m, 1H), 3.06 (m, 2H), 3.88 (m, 1H), 7.65(m, 1H), 8.25 (m, 2H), 10.23 (brs, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ (ppm) 26.3, 30.9, 47.4, 61.0, 114.3, 126.5, 137.8, 146.6, 149.5, 174.4; IR (neat): 3346, 3229, 2948, 1680, 1533, 1417, 1301, 1097, 846, 749, 535; HRMS (ESI-MS) exact mass calcd for $(C_{10}H_{11}ClN_2O+Na)^+$; requires 233.0458 m/z, found, 233.0467 m/z.

Typical Procedure for Aldol Reaction of 13h. To a mixture of anhydrous acetone (1 mL) and toluene (3 mL) were added the corresponding α-keto acid (0.5 mmol) and catalyst **8e** (0.1 mmol). The resulting mixture was stirred at 0 °C for 72 h. The reaction mixture was treated with CH_2N_2 solution in ether for 20 min. After removal of solvent, the residue was purified by flash column chromatography on silica gel (eluent, hexane/ethyl acetate = 7/1) to give the pure adducts **13h** in 93% yield.

2-Nitrobenzyl-2-hydroxy-4-oxo-2-phenylpentanoic acid methyl ester (13h): mp 85−86 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 2.13 (s, 3H), 2.81 (d, J = 17.3 Hz, 1H), 3.15 (d, J = 17.4 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.67 (s, 3H), 3.71 (s, 1H), 7.35−7.42 (m, 2H), 7.48−7.50 (m, 1H), 7.81−7.84 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ (ppm) 30.7, 40.0, 51.2, 52.9, 75.6, 124.6, 128.2, 129.3, 132.2, 133.3, 151.0, 174.6, 206.7; IR (neat) 3540, 2938, 1737, 1414, 1340, 1214, 1145, 797, 739, 680, 603, 516 cm^{-1}; HRMS (ESI-MS) exact mass calcd for $(C_{13}H_{15}N_1O_6 + Na)^+$ requires 304.0792 *m/z*, found 304.0785 *m/z*. Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min, major-isomer, t_R 10.630 min, minor-isomer, t_R 12.183 min.

Typical Procedure for the Preparation of 14a.[39] Acetic acid (300 μL) was added to a suspension of $NaBH(OAc)_3$ (127 mg, 0.6 mmol) in THF (2 mL) at 0 °C. After 10 min, a solution of aldol product **13a** (0.2 mmol) in THF (1 mL) was added. The reaction was stirred for 5 h at 0 °C, and then warmed to room temperature. HCl (1 N, 3 mL) was added to the reaction solution and the two-phase mixture was stirred for an additional 3 h. After neutralizing with 20% NaOH solution, the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (eluent, hexane/ethyl acetate = 3/1) to give **14a** in 94% yield.

3-Hydroxy-5-methyl-3-phenyldihydrofuran-2(3*H*)-one (14a): mp 63−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.39 (d, J = 2.6 Hz, 3H), 2.04 (dd, J_1 = 13.7 Hz, J_2 = 8.6 Hz, 1H), 2.68 (dd, J_1 = 13.7 Hz, J_2 = 5.8 Hz, 1H), 3.69 (br s, 1H), 4.82−4.87 (m, 1H), 7.30−7.40 (m, 5H); IR (neat) 3403, 2977, 1766, 1494, 1436, 1379, 1340, 1184, 1117, 1029, 962, 865, 778, 719, 680, 651, 565, 535, 467 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.6, 47.1, 74.9, 78.8, 125.4, 128.3, 128.5, 140.4, 177.0; HRMS (ESI-MS) exact mass calcd for $(C_{11}H_{12}O_3 + Na)^+$ requires 215.0679 *m*/*z*, found 215.0669 *m*/*z*.

(39) Aggarwal, V. K.; Bae, I.; Lee, H. Y. *Tetrahedron* **2004**, *60*, 9725.

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Supporting Information Available: Characterization of new compounds, ^{1}HNMR and ^{13}CNMR spectra of new compounds, selected HPLC spectra of aldol products, calculated energies, and Cartesian coordinates of the calculated structures as well as CIF files and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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