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Asymmetric Direct Aldol Reaction of Functionalized Ketones Catalyzed by Amine Organocatalysts Based on Bispidine

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Aldol condensation is one of the basic reactions for creating a C−C bond in nature.[1] Since the pioneering work of List, Barbas, and co-workers in 2000,[2] organocatalyst as a simple chemical mimic for enzymes has received much attention in the direct aldol reaction.[3] Among these successful examples, the organocatalysts utilized in the direct aldol reaction mainly employed secondary amine of the proline moiety[3a,b] or primary amine of the chiral diamine moiety (diaminocyclohexanes)[3p] to form the enamine intermediate. Despite these successes, the development of the efficient organocatalysts for the direct aldol reactions of synthetically important functionalized ketones is still a challenge and has become a much attempted research endeavor.[4] Bispidine as the structural core of sparteine opened up the opportunity to develop a new catalyst by introduction of an appropriate chiral group.[5] Herein, we report a novel organocatalyst by introducing facile amino acids into the bicyclic bispidine framework for the direct aldol reaction of functionalized ketones (Figure 1). High enantioselectivities (up to 98% ee) were obtained for a broad range of substrates including α-keto phosphonates, α-keto esters, as well as α,α-dialkoxy ketones as aldol reaction acceptors under mild conditions.

In our initial studies, the direct aldol reaction between diethyl benzoyl phosphonate and acetone was selected as a benchmark for catalyst evaluation. Some screening results are listed in Table 1. Twenty mol % of catalyst **1a** derived from L-phenylalanine promoted this reaction with 80% yield and 78% ee (Table 1, entry 1). Other catalysts derived from L-phenylglycine, L-leucine, L-proline, L-valine, and L-4-nitrophenylalanine were also screened, but no superior result was obtained (Table 1, entries 2−6). To obtain higher enantioselectivity, some acids were employed as additives (Table 1, entries 7−11). The weak acidic additives such as HCOOH were shown to be suitable for this reaction, affording the product with 95% yield and 96% ee (Table 1, entry 7), while stronger acids, such as TFA and TsOH, made the reaction sluggish with only trace product (Table 1, entries 10 and 11). Other conditions were also optimized for further improving reactivity and enantioselectivity (see Supporting Information). To our delight, the loading of catalyst could be reduced to 5 mol % with the same enantioselectivity and reactivity (Table 1, entry 12). Extensive screening showed that the optimized conditions were **1a**/HCOOH = 1/1, 0.1 mmol diethyl benzoyl phosphonate and 0.5 mL of acetone at 0 °C.

Application scope of the catalytic system was then examined under the optimal conditions. As summarized in Table 2, optically active tertiary α-hydroxyphosphonates were obtained with up to 97% isolated yield and 97% ee. It appeared that the size of

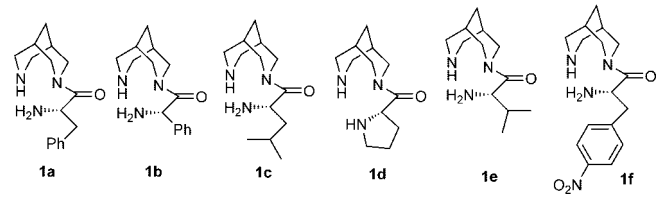
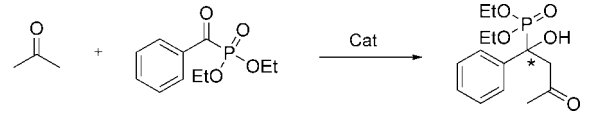


Figure 1. Structures of the catalysts studied.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	yield %[b]	ee %[c]
1	**1a**	80	78
2	**1b**	95	69
3	**1c**	60	67
4	**1d**	98	−38
5	**1e**	NR	
6	**1f**	34	27
7[d]	**1a**/HCOOH	95	96
8[d]	**1a**/CH_3COOH	92	88
9[d]	**1a**/PhCOOH	74	88
10[d]	**1a**/TsOH	trace	
11[d]	**1a**/TFA	trace	
12[d,e]	**1a**/HCOOH	94	96

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol diethyl benzoyl phosphonate, 0.5 mL of acetone, and 20 mol % catalyst loading at 0 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] **1a**/acid = 1/1. [e] With 5 mol % catalyst loading, reaction time is 48 h.

phosphonate had no effect on both yield and enantioselectivity (Table 2, entries 1−3). With benzoyl phosphonate, the methyl, ethyl, and isopropyl esters performed the corresponding products with nearly the same yields and enantioselectivities. Different substituted benzoyl phosphonates were also good substrates for this reaction. The electronic nature of the *para*- and *meta*-substituents did not influence the enantioselectivity. Either electron-rich methyl and methoxyl substituents or electron-deficient halogen substituents all underwent smoothly the reaction with acetone in moderate to high yields and 94−96% ee (Table 2, entries 4−9). Moreover, thiophene-2-carbonyl phosphonate was tested with 80% yield and 89% ee (Table 2, entry 10).

Further substrate exploration indicated that aldol reaction of acetone with α-keto esters could also be achieved to produce β-hydroxycarboxylic esters under optimal conditions. As shown in Table 2, the reactions with a variety of aromatic α-keto esters proceeded smoothly to generate aldol adducts with a tertiary alcohol in high enantioselectivities of up to 94% ee regardless of the electronic and sterical nature of the substituted keto esters (Table 2, entries 11−18). Heteroaromatic α-keto esters also succeed with

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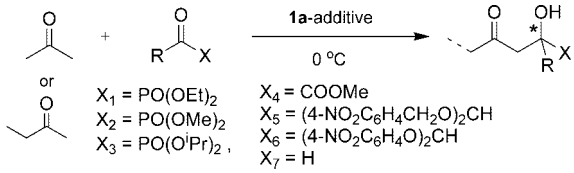
Table 2. Substrate Scope for the Asymmetric Direct Aldol Reaction[a]



entry	R	X	*t*	cat mol %	yield %[b]	ee %[c]
1	Ph	X_1	48 h	5	94	96
2	Ph	X_2	22 h	10	97	96
3	Ph	X_3	33 h	10	93	97
4	4-MeC_6H_4	X_1	48 h	5	72	96
5	4-$MeOC_6H_4$	X_2	96 h	5	75	94
6	4-ClC_6H_4	X_1	22 h	10	94	96
7	3-MeC_6H_4	X_1	38 h	5	90	95
8	3-BrC_6H_4	X_2	17 h	20	91	94
9	3-BrC_6H_4	X_1	48 h	10	85	93
10	2-thiophenyl	X_1	96 h	10	80	89
11	Ph	X_4	6 days	30	91	94(*R*)[h]
12	4-MeC_6H_4	X_4	6 days	30	52	94
13	4-$MeOC_6H_4$	X_4	6 days	30	56	94
14	4-FC_6H_4	X_4	4 days	30	96	93
15	3-MeC_6H_4	X_4	6 days	30	83	93
16	3-FC_6H_4	X_4	3 days	30	92	91
17	2-thiophenyl	X_4	5 days	30	85	91
18	2-naphthyl	X_4	6 days	30	90	91
19	4-$NO_2C_6H_4$	X_5	4 days	30	90	98
20	3-$NO_2C_6H_4$	X_5	4 days	30	83	98
21[d]	Ph	X_6	4 days	30	35	82
22[d]	4-ClC_6H_4	X_6	10 days	30	92	86
23[e]	4-$NO_2C_6H_4$	X_7	2 days	30	70	91
24[e,f]	4-$NO_2C_6H_4$	X_7	2 days	30	97	96
25[g]	Ph	X_1	3 days	20	65	93
26[g]	Ph	X_4	6 days	30	41	90
27[g]	4-$NO_2C_6H_4$	X_5	4.5 days	30	40	96
28[e,g]	4-$NO_2C_6H_4$	X_7	3 days	30	35	90

[a] Unless otherwise noted, all reactions were carried out with 0.1 mmol functionalized ketone, 0.5 mL of acetone, and **1a**/HCOOH (1/1) at 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] With 30 mol % catalyst system **1a**/2,4-dinitrophenol (1/1). [e] The reaction was carried out with 0.1 mmol 4-$NO_2C_6H_4CHO$, 0.5 mL of acetone, and **1a**/3,3′,5,5′-tetrabromobiphenol (1/1) at 0 °C. [f] Cyclohexanone as donor, dr 4:1. [g] 2-Butanone (0.5 mL) was used instead of acetone. [h] See refs4d, e.

85% yield and 91% ee (Table 2, entry 17). Another kind of important functional substrate, α,α-dialkoxy ketones, was also examined for the first time in the presence of catalyst **1a** and different additives (Table 2, entries 19−22). The relative lower reaction rate could be compensated by prolonging reaction time, and up to 98% ee was obtained for electron-deficient aromatic acetal ketones. When 4-nitrobenzaldehyde was used as an aldol reaction acceptor, both acetone and cyclohexanone could react smoothly with high yields and 91 and 96% ee, respectively (Table 2, entries 23 and 24). The reactions between 2-butanone and different functional ketones furnished linear aldol adducts with up to 96% ee and moderate yields (entries 25−27), while 4-nitrobenzaldehyde provided a mixture aldol adducts with high ee (Table 2, entry 28, see Supporting Information).

The mechanism of direct aldol reaction between α-keto ester and acetone catalyzed by the primary−secondary diamine catalyst **1a** has been investigated by theoretical simulation as shown in Figure 2. Simillar to the diamine catalyst,[3p] in the enamine complex from the primary amine of **1a** and acetone, the phenyl group was positioned equatorially with the enamine and shielded one face of the enamine, while the protonated piperidine could interact with the keto group by hydrogen bond[3l,6] and position the attachment to the unshielded face of the enamine. The H-bond between the substrate and catalyst **1a** in **TS2** was shorter than that in **TS1**, which indicated stronger interaction to keto in **TS2**. On the other hand, **TS2** was also energetically more stable than **TS1** by ∼3.7 kcal/mol. Thus, **TS2** was found to be the favorable transition state and led to the formation of the major *R*-product in accordance with the experimental results.

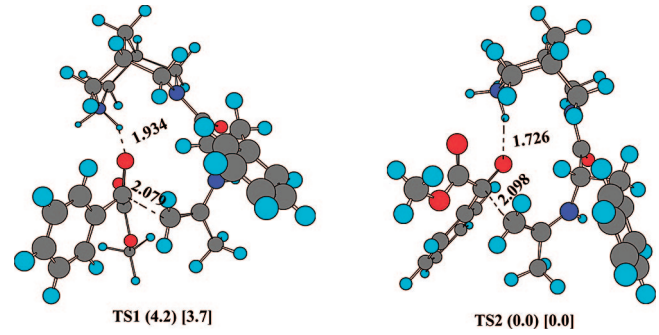


Figure 2. The calculated transition state of aldol reaction of keto ester with acetone catalyzed by **1a**-HCOOH. The geometries were optimized at the HF/6-31G* level. The relative energies (kcal/mol) are with HF/6-31G* in () and B3LYP/6-311G** and IEFPCM (acetone) in [ ].

In conclusion, we have presented the example of introducing the amino acids into the bispidine framework as catalysts for highly enantioselective direct aldol reactions of functionalized ketones. Catalyst **1a** demonstrated high enantioselectivity and yield (up to 97% yield and 98% ee) for a wide substrate scope including α-keto phosphonates, α-keto esters, and α,α-dialkoxy ketones under mild conditions. A theoretical study of transition structures revealed that protonated piperidine was important for the reactivity and enantioselectivity of this reaction. Further exploration of this catalyst in other important reactions is underway in our laboratory.

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Supporting Information Available: Experimental procedures, spectral and analytical data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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