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SHORT COMMUNICATION

Chiral Primary Amine Organocatalysts for *Syn*-selective Asymmetric Cross-Aldol Reactions

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Abstract: Based on the "acid-base" interaction strategy, organocatalysts for the asymmetric cross-aldol reaction were synthesized by the in situ combination of chiral primary amines with protonic acids. Unlike general secondary amine catalysts that give *anti*-selective products, as-prepared primary amine catalysts can give *syn*-selective cross-aldol products with high yield and high selectivity (up to 90% yield, 90:10 *syn*/*anti* ratio, 90% ee). Compared with the complex synthesis of the reported catalysts, the primary amine catalyst that gave the best results was easily prepared using commercial available (1*S*,2*S*)-(+)-cyclohexanediamine.

Key words: chiral primary amine; organocatalysis; asymmetric catalysis; cross-aldol reaction

The aldol reaction is one of the most important carbon-carbon bond forming reactions in organic chemistry [1,2]. Since the pioneering work on the L-proline catalyzed asymmetric direct aldol reaction was reported by List et al. [3] in 2000, organocatalytic aldol reactions have become the most powerful and versatile tools to synthesize optically active *β*-hydroxy compounds [4,5]. Among these aldol reactions, asymmetric cross-aldol reactions of aldehydes can provide an attractive strategy for the construction of chiral *α*-substituted *β*-hydroxy aldehydes, which are important synthons in the synthesis of polypropionate and polyacetate products.

In 2002, Northrup et al. [6] reported the first asymmetric cross-aldol reaction of aldehydes using proline as a catalyst. Since then, a variety of organocatalysts have been designed and synthesized for this kind of cross-aldol reaction and the products are mainly *anti*-selective [7]. Recently, Kano et al. [8,9] reported *syn*-selective cross-aldol reactions that were catalyzed by axially chiral amino sulfonamide with high diastereoselectivity and enantioselectivity, however, the synthetic routes to obtain the catalyst are too convoluted. During our data collection for this paper, Li et al. [10] reported *syn*-selective cross-aldol reactions with good enantioselectivity that were catalyzed by chiral primary-tertiary diamine-Brönsted acid salts, however, the substrate scope and enantioselectivities were limited. Excellent *syn*-selectivities and enantioselectivities have previously been obtained while these catalysts have been used to catalyze the aldol reaction between aliphatic ketones and aromatic aldehydes [11]. Herein, we report the asymmetric *syn*-selective cross-aldol reaction of aldehydes (up to 90% yield, 90:10 *syn*/*anti* ratio, 90% ee), using easily prepared primary amine catalysts.

Diastereoselectivity control in these reactions depends on finding an appropriate catalyst based on a reasonable analysis of the reaction mechanism. Similar to the previously proposed mechanism [12], mechanism (I) for the proline catalytic cross-aldol reaction (Scheme 1) shows that the *E*-enamine transition state (TS) is the main factor that determines *anti*-selectivity in this reaction, and the carboxylic acid group of L-proline provides a hydrogen bond to stabilize the TS. However, the mechanism (II), we proposed for the primary amines catalyzed cross-aldol reaction, shows that *syn*-selectivity could be reasoned by the *Z*-enamine TS, and the N-H•O hydrogen bonds are assumed to stabilize the *Z*-enamine TS. Based on this model, various primary amines **1**–**7** were screened for the *syn*-selective asymmetric cross-aldol reaction (Scheme 2).

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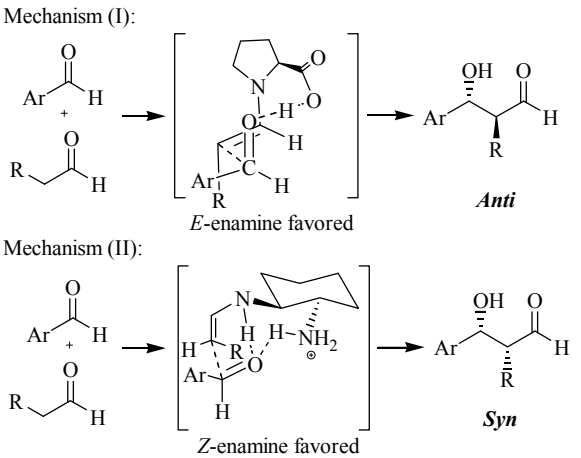
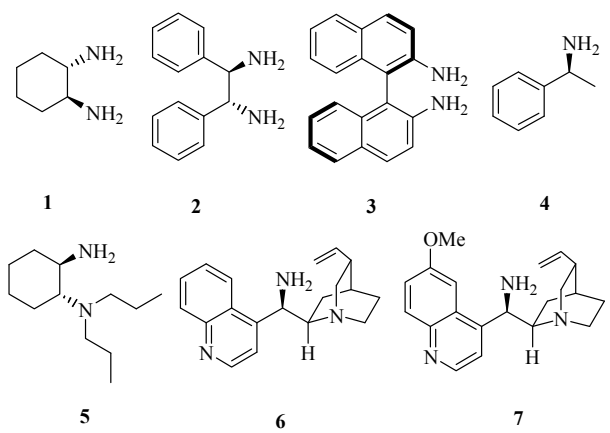


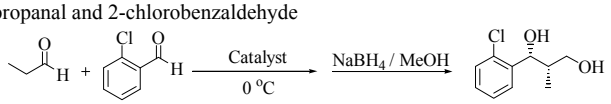
Scheme 1. Proposed mechanisms. (I) *Anti*-aldol transition state (TS) favored when using proline and its derivatives; (II) *Syn*-aldol TS favored when using primary amines.



Scheme 2. Chiral primary amines for the asymmetric cross-aldol reaction.

The cross-aldol reaction of propanal and 2-chlorobenzaldehyde was selected as a model reaction. The catalysts were prepared in-situ by stirring 0.1 mmol primary amine and 0.2 mmol trifluoroacetic acid (TFA) in CH_2Cl_2 for 0.5 h. After evaporating the solvent under reduced pressure, the residues obtained were used directly as catalysts for the reaction. All the aldol reaction products are known compounds [10,13]. The reaction results are listed in Table 1. ^{1}H NMR of the aldol products **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.89 (3H, m), 2.09–2.14 (1H, m), 2.58 (2H, brs), 3.68–3.79 (2H, m), 5.31(1H, d, J = 7.2 Hz), 7.20–7.25 (1H, m), 7.30–7.34 (2H, m), 7.56–7.58 (1H, d, J = 7.6 Hz); Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (*n*-hexane:2-propanol = 99:1, λ = 254 nm, 1.2 mL/min; major enantiomer t_r = 19.0 min, minor enantiomer t_r = 28 min, after conversion to the monobenzoyl ester [13]. Except for the primary amine catalysts **3** and **4** which gave trace amounts of the product (entries 3 and 4), all the other primary amine catalysts gave *syn*-selective cross-aldol products in accordance with the proposed mechanism (II). Using primary amine **3**, many side reactions were found by TLC detection. No products were found when using primary amine **4** and this may be attributed to the lack of hydrogen bonds that would stabilize the TS as proposed in mechanism (II). The best diastereoselectivity and enantioselectivity (82:18 *syn*/*anti* ratio, 79% ee) were achieved in the model reaction when using **1** [(1*S*,2*S*)-(+)-cyclohexanediamine] as the catalyst (entry 1). The commercially available (1*S*,2*S*)-(+)-cyclohexanediamine was then chosen as the primary amine to optimize the reaction conditions.

Table 1 Chiral primary amine catalysts for the cross-aldol reaction of propanal and 2-chlorobenzaldehyde



8 **9** **10**

Entry	Primary amine	Yield[a] (%)	*Syn*/*Anti*[b]	ee[b] (%)
1	**1**	79	82:18	79
2	**2**	73	76:24	–65
3[c]	**3**	—	—	—
4[c]	**4**	—	—	—
5	**5**	80	75:25	–55
6	**6**	83	78:22	27
7	**7**	87	74:26	29

Reaction conditions: in situ prepared catalysts with 0.1 mmol primary amine and 0.2 mmol trifluoroacetic acid (TFA), 1 mmol 2-chlorobenzaldehyde, 0.36 ml propanal, 0 °C, 72 h.
[a]Isolated yield. [b]Determined by chiral phase HPLC after conversion to the monobenzoyl ester. [c]No obvious aldol product was detected.

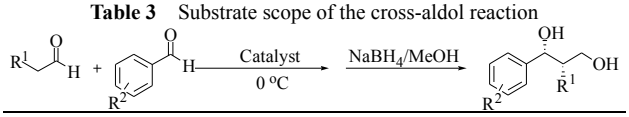
From the transition state model, the hydrogen-bond between NH_3^+ and the carbonyl group plays an important role in the *syn*-selectivity of the cross-aldol reaction of aldehydes. The strength of the hydrogen bond is dependent on the acidity of the additives. Therefore, different acid additives such as TFA, triflic acid (TfOH), acetic acid (HOAc), $H_3PW_{12}O_{40}$, and chiral camphorsulfonic acid (L-CSA) were screened in our work (Table 2). Higher yields, diastereoselectivities, and enantioselectivities (80% yield, 85:15 *syn*/*anti*, 90% ee) were obtained when using TfOH (Table 2, entry 2 vs entries 1, 3–5). After

Table 2 Optimization of the reaction conditions for primary amine **1** with different protonic acid additives

Entry	Additive	Yield[a] (%)	*Syn*/*Anti*[b]	ee[b] (%)
1	0.2 mmol TFA	73	82:18	79
2	0.2 mmol TfOH	80	85:15	90
3	0.2 mmol HOAc	69	68:32	38
4	0.067 mmol $H_3PW_{12}O_{40}$	75	69:31	64
5	0.2 mmol L-CSA	60	84:16	40
6	0.1 mmol TfOH	70	77:23	85
7	0.15 mmol TfOH	90	90:10	90

Reaction conditions: in situ prepared catalysts with 0.1 mmol primary amine **1** and the corresponding protonic acid additives, 1 mmol 2-chlorobenzaldehyde, 0.36 ml propanal, 0 °C, 72 h.
[a]Isolated yield. [b]Determined by chiral phase HPLC after conversion to the monobenzoyl ester.

Table 3 Substrate scope of the cross-aldol reaction



Entry	R^1	R^2	Time (h)	Yield[a] (%)	*Syn*/*Anti*[b]	ee[b] (%)
1	Me	4-NO_2	36	71	63:37	72
2	Me	3-NO_2	36	78	56:44	70
3	Me	2-NO_2	36	67	64:36	76
4[c]	Me	4-F	80	69	61:39	72
5[c]	Me	4-Cl	80	60	68:32	80
6[d]	Et	2-Cl	72	—	—	—
7[d]	*i*-Pr	2-Cl	72	—	—	—

Reaction conditions: in situ synthesized catalysts with 0.1 mmol primary amine **1** and 0.15 mmol TfOH, 1 mmol aromatic aldehyde, 0.36 ml propanal, 0 °C.

[a]Isolated yield. [b]Determined by chiral phase HPLC. [c]Determined by chiral phase HPLC after conversion to the monobenzoyl ester. [d]No obvious aldol product was detected.

that, different ratios of (1*S*,2*S*)-(+)-cyclohexanediamine to TfOH were also investigated (entries 6 and 7). The best result was a 90% yield, 90:10 *syn*/*anti*, and 90% ee for the 1:1.5 ratio (entry 7 vs entries 2 and 6).

Under the optimized conditions (Table 2, entry 7), the scope of the substrates in the cross-aldol reactions was expanded to a series of aldehyde donors and aromatic aldehyde acceptors (Table 3). In all these cases, *syn*-selective cross-aldol products were obtained and moderate diastereoselectivities as well as good enantioselectivities characterized the cross-aldol reactions of propanal with the other aromatic aldehydes. Unfortunately, no desired cross-aldol products were obtained when *n*-butyraldehyde and 3-methyl butanal were used as aldehyde donors and the mechanism for this phenomenon remains unclear [10].

In summary, primary amine organocatalysts based on our proposed mechanism for catalyst design efficiently catalyzed the *syn*-selective cross-aldol reaction of aldehydes with up to 90% yield, 90:10 *syn*/*anti*, and 90% ee. Compared with the complex synthesis of the reported catalysts, we present primary amine catalysts prepared from commercially available (1*S*,2*S*)-(+)-cyclohexanediamine. This paper may offer a new method to design catalysts for different selectivities in various reactions.

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