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Direct asymmetric aldol reaction of acetone with α-ketoesters catalyzed by primary–tertiary diamine organocatalysts

Zhaoqin Jiang, Yixin Lu *

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore
Medicinal Chemistry Program, Life Sciences Institute, National University of Singapore, Singapore

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ABSTRACT

Novel primary–tertiary diamine organocatalysts derived from L-serine were utilized to promote enantioselective aldol reaction of acetone with α-ketoesters. The desired products were obtained in high yields and with good to excellent enantioselectivities (up to 95% ee).

The aldol reaction is an important reaction for the construction of β-hydroxy carbonyl compounds and has drawn a great deal of attention from synthetic organic chemists.[1] Asymmetric organocatalysis and stereoselective synthetic methods based on small organic molecules are well established as practical approaches to access chiral molecules.[2] Since the seminal discovery by List, Barbas and Lerner of proline-catalyzed intermolecular aldol reactions via enamine intermediates in 2000,[3] proline and its numerous structural analogues have found wide applications in asymmetric aldol reactions.[4] Chiral primary amines have emerged as powerful and versatile organic catalysts in asymmetric synthesis.[5] It is noteworthy that chiral primary amine-promoted reactions are often complementary to those catalyzed by secondary amines. Our group has actively investigated primary amino acid/amine-catalyzed organocatalytic reactions. We demonstrated for the first time that natural tryptophan was an effective catalyst in intermolecular aldol reactions.[6] We also utilized L-threonine-derived organocatalysts to promote highly enantioselective aldol and Mannich reactions of hydroxyacetone, as well as conjugate additions of branched aldehydes to vinyl sulfone.[7] By employing a cinchonidine-derived primary amine, we achieved the first highly enantioselective conjugate addition of ketones to vinyl sulfone.[8] We also introduced a novel tryptophan-based bifunctional thiourea catalyst that was effective in promoting enantioselective Mannich reactions of α-fluoro-β-ketoesters.[9] In this Letter, we demonstrate that a novel serine-derived primary–tertiary diamine catalyst promotes the asymmetric addition of acetone to α-ketoesters.

In primary amine-catalyzed organocatalytic reactions occurring via the enamine mechanism, cyclic ketones are the most commonly used substrates. This is likely due to the ready formation of the key enamine intermediates from cyclic ketones and primary amines. In an effort to expand the scope of primary amine-catalyzed organocatalytic reactions, we became interested in utilizing simple acyclic ketones as potential nucleophiles in asymmetric carbon–carbon bond formation. Towards this end, we chose to focus our efforts on the aldol reaction of acetone with α-ketoesters as such reactions are expected to produce chiral tertiary alcohols which are important intermediates in medicinal chemistry.[10] Although there are a few reports on the use of α-ketoesters/acids as electrophiles in organocatalytic reactions, the catalysts employed in these studies are all secondary amines.[11] We envisage that primary amines can be applied to activate acyclic ketone substrates in the direct aldol reaction, which may broaden the substrate scope for reactions activated via primary amine-induced enamine intermediates.

The catalysts employed in our study are shown in Figure 1. *O*-TBDPS-L-threonine **2a** was one of the most effective catalysts in our previous reports,[7] and thus we also prepared its secondary amine analogue **2b**. Moreover, *O*-acylated threonine derivatives **1** were synthesized as well. Diamine organocatalysts, in particular, diamine-Brønsted acid-type catalysts, have been widely used in

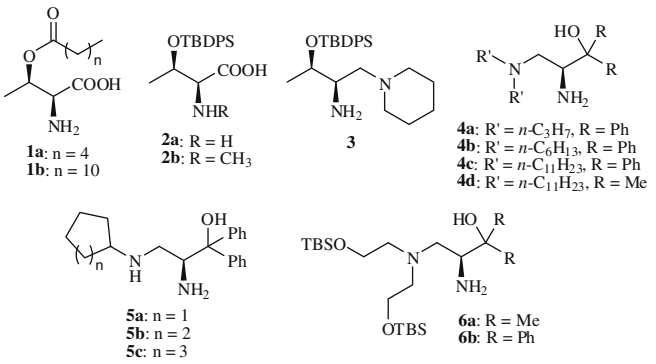

Figure 1. Organocatalysts derived from L-serine and L-threonine.

* Corresponding author. Tel.: +65 6516 1569; fax: +65 6779 1691.
E-mail address: chmlyx@nus.edu.sg (Y. Lu).

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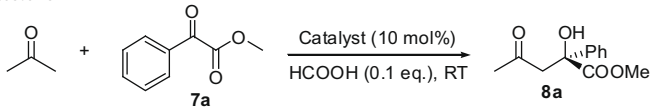
Table 1
Catalyst screening for the direct aldol reaction of methyl phenylglyoxylate with acetone[a]



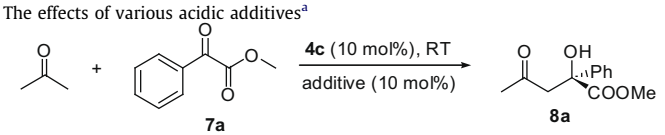
Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	**1a**	48	29	−23[f]
2[d]	**1b**	144	—	—
3[d]	**2a**	18	52	−32[f]
4[d]	**2b**	60	24	−18[f]
5	**3**	13	91	77
6	**4a**	48	89	74
7	**4b**	12	93	74
8[d]	**4c**	72	96	77
9	**4c**	**48**	**96**	**88**
10[e]	**4c**	72	98	84
11	**4d**	15	86	87
12[e]	**4d**	37	98	78
13	**5a**	24	92	41
14	**5b**	19	91	59
15	**5c**	48	91	46
16	**6a**	24	89	51
17	**6b**	96	66	64

[a] The reaction was performed employing methyl phenylglyoxylate (0.25 mmol), acetone (1.25 mmol), catalyst (0.025 mmol) and formic acid (0.025 mmol) at room temperature.
[b] Isolated yield.
[c] The ee value was determined by HPLC analysis on a chiral phase.
[d] No additive was used.
[e] Reaction was performed at 0 °C.
[f] The opposite enantiomer was observed.

asymmetric organocatalysis.[12] Addition of an acid to the primary–tertiary diamine system is believed to facilitate the formation of enamine intermediates and promote the formation of carbon–carbon bonds via interaction with electrophiles. Moreover, the acid component can be easily varied, and with judicious selection, hydrogen-bonding networks between substrates and catalysts are expected to work cooperatively, thus offering new reactivity and selectivity. A few diamine catalysts, **3**, derived from natural threonine, and **5** and **6** from serine were thus prepared intending to incorporate steric factors and hydrogen-bonding elements into our catalyst design.

The direct aldol reaction of acetone with methyl phenylglyoxylate **7a** was chosen as a model reaction for examining the catalytic effects of various catalysts. The results are summarized in Table 1. *O*-Acylated and *O*-silylated threonine derivatives were not effective, affording the desired products in very poor yields and with very low enantioselectivity (entries 1–4). Diamine **3** derived from *O*-TBDPS-threonine, together with formic acid, proved to be a good catalytic system, affording the desired product in high yield and with good enantioselectivity (entry 5). Diamines **4**, prepared from L-serine, were shown to be efficient catalysts, yielding the desired aldol products in excellent yields and with generally high enantioselectivity (entries 6–12). In particular, when diamine **4c** was employed as the catalyst, the aldol product was obtained in 88% ee (entry 9). Secondary-primary diamine catalysts **5** and tertiary–primary diamine catalysts **6** were found to be less effective, yielding the products with moderate enantioselectivities (entries 13–17).

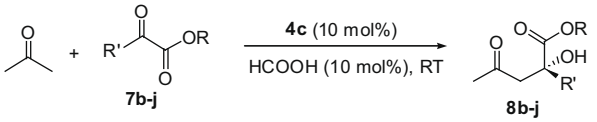
Table 2
The effects of various acidic additives[a]

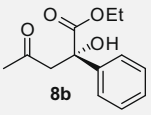
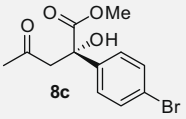
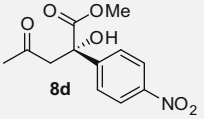
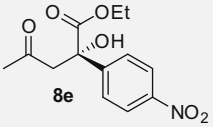
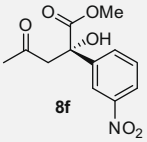
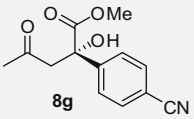
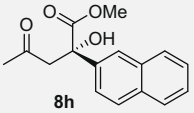
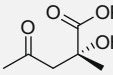
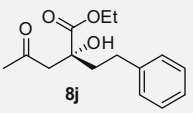


Entry	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	CH_3COOH	22	98	79
2	CF_3COOH	72	93	85
3	C_6H_5COOH	96	93	80
4	*m*-$O_2NC_6H_4COOH$	19	95	79
5	*p*-$O_2NC_6H_4COOH$	72	92	75
6	HCOOH	48	96	88

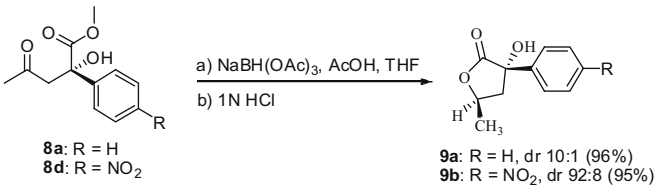
[a] The reaction was performed employing methyl phenylglyoxylate (0.25 mmol), acetone (1.25 mmol), catalyst **4c** (0.025 mmol) and additive (0.025 mmol) at room temperature.
[b] Isolated yield.
[c] The ee value was determined by HPLC analysis on a chiral phase.

Table 3
The aldol reaction of acetone with various α-ketoesters catalyzed by diamine catalyst **4c**[a]



Entry	Product	Time (d)	Yield[b] (%)	ee[c] (%)
1	 **8b**	2	61	78
2	 **8c**	3	96	76
3	 **8d**	1.5	73	95
4	 **8e**	1.5	97	80
5	 **8f**	2	88	74
6	 **8g**	2	91	74
7	 **8h**	1	69	74
8	 **8i**	1.5	73	76
9	 **8j**	1	83	57

[a] The reaction was performed employing ketoester (0.25 mmol), acetone (1.25 mmol), catalyst **4c** (0.025 mmol) and formic acid (0.025 mmol) at room temperature.
[b] Isolated yield.
[c] The ee value was determined by HPLC analysis on a chiral phase.



Scheme 1. Preparation of chiral lactones.

Since the acidic additive was important for the reactions, we subsequently examined the effects of various acidic additives on the reaction. As shown in Table 2, formic acid was the best additive among a number of acids examined.

Having established the optimized conditions, the reaction scope was next examined (Table 3). Various α-ketoesters were employed and in general, the aldol products were obtained in moderate to excellent yields and with good enantioselectivities. In addition to aryl ketoesters, alkyl ketoesters were also employed (entries 8 and 9). Unfortunately, we could not extend the reaction to include acyclic ketones other than acetone.

The aldol product is rich in functionality, which allows for simple synthetic manipulations. Thus, aldol product **8a** was converted into lactone **9a** in 96% yield and a 10:1 diastereomeric ratio, following a literature procedure.[11c] Similarly, lactone **9b** was prepared from **8d** in 95% yield and with excellent diastereoselectivity (Scheme 1).

In conclusion, we have prepared a number of novel diamine organocatalysts and investigated their effects on the asymmetric direct aldol reaction of acetone with α-ketoesters. Tertiary-primary diamine catalysts derived from serine, in combination with formic acid, proved to be the most effective, affording the desired aldol products with up to 95% ee. Investigations on the extension of the catalysts described herein to other asymmetric carbon–carbon bond-forming reactions are in progress in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.044.

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