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Design of Highly Enantioselective Organocatalysts Based on Molecular Recognition

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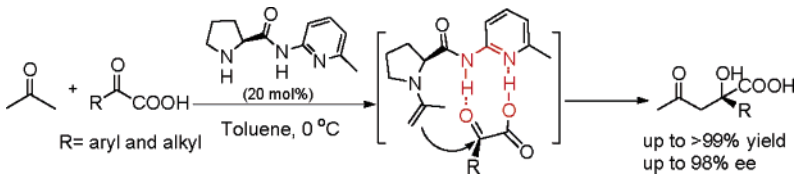
ABSTRACT



Various organocatalysts have been designed based on molecular recognition to catalyze the asymmetric direct aldol reaction of ketones with aryl and alkyl α-keto acids, affording β-hydroxyl carboxylic acids with a tertiary stereogenic center with excellent enantioselectivities of up to 98% ee. A linear effect was observed for the reaction, demonstrating a single molecule of the catalyst involved in the catalysis.

The aldol reaction is one of the most important carbon−carbon bond-forming reactions in organic synthesis and has been studied extensively.[1] Since the seminal findings that L-proline could catalyze the direct aldol reaction,[2,3] many chiral organocatalysts have been discovered for the direct aldol reaction.[4−10] In contrast to organocatalyzed direct aldolizations with aldehydes as acceptors, however, those related with ketones as acceptors were rarely reported and thus are even more challenging. Recently, a L-proline-catalyzed direct aldol reaction of α-keto esters with aldehydes was reported.[11] In this case, only two specific α-keto esters, which contain two highly electron-withdrawing groups to

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activate the keto function, were investigated as aldol acceptors.[11] Most recently, the proline-catalyzed asymmetric aldol reaction between cyclohexanone and phenylglyoxylate was discovered.[12] However, the organocatalyzed asymmetric aldol reaction of ketone with keto acids has not been reported yet. We report here the direct aldol reaction of ketones with α-keto acids catalyzed by an organic molecule to directly form β-hydroxy carboxylic acids with a tertiary stereogenic center with high enantioselectivities of up to 98% ee.

Molecular recognition phenomena are critically important in the actions of enzymes on substrates. A large number of enzyme-mimetic systems such as crown ethers,[13] cryptands,[14] cyclodextrins,[15] and capsules[16] have been designed as artificial receptor sites to bind appropriate guest molecules or ions. Since the pioneering finding by Hamilton and coworkers that aminopyridine is a good site for the formation of hydrogen bonds specifically with a carboxyl group (**1**, Figure 1),[17] aminopyridine has been widely used in the self-assembly[18] and molecular recognition of carboxylic acids.[19] Molecular recognition has also been found as one of the factors to design organocatalysts for other reactions.[20] In our search for structurally diverse organocatalysts, we recently found that L-prolinamide derivatives catalyzed the direct aldol reaction via enamine catalysis.[9] Stimulated by these findings and Hamilton's molecular recognition model **1** of carboxylic acid with aminopyrodine (Figure 1), we reasoned that the combination of pyrrolidine-2-carboxylic acid amide and aminopyrodine in a single molecule could lead to a kind of chiral organocatalysts **3a**−**g**, and they would catalyze the direct aldol reaction of ketone with α-keto acids via a possible transition state **2a** or **2b** (Figure 1). Principally, **2a** would be more stable than **2b**.[17] But **2b** would more easily occur with the aldol reaction than **2a** because the keto group in **2b** is activated by a hydrogen bond.[9]

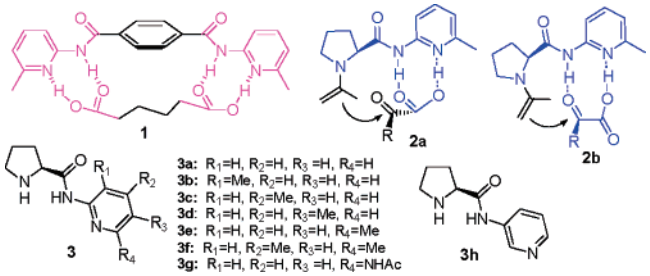
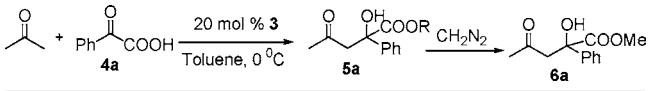


Figure 1. General strategy for the design of new organocatalysts **3**.

It was found that prolinamides **3a**−**g** were highly catalytically active for the direct aldol reaction of acetone with benzoylformic acid (**4a**) to generate an aldol product **5a** that directly reacted with CH_2N_2 to give **6a** for *the convenient HPLC analysis* (Table 1). In the presence of 20 mol % of **3a**, the reaction conditions were optimized and the best results were obtained when the reaction was performed in toluene at 0 °C. Compared with **3a**, organocatalysts **3b**−**e**, which contain an additional methyl group on the pyridine ring, catalyzed the direct aldol reaction in high yield with varying enantioselectivities that depended on the position of the methyl group (Table 1, entries 1−5). The best result was obtained with catalyst **3e** (entry 5). One more methyl group was introduced to the pyridine, as shown in **3f**, and this resulted in a decrease in enantioselectivity (entry 6). Organocatalyst **3g**, which was modified by replacing the methyl group with an acetylamino group, gave a dramatically deteriorated yield and enantioselectivity, indicating that the introduction of an additional hydrogen bond donor negatively

Table 1. Direct Aldol Reaction of Acetone and Benzoylformic Acid Catalyzed by Organocatalyst **3a**−**g**[a]



entry	catalyst[a]	4	yield (%)[b]	ee (%)[c]
1	**3a**	**4a**	98	87
2	**3b**	**4a**	86	79
3	**3c**	**4a**	86	87
4	**3d**	**4a**	90	90
5	**3e**	**4a**	>99	92
6	**3f**	**4a**	>99	90
7	**3g**	**4a**	30	74
8	**3h**	**4a**	22	−9
9	**3e**	**4a**	>99	93[d]

[a] A mixture of benzoylformic acid (0.5 mmol), catalyst (0.1 mmol), and acetone (1.0 mL) in toluene (2.0 mL) was stirred for 48 h. [b] Isolated yield of **6a**. [c] The ee value of **6a** and was determined by chiral HPLC. [d] The reaction was performed in toluene (3.0 mL)

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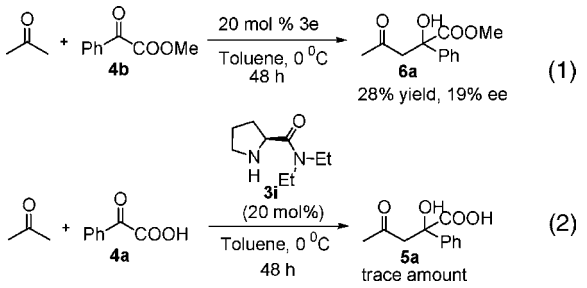
affected the catalytic performance (entry 7). However, catalyst **3h** derived from 3-aminopyridine, which is principally unable to form double hydrogen bonds with the substrate, catalyzed the direct aldol reaction of acetone with benzoylformic acid in very low yield (22%) and enantioselectivity (−9% ee) with a reversed configuration (Table 1, entry 8), which demonstrates the importance of the double hydrogen bonds and that the reaction very likely proceeds via the transition state **2**. Fine-tuning the ratio of toluene to acetone resulted in the highest level of enantioselectivity (93% ee) and a nearly quantitative yield for the reaction of acetone and benzoylformic acid catalyzed by **3e** (entry 9).

The aldolization of methyl benzoylformic ester (**4b**) with acetone in the presence of **3e**, however, yielded **6a** in a 28% yield with poor enantioselectivity (eq 1), implying that the interaction between carboxylic acid and pyridinyl group is important for the reaction and a single hydrogen bond is not efficient enough to activate the keto group. The use of L-proline amide **3i**, which is unable to provide a proton to form the hydrogen bond, to catalyze the aldol reaction of **4a** with acetone gave **5a** in a trace amount (eq 2), indicating that the hydrogen bond formed between the keto and amide exists and plays a crucial role in promoting the reaction. Thus, this organocatalyzed reaction proceeds more likely via **2b** rather than **2a**.



Despite the preceding positive evidence to support our proposed transition structure **2b** for the aldol reaction, more evidence is still required. Recently, chiral molecules either bearing multiple hydrogen-bond donors[21] or containing pyrrolidinyl[22] and pyridinyl groups,[23] which are similar to the building blocks of organocatalysts **3**, have been designed for the enantiomeric recognition of mandelic acid. The multiple hydrogen bonds between the carboxylic acid and the host are considered to be responsible for chiral recognition.[21] We studied the bonding properties of **3e** with racemic mandelic acid in $CDCl_3$ by ^{1}HNMR spectroscopy to further prove the existence of hydrogen bonds between the keto acid and the aminopyrodine of **3e** (Figure 2, see the Supporting Information for details).[22,23] The chemical shift of the proton on the stereogenic centers of two enantiomers of mandelic acid is obviously different in the presence of stoichiometric amounts of **3e** (peak a). Enantioselective recognition was also observed with Cbz-**3e** as a receptor (peak b). On the contrary, two enantiomers could not be distinguished by ^{1}HNMR spectroscopy with **3h** as a host peak c). The racemic aldol product **5a** was also recognized by **3e** based on ^{1}HNMR spectroscopy of the mixture of **3e** and **2a** (see the Supporting Information). These facts also implied that the α-keto group of the acceptor was interacting with the proline amide, and the transition structure **2b** is therefore more possible than **2a**.

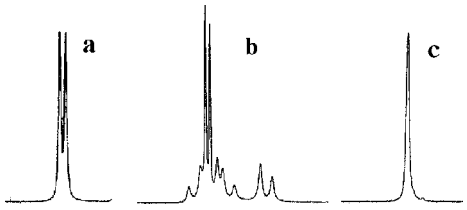


Figure 2. ^{1}HNMR spectra of mixtures of racemic mandelic acid with different host molecules: (a) racemic mandelic acid and receptor **3e**; (b) racemic mandelic acid and receptor Cbz-**3e**; and (c) racemic mandelic acid and receptor **3h**.

A linear effect was observed for the reaction of benzoylformic acid (**4a**) with acetone with 20 mol % of **3e** in toluene (Figure 3). This result is consistent with the proposed transition state **2b** (Figure 1), and thus, a single molecule of **3e** participates in the reaction.

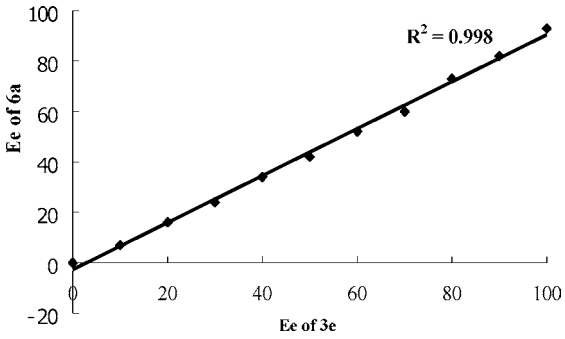


Figure 3. Linear effect in the **3e** catalyzed direct aldol reaction of benzoylformic acid (**4a**) with acetone in toluene.

The generality of catalyst **3e** at catalyzing direct aldol reactions of ketones with a variety of α-keto acids including both aromatic and aliphatic acids was examined under optimal conditions (Table 2). The aldol reactions proceeded smoothly to generate aldol adducts with a tertiary center in high yields of up to >99% and with high enantioselectivities of up to 98% ee regardless of the electronic and sterical nature of the substituent of the keto acids. Cyclopentanone can also react with benzoylformic acid in a moderate yield with a diastereomeric ratio of 2:1 in favor of the *syn*-isomer and 81% ee for *anti*-product. The absolute configuration of **6c** was determined to be *R* by *X*-ray crystallography (see the Supporting Information). However, the *β*-keto acid does

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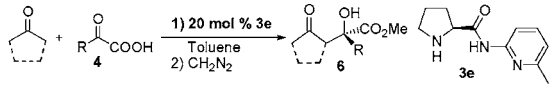
Table 2. Direct Aldol Reactions of Ketone and Keto Acid[a]



product	yield (%)[b]	ee (%)[c]	product		yield (%)[b]	ee (%)[c]
6a	>99	93	6e		78	92
6b	>99	93	6f		85	95
6c	78	93	6g		96	96
6d	75	98	6h	*anti*[d]	20	81
				syn	40	24

[a] A mixture of keto acid (0.5 mmol), catalyst **3e** (0.1 mmol), and acetone (1.0 mL) in toluene (3.0 mL) was stirred for 48 h at 0 °C. [b] Isolated yield. [c] The ee values were determined by chiral HPLC. [d] Determined by X-ray crystallography of a single crystal (see the Supporting Information).

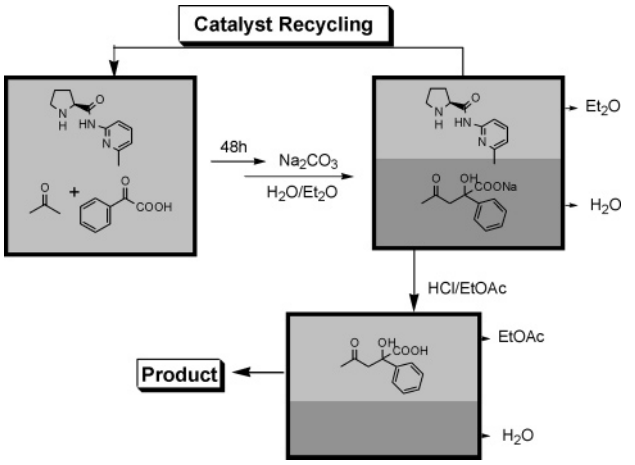
not react with acetone catalyzed by **3h** under the optimal conditions.[24]

Since the aldol product is a β-hydroxy carboxylic acid and the catalyst is an organic base, it is very convenient to separate the product and the catalyst by an acid−base conversion strategy, as illustrated in Scheme 1. Recycling of the catalyst is therefore allowed. After the aldol reaction of benzoylformic acid with acetone is quenched with aqueous Na_2CO_3, the product exists in the basic aqueous layer, whereas organocatalyst **3e** remains in the organic layer. Evaporation of the organic solution to dryness recovers the organocatalyst **3e**, which can be reused to catalyze the aldol reaction. The aldol product in the aqueous layer was obtained by extraction after the pH was adjusted to 6. After two recyclings, catalyst **3e** is still active enough to catalyze the direct aldol reaction of acetone and benzylformic acid in moderate yield and a slightly decreased enantioselectivity (Table 3).

In conclusion, we have designed a family of organocatalysts based on molecular recognition to catalyze the asymmetric direct aldol reaction of ketone with α-keto acids to afford β-hydroxyl carboxylic acids with a tertiary stereogenic center with excellent enantioselectivities of up to 98% ee. The high enantioselectivity of the organocatalyst comes from

(24) The aldolization of 3-oxo-3-phenylpropionic acid with acetone catalyzed by **3h** was examined to result in no reaction.

Scheme 1. Diagram of the Catalyst Recycling



the transition state stabilized by the double hydrogen bonds formed between 2-aminopyridine and both the keto and carboxyl groups of the organocatalyst **3e**. A linear effect was

Table 3. Catalyst Recycling[a]

entry	recycle	yield (%)[b]	ee (%)[c]
1	1st	99	93
2	2nd	90	93
3	3rd	62	89

[a] The procedure for catalyst recycling is presented in the Supporting Information. [b] Isolated yield. [c] The ee values ware determined by chiral HPLC.

observed for the reaction, demonstrating a single molecule of the catalyst involved in the catalysis. On the basis of their different chemical properties, the aldol product and organocatalyst **3e** were conveniently separated to allow for easy recycling of the organocatalyst.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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