

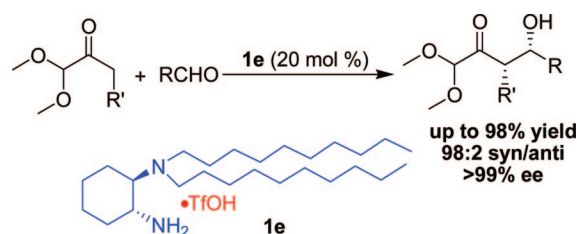
Asymmetric Direct Aldol Reactions of
Pyruvic DerivativesSanzhong Luo,^{*,†} Hui Xu,[†] Liujuan Chen,[†] and Jin-Pei Cheng^{*,†,‡}

Beijing National Laboratory for Molecular Sciences (BNLMS), Center for Chemical Biology, Institute of Chemistry and Graduate School, Chinese Academy of Sciences, Beijing 100080, China, and Department of Chemistry and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

luosz@iccas.ac.cn

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ABSTRACT



Simple chiral primary–tertiary diamine–Brønsted acid conjugates such as **1e** can effectively catalyze the direct aldol reactions of pyruvic derivatives with excellent syn diastereoselectivities and enantioselectivities, thus functionally mimicking the pyruvate-dependent type I aldolases.

The aldol reaction represents one of the most powerful carbon–carbon bond-forming reactions for both nature and synthetic chemistry.¹ Among the variants of asymmetric aldol reactions, pyruvate-dependent aldol reactions are of particular interest as these processes are vital steps in the in vivo formations of sialic acids, which are essential sugar units for signal transduction in a plethora of biological processes.² Accordingly, the evolved pyruvate-dependent aldolases have been explored for the enzymatic synthesis of sialic acid derivatives.^{2b} On the other hand, chemists have long been pursuing simple chemical mimics for catalyzing pyruvate–aldol reactions, but it remains an elusive goal despite the breakthroughs in many other asymmetric aldol reactions.¹ Jørgenson recently developed chiral copper-bisoxazoline catalysts for asymmetric aldol reactions of pyruvates.³

Though good enantioselectivities were achieved, the reactions were limited to pyruvate-type acceptors. Asymmetric enamine catalysis, resembling mechanistically natural enzymatic processes, represents one of the most prominent recent advances in modern aldol reactions.⁴ In this context, the enamine catalysts have also been attempted in pyruvate aldol reactions but demonstrated poor activity and thus only worked with a few selected substrates.⁵ In these cases, the applied catalysts are exclusively secondary amines, e.g., chiral pyrrolidines. This fact stands in contrast to the natural pyruvate-dependent aldolase wherein the primary amine of lysine is involved in catalysis.

Recently, chiral primary amines have been shown to be viable enamine catalysts that attain a new level of catalysis beyond traditional secondary amine catalysts.⁶ In this vein, the research groups of Barbas^{6f,7} and Gong⁸ as well as our research group⁹ have recently reported successful applications of chiral primary amines as syn-selective aldol catalysts. Inspired by the natural primary amine catalysis in pyruvate-dependent

[†] Chinese Academy of Sciences.[‡] Nankai University.

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aldolase,¹⁰ we have explored chiral primary amines in pyruvate–aldol reactions. Herein, we report chiral primary–tertiary diamine–Brønsted acid conjugates as effective and general catalysts for the diastereo- and enantioselective direct aldol reactions of pyruvic donors, thus functionally mimicking the natural pyruvate-dependent type I aldolase.^{1a,2a}

As a starting point, a variety of pyruvic derivatives were briefly screened and pyruvic aldehyde acetals (e.g., **4a**) were identified as workable aldol donors in the catalysis of primary–tertiary diamine **1**. Only one report by Enders has examined pyruvic aldehyde dimethyl acetal as a mask of

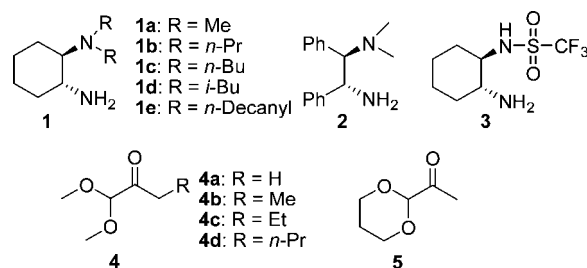


Figure 1. Chiral primary amine catalysts and pyruvic derivatives.

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pyruvate in the proline-catalyzed direct aldol reactions.^{5c} The reactions were very sluggish; however, only two aliphatic aldehydes acceptors were tested which gave low yields but good ee's. We then selected the reaction of **4a** and *p*-nitrobenzaldehyde as a model for subsequent screening. Notably, while both L-alanine and L-proline were totally ineffective for catalysis of this reaction (Table 1, entries 1

Table 1. Selected Screening Results

entry ^a	cat. (mol %)	solvent	yield ^a (%)	ee ^b (%)
1	L-alanine	neat	trace	nd
2	L-proline	neat	trace	nd
3	1a /TfOH	neat	44	64%
4	1a	neat	trace	nd
5	1b /TfOH	neat	42	84
6	1c /TfOH	neat	66	88
7	1d /TfOH	neat	6	32
8	1e /TfOH	neat	44	91
9	2	neat	trace	nd
10	3	neat	45	36
11 ^c	1c /TfOH	NMP	62	92
12 ^c	1e /TfOH	NMP	71	93
13 ^{d,e}	1e /TfOH	NMP	90	93
14 ^d	1e /TfOH	H ₂ O	71	90

^a Yield of isolated product. ^b Determined by chiral HPLC analysis. ^c 5 mol % of *m*-NO₂PhCOOH was added. ^d In the presence of 20 mol % of catalyst. ^e 10 mol % of *m*-NO₂PhCOOH was added. nd: not determined.

and **2**), simple primary–tertiary vicinal diamines such as *trans*-*N,N*-dialkylated diaminocyclohexanes **1** turned out to be very effective catalysts when combined with TfOH. Among this series of catalysts examined, cyclohexanediamine **1c** gave the best yield while **1e** offered the best enantioselectivity (Table 1, entries 5 and 6). Similar diphenylethylene diamine **2** was virtually inactive for catalysis (Table 1, entry 8). The primary–sulfamide conjugate **3** also exhibited much lower enantioselectivity (Table 1, entry 9). These results highlight the importance of the *N,N*-dialkylated diaminocyclohexanes skeleton. Consistent with our previous observations,⁹ a strong brønsted acid such as TfOH is essential for

catalysis, and the reaction barely occurred in the absence of TfOH (Table 1, entry 4).

The reaction was further optimized using both catalysts **1c** and **1e** by screening weak acid additives and solvents (see the Supporting Information for details). Improved yield and enantioselectivity were achieved using *N*-methylpyrrolidine (NMP) as the solvent and *m*-nitrobenzoic acid as the weak acidic additive. Under these conditions, catalyst **1e** gave slightly better results than that of **1c**. The reaction in the presence of 10 mol % of **1e** provided 71% yield and 93% ee, and the yield could be improved to 90% with 20 mol % of catalyst loading (Table 1, entries 12 and 13). It is noted that the catalysis of **1e** could also be conducted in bulk water (>40 equiv) affording comparable results (71% yield, 90% ee, Table 1, entry 14).

With **1e** as the optimal catalyst, we next explored a variety of pyruvic acetal derivatives and aldehydes to determine the scopes and limitations of the current catalysis (Table 2). Aromatic aldehydes were shown to be excellent aldol acceptors in the reactions with pyruvic aldehyde dimethyl acetal **4a**. Excellent enantioselectivities and good yields were achieved in most of these reactions (Table 2, entries 1–10). The reactions with aliphatic aldehydes gave mainly the dimerization product of **4a** instead of the desired cross-aldol products, probably due to the lower reactivity of aliphatic aldehydes as acceptors and also their ease to self-condensation as previously observed in primary aminocatalysis.^{9,11} Activated carbonyls such as 2,2-dimethoxyacetaldehyde and 2,2,2-trifluoro-1-phenylethanone also worked well in the present reactions to give quite good yields and moderate enantioselectivities (Table 2, entries 11 and 12). The reactions in pure water conditions (conditions B) have also been examined, showing comparable yields but slightly decreased enantioselectivities (Table 2, entries 2, 4, and 6).

In regard to the pyruvic aldehyde derivatives, the use of a cyclic acetal **5** led to improved enantioselectivity compared with that of dimethyl acetal **4a** (Table 2, entries 13 and 14). For example, the enantioselectivity was increased from 93% ee to 98% ee by using cyclic acetal **5** instead of **4a**. Pyruvic acetals with longer alkyl chains such as **4b–d** are also applicable in the reactions. Excellent dia- (>90:10, syn/anti) and enantioselectivities (>99% ee) and moderate yields were obtained in the reactions of **4b–d** with aromatic aldehydes (Table 2, entries 15–21). It is noted that the branched aldol products were obtained with remarkably syn diastereoselectivities. *To the best of our knowledge, this represents the first example of an asymmetric syn-selective pyruvate-type aldol reaction.* Substituted pyruvic acids were previously examined in chiral pyrrolidine-catalyzed aldol reaction; however, the resulted isotetronic acids products are depleted of any diastereoselectivity.^{5b}

To demonstrate the utility of the current aldol reaction, the diacetal aldol products, e.g., **7** and **18**, were first reduced by NaBH₄ to give 1,3-diol products (syn/anti = 5:1), which upon treatment with acid afforded the furanose type products

Table 2. Substrate Scope

entry	products	condition	yield (%) ^a	syn /anti ^b	ee (%) ^c
1		A, 36 h	90	----	93
2		B, 33 h	88	----	91
3		A, 72 h	94	----	94
4		B, 48 h	90	----	86
5		A, 72 h	98	----	94
6		B, 48 h	86	----	88
7		A, 72 h	63	----	91
8		A, 72 h	76	----	93
9		A, 96 h	43	----	91
10		A, 96 h	50	----	91
11		A, 72 h	88	----	49
12		A, 48 h	95	----	59
13		A, 36 h	93	----	98
14		A, 48 h	70	----	97
15		A, 96 h	65	96:4	97
16		A, 96 h	58	97:3	>99
17		A, 96 h	41	98:2	>99
18		A, 96 h	52	95:5	99
19		A, 96 h	33	97:3	>99
20		A, 96 h	32	95:5	99
21		A, 120 h	30	90:10	>99

* Conditions A: 0.25 mmol of aldehyde, 1.0 mmol of pyruvic derivative, and 10 mol % of *m*-NO₂PhCOOH in 100 μ L of NMP. Conditions B: 0.25 mmol of aldehyde and 1.0 mmol of pyruvic derivative in 200 μ L of H₂O. ^a Yield of isolated product. ^b Determined by ¹H NMR. ^c Determined by chiral HPLC analysis.

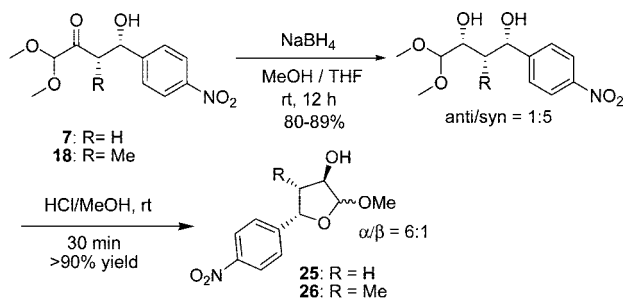
25 and **26** in high yields and unchanged enantioselectivities (Scheme 1). These products are important precursors for the synthesis of bioactive compounds.¹²

We obtained single crystals of 3-4'-bromobenzoyl-**25** (compound **25b**, see the Supporting Information), and the

(11) In a control reaction without aldehyde acceptors, the dimerization product of **4a** was isolated with 40% yield and 19% ee.

(12) For examples, see: (a) Lemoine, R. C.; Magon, A.; Hecker, S. J. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1121–1123. (b) Lin, A. J.; Benjamin, R. S.; Rao, P. N.; Loo, T. L. *J. Med. Chem.* **1979**, 22, 1096–1110.

Scheme 1. Synthetic Applications

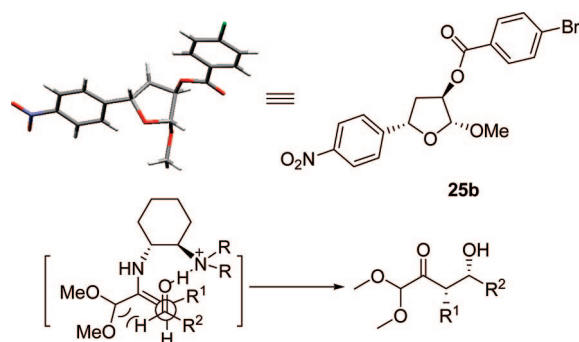


absolute configuration was then determined by X-ray crystallographic analysis (see the Supporting Information for details).¹³ The absolute configurations of the aldol products were therefore determined by analogy. The syn-relative configurations were determined by ¹H NMR and NOESY analysis of product **18** and **26**, respectively. Consistent with our previous studies, these configurations may be rationalized by a Z-enamine transition state as illustrated in Scheme 2.

In summary, we have developed highly efficient and stereoselective pyruvate–aldol reactions catalyzed by simple chiral primary–tertiary diamines. The present reactions accommodated a range of pyruvic donors and carbonyl acceptors with exceedingly high enantioselectivities and remarkable diastereoselectivities. The rather mild reaction conditions, the excellent stereocontrol, as well as the availability of both enantiomers of the chiral primary amines make

(13) Crystal data for **25b**: CCDC 675220 contains the supplementary crystallographic data for compounds **25b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. X-ray Crystal Structure of **25b** and Proposed Transition State



the current pyruvate–aldol reaction an attractive protocol for the synthesis of furanoses. Applications in natural product synthesis and further explorations of chiral primary amines in other enamine reactions are currently underway in our laboratory.

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

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