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Asymmetric Direct Aldol Reaction of α-Keto Esters and Acetone Catalyzed by Bifunctional Organocatalysts

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Abstract: A type of C_2-symmetrical bisprolinamide has been developed for the asymmetric aldol reaction between acetone and α-keto esters, which furnishes the chiral tertiary alcohols in high yields (up to 99%) with high enantioselectivities (up to 94% *ee*). Aliphatic, heteroaromatic and aromatic α-keto esters including those with electron-donating or electron-withdrawing group substituents were found to be suitable substrates in the presence of bisprolinamide **2a** (15 mol%) and AcOH (150 mol%) with reaction times of no more than 16 h. This process is easily manipulated with readily available reagents. The geometry of catalyst **2a** was fully optimized at the B3LYP/6-31G(d) level with all electron calculations. Based on the experimental investigations and DFT calculations of catalyst **2a**, a possible transition state **A** has been proposed to explain the origin of the activation and asymmetric inductivity.

Keywords: aldol reaction; bisprolinamide; DFT; α-keto esters; organocatalysts

Because the aldol reaction is one of the most powerful reactions in constructing carbon-carbon bonds for β-hydroxy carbonyl compounds,[1] great attention has been paid to its asymmetric versions.[2–7] In contrast to the previously reported organocatalyzed direct aldolization, to the best of our knowledge, chiral tertiary alcohols which are key medical intermediates,[8] were rarely reported.[9] Therefore, the aldol reaction of α-keto esters with acetone would be significant. In our previous studies, ligand **1a** only complexed with Ti(O-*i*-Pr)$_4$ to dually catalyze the asymmetric cyanosilylation of aldehydes and ketones.[10] For aldol reaction, the same two amino units of **1a** could be expected to respectively activate acetone *via* an active enamine and α-keto esters *via* a hydrogen bonding interaction as a bifunctional organocatalyst. Herein, we report on bifunctional organocatalysts for the highly reactive and enantioselective aldol reaction between acetone and α-keto esters.

Initially, the aldolization of methyl phenylglyoxylate and acetone was selected as model reaction and the catalytic activities of organocatalysts (**1a**, **b** and **2a**–**c**) (Figure 1) were evaluated, with the results summarized in Table 1. L-Proline derivative **1a** with the backbone of (*R*,*R*)-1,2-diphenylethylenediamine was superior to that with the (*R*,*R*)-1,2-diaminocyclohexane structure (Table 1, entries 1 and 2). L-Piperidine-2-carboxylic acid derivative **2b** or L-2-amino-2-phenylacetic acid derivative **2c** which contain a primary amine gave complete failure or inferior results (Table 1, entries 4 and 5), and D-proline derivative **2a** gave the aldol adduct in good yield with moderate enantioselectivity (Table 1, entry 3). The substitution of ethyl or cyclopentyl for the methyl ester group of the substrate produced lower enantioselectivity (Table 1, entries 6 and 7). The good enantioselectivity

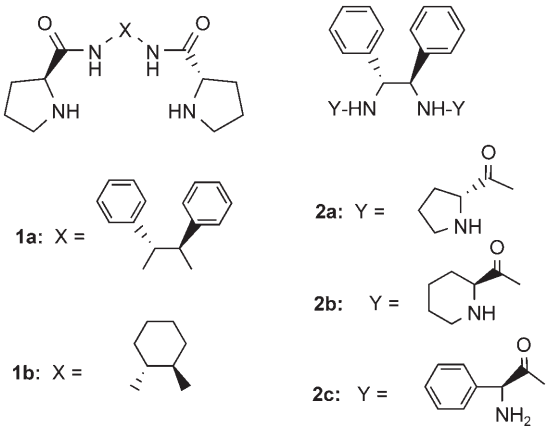
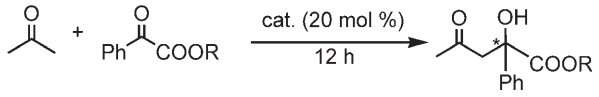


Figure 1. Catalysts evaluated in this study.

Table 1. Asymmetric aldol reaction of acetone with phenylglyoxylate esters under indicated conditions.

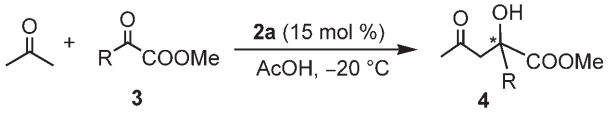


Entry[a]	Catalyst	R	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	Me	0	91	32
2	**1b**	Me	0	90	28
3	**2a**	Me	0	92	53
4	**2b**	Me	0	trace	n.d.[d]
5	**2c**	Me	0	41	62
6	**2a**	Et	0	82	35
7	**2a**	Cyclopentyl	0	75	38
8	**2a**	Me	−20	91	75

[a] All reactions were run on a 0.1-mmol scale of phenylglyoxylate ester in 0.2 mL acetone.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Not determined.

of 75% *ee* was obtained by decreasing the temperature from 0 to −20 °C without any loss of the yield in 12 h (Table 1, entry 8). Systematic screening studies including various additives, reaction temperature and catalyst loading established that organocatalyst **2a** (15 mol%) with the combined use of AcOH (150 mol%) at −20 °C enabled the efficient formation of the product in 92% yield with 93% *ee* in 16 h (Table 2, entry 1).

Table 2. Catalyst **2a**-promoted asymmetric aldol reaction of acetone with α-keto esters under optimum conditions.



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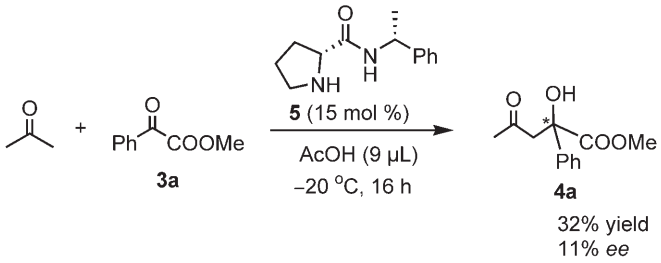
Entry[a]	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph (**3a**)	16	92	93 (*S*)[d]
2	3-$CH_3C_6H_4$ (**3b**)	16	99	94
3	4-$CH_3C_6H_4$ (**3c**)	12	99	94
4	2-$CH_3OC_6H_4$ (**3d**)	16	90	64
5	4-$CH_3OC_6H_4$ (**3e**)	16	82	92
6	3-FC_6H_4 (**3f**)	12	90	80
7	2-Thiophenyl (**3g**)	16	86	80 (*S*)[d]
8	1-Naphthyl (**3h**)	16	82	70
9	2-Naphthyl (**3i**)	12	94	92
10	Cyclohexyl (**3j**)	12	92	93

[a] All reactions were run on a 0.1-mmol scale of α-keto esters in 0.2 mL acetone.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The absolute configurations were established as *S* by comparison of the literature (see ref.[9]).

Under the optimal conditions, the substrate generality was investigated. As shown in Table 2, the aldol reactions proceeded smoothly to generate aldol adducts with chiral tertiary alcohols in high yields (up to 99%) with high enantioselectivities (up to 94% *ee*). The use of aromatic rings with neutral groups (Table 2, entry 1), electron-donating groups (Table 2, entries 2–5) or with-drawing groups (Table 2, entry 6) was well tolerated in the reactions. The reaction of a heteroaromatic ring compound proceeded in good yield and enantioselectivity (Table 2, entry 7). The fused ring compounds provided good yields and asymmetric inductivities. Probably owing to steric hindrance, both the reactivity and enantioselectivity of α-keto esters with a naphthyl on the α-position were inferior to those on the β-position (Table 2, entry 8 *versus* entry 9). In addition, the use of aliphatic rings also showed execellent yield and enantioselectivity (Table 2, entry 10). When using cyclohexone, 3-pentanone or 2-butanone as a donor, only poor yields were obtained.

The aldolization of substrate **3a** with acetone in the presence of **5**, half of the C_2-symmetric structure, produced **4a** in 32% yield with poor enantioselectivity (Scheme 1), which revealed that the cooperation of



Scheme 1.

the two spread amino units played a crucial role in affording the excellent yield and asymmetric inductivity. Using the Gaussian program package, the geometry of catalyst **2a** was optimized at the B3LYP/6-31G(d) level (Figure 2). The modelling calculation showed that the two phenyl rings of the diamine moiety are bent forwards and backwards, and the two pyrrole units are bent upwards and downwards, respectively, which facilitated conjugate addition between the activated donor and acceptor in two planarities. On the basis of the observed absolute configuration of methyl 2-hydroxy-4-oxo-2-penylpentanoate (Table 2, entry 1), a possible transition state **A** has been proposed (Figure 3). The interaction between acetone and a pyrrole unit gives the active enamine. Meanwhile the α-keto ester is activated by hydrogen bonding *via* oxides coordinating to the hydrogens on the amide and the protonated amine groups. The *Re* face of the methyl phenylglyoxylate is much more accessi-

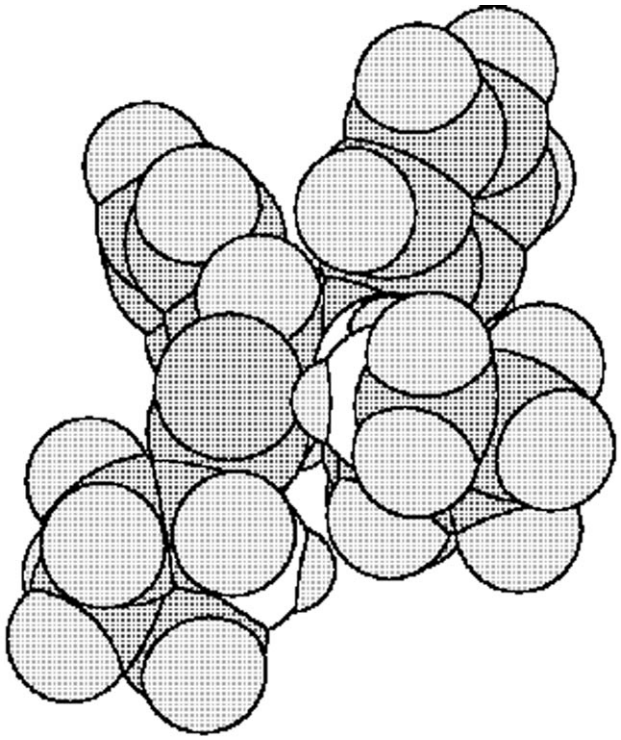


Figure 2. Optimized geometry of catalyst **2a** at the B3LYP/6-31G(d) level.

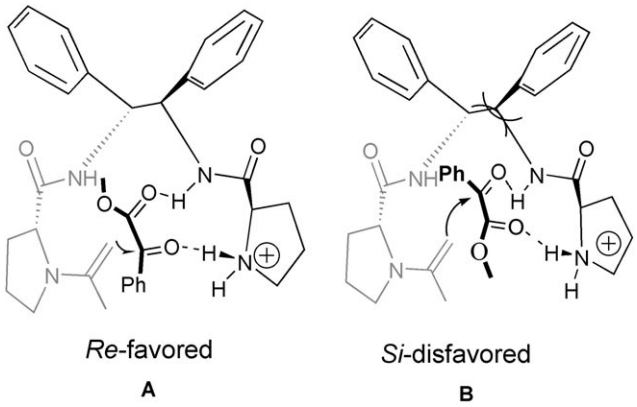


Figure 3. Proposed transition state (**A** or **B**) for the catalytic asymmetric aldol reaction.

ble to the enamine than the *Si* face, since the interaction of the *Si* face and the active enamine will strongly increase the repulsion between phenyl subunits as in transition state **B**.

In conclusion, we have developed a bifunctional organocatalyst for the asymmetric aldol reaction. Aliphatic, heteroaromatic, and aromatic α-keto esters were converted well in excellent yields (up to 99%) with high enantioselectivities (up to 94% *ee*). The optimal organocatalyst **2a** only requires a simple two-step synthesis to give an excellent yield from commercially available materials. This contribution provides a simple and practical synthetic strategy for the direct formation of chiral tertiary alcohols from the ketones. DFT investigations have also been employed to provide some important information for a proposal of the transition state. Further efforts should be devoted to the optimization of the catalyst to enhance enantioselectivity and reactivity, and clarify the mechanism of the reaction.

Experimental Section

Materials and Methods

All the catalytic manipulations were carried out under air in a closed system. The ^{1}H NMR spectra were recorded on a Bruker instrument (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.26$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR data were collected on a Bruker instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, $\delta = 77.0$). HR-MS were recorded on a Bruker Daltonics Data Analysis system. Enantiomer ratios were determined by chiral HPLC analysis on Daicel Chiralcel AD in comparison with the authentic racemates. Commercial grade reagents were used without further purification. Optical rotations were measured on a Rudolph Research analytical instrument with a sodium lamp and are reported as follows: $[\alpha]_D^T$(c=g/100 mL, solvent).

General Procedure for the Direct Aldol Reaction

Aldol reactions were carried out in test tubes with magnetic stirring and no special precautions were taken to exclude water or air from the reaction vessel. Acetone was purified by the usual methods. α-Keto esters were prepared according to literature procedures.[11] A series of C_2-symmetrical bisprolinamide organocatalysts (**1a**, **b** and **2a**–**c**) were prepared according to the methods reported in the literature[10].

To a stirred solution of catalyst **2a** (6.1 mg, 0.015 mmol) in anhydrous acetone (0.2 mL) was added the methyl phenylglyoxylate (15.0 μL, 0.1 mmol) at −20 °C, followed by AcOH (9 μL, 0.15 mmol). The resulting mixture was stirred at −20 °C for 12–16 h. The mixture was purified by flash chromatography by using EtOAc/PE (1:4) as the eluent to afford **4a** as a white solid; yield: 20.4 mg (92% yield, 93% *ee*).

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