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Chiral 1,2-diaminocyclohexane as organocatalyst for enantioselective aldol reaction

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ABSTRACT

A simple and commercially available chiral 1,2-diaminocyclohexane as catalyst, hexanedioic acid as co-catalyst could efficiently catalyze the asymmetric aldol reaction in MeOH–H_2O. Cyclic ketones as aldol substrates gave the *anti*-β-hydroxyketone products with moderate to good yields, diastereoselectivity and enantioselectivity (up to 78% yield, >20:1 anti/*syn*, 94% ee). Hydroxyacetone as aldol substrate afforded the *syn*-α, β-dihydroxyketones as major products in up to 85% yield with good enantioselectivity (up to >20:1 *syn*/*anti*, 93% ee).

Aldol reaction, which generated many biologically active β-hydroxy products, is regarded as one of the most important carbon–carbon formation reactions.[1] Since the pioneering work was reported by List that L-proline **1** could catalyze the intermolecular aldol reaction,[2] the organocatalytic asymmetric aldol reaction has been at the center of research in asymmetric catalysis fields.[3] Many kinds of efficient organic catalysts have been developed for asymmetric aldol reaction with high yield and excellent enantioselectivity, such as **2**,[4] **3**,[5] **4**,[6] **5**,[7] **6**,[8] and **7**[9] (Fig. 1).

Similar to the proline and non-proline-derived secondary amine catalysts, primary amine organocatalysts **8**[10] and **9**[11](Fig. 2) from natural acyclic amino acids also showed good asymmetric catalytic action for aldol reaction. Recently, Luo et al. reported a new kind of primary amine catalyst **10** (Fig. 2) derived from chiral 1,2-diaminocyclohexane, which catalyzed the aldol reaction affording the aldol products in excellent yields (up to 95%) and enantioslectivity (up to 96% ee).[12] These wonderful results attracted more organic chemists turning their attention on the primary amine-based organocatalysts.[13]

To our best known, most of the primary amine-typed catalysts, such as catalysts **8**–**10**, suffered from the inconvenient synthesis from natural amino acid or diaminocyclohexane **11** (Fig. 2). In previous study, we disclosed that simple and commercially available chiral 1,2-diaminocyclohexane **11** could act as an effective organocatalyst in the Micheal addition reactions of γ-butenolides[14] and cyclopentanone[15] with chalcones to give products with up to 99% ee. These findings encouraged us to explore a possibility of **11** to catalyze the direct aldol reaction. Herein, we present the primary results of catalytic efficiency of **11** for asymmetric aldol reaction.

As shown in Table 1, with hexanedioic acid (20 mol %) as co-catalyst and methanol as solvents, the aldol products **14** was formed in 40% isolated yield with 4:1 *anti*/*syn* ratio. The major diastereomer, *anti*-**14a**, had 89% ee. Further studies showed that the yield of **14a** could be dramatically increased to 75% when a 1:1 MeOH–H_2O mixture was used as solvent.

Subsequently, the effects of different additives, temperature, and catalyst loading on the reaction were tested. It is worthy to note that the acid as an additive played an important role in this reaction. Replacing hexanedioic acid with AcOH or TFA, the yield and the enantioselectivity significantly decreased (entries 9 and 10, Table 1). The catalyst **11** lost completely the catalytic capability in the absence of acid (entry 11, Table 1). Lowering the temperature (0 °C, entry 12, Table 1) and reducing the catalyst loading (10 mol %, 5 mol %, entries 13 and 14, Table 1) were detrimental to the results.

With the optimized conditions in hand, the scope of the reaction was then explored and the results were showed in Table 2. It appears that aromatic aldehydes with electron-withdrawing groups could react with cyclohexanone **12a** affording the corresponding products in good yields (40–78%) with moderate to high diastereoselectivity and good enantioselectivity (**13a**–**13e**, entries 1–5, Table 2). Among them, the reaction with 2-nitrobenzaldehyde **13c** and 2-trifluoromethylbenzaldehyde **13e** gave exceptional high *anti*/*syn* ratio (>20:1). These results indicated that the *ortho* substituents were critical for the diastereoselectivity of the reaction. Reaction of aldehydes **13f**–**13g** with cyclohexanone **12a** gave the moderate ee values (entries 6 and 7, Table 2). While reaction of

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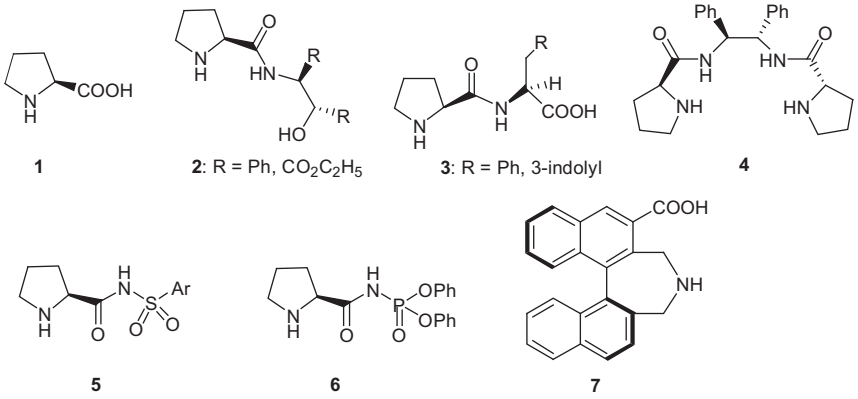


Figure 1. Secondary amine-typed organocatalysts.

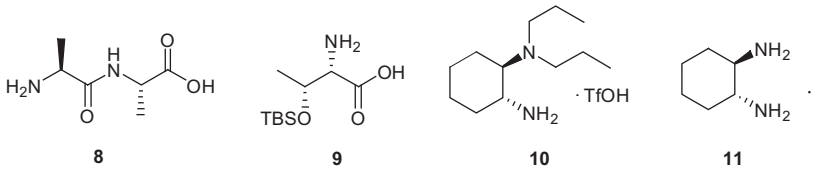
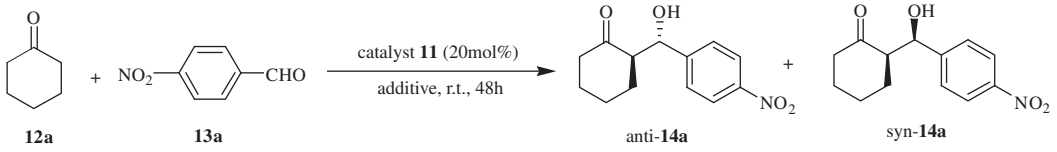


Figure 2. Primary amine-typed organocatalysts.

Table 1
Reaction condition screening for the reaction of cyclohexanone and 4-nitrobenzaldehyde[a]



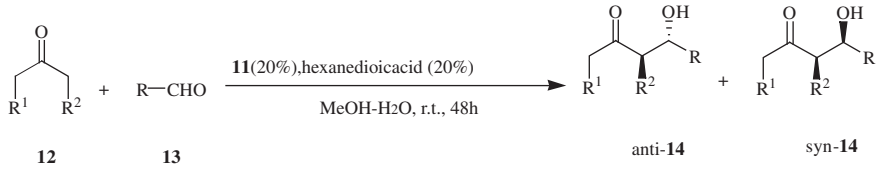
Entry	Additive	Solvent	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	HDA (20 mol %)	MeOH	40	4:1	89
2	HDA (20 mol %)	H_2O	20	2:1	92
3	HDA (20 mol %)	THF	—	—	—
4	HDA (20 mol %)	DMSO	—	—	—
5	HDA (20 mol %)	DMF	—	—	—
6	HDA (20 mol %)	PhMe	—	—	—
7	HDA (20 mol %)	MeOH/$CHCl_3$	Trace	—	—
8	HDA (20 mol %)	MeOH/H_2O	75	4:1	93
9	AcOH (40 mol%)	MeOH/H_2O	20	3:1	75
10	TFA (40 mol%)	MeOH/H_2O	Trace	—	—
11	—	MeOH/H_2O	0	—	—
12	HDA (20 mol %)	MeOH/H_2O	5[e]	—	—
13	HDA (10 mol %)	MeOH/H_2O	30[f]	2:1	90
14	HDA (5 mol %)	MeOH/H_2O	10[g]	—	89

[a] The reaction was performed with aldehyde (0.2 mmol), cyclohexanone (0.6 mmol) for 48 h.
[b] Isolated combined yields of *anti*-**14a** and *syn*-**14a**.
[c] Determined by ^{1}H NMR.
[d] ee% of *anti*-**14a**, determined by chiral HPLC.
[e] The reaction was carried out at 0 °C.
[f] Using 10 mol % catalyst **11**.
[g] Using 5 mol % catalyst **11**.

4-nitrobenzaldehyde **13a** with cyclopentanone **12b** provided low ee value (40% yield, 26% ee, entry 8, Table 2). It showed that decrease of ring size of cyclohexanone was unfavorable for the yield and enantioselectivity.

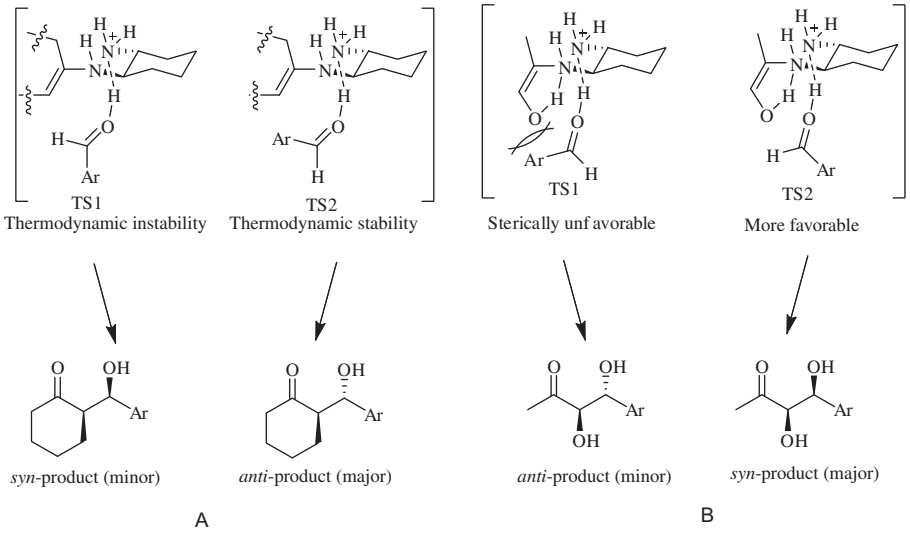
Hydroxyacetone-based aldol reaction is of considerable importance to provide expedient access to both natural carbohydrates and unnatural polyhydroxylated molecules.[16] Many kinds of organocatalysts have been developed for this reaction. Gong's

Table 2
Reaction of different ketones with aldehydes[a]



Entry	R^1, R^2	R	Yield of products[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	$-(CH_2)_3-$ (**12a**)	4-NO_2-phenyl (**13a**)	75 (**14a**)	4:1	93
2	$-(CH_2)_3-$ (**12a**)	3-NO_2-phenyl (**13b**)	78 (**14b**)	5:1	90
3	$-(CH_2)_3-$ (**12a**)	2-NO_2-phenyl (**13c**)	40 (**14c**)	>20:1	94
4	$-(CH_2)_3-$ (**12a**)	4-CF_3-phenyl (**13d**)	74 (**14d**)	3:1	84
5	$-(CH_2)_3-$ (**12a**)	2-CF_3-phenyl (**13e**)	70 (**14e**)	>20:1	90
6	$-(CH_2)_3-$ (**12a**)	4-Pyridinyl (**13f**)	50 (**14f**)	1:1	81
7	$-(CH_2)_3-$ (**12a**)	3-Pyridinyl (**13g**)	70 (**14g**)	2:1	62
8	$-(CH_2)_2-$ (**12b**)	**13a**	40 (**14h**)	1:2	26
9	H, OH (**12c**)	**13a**	80 (**14i**)	2:3	63
10	**12c**	**13b**	85 (**14j**)	3:7	85
11	**12c**	**13c**	85 (**14k**)	<1:20	89
12	**12c**	**13d**	50 (**14l**)	2:3	50
13	**12c**	**13e**	68 (**14m**)	<1:20	93
14	**12c**	2-Cl-phenyl (**13h**)	65 (**14n**)[e]	<1:20	89

[a] The reaction was performed with aldehyde (0.2 mmol), cyclohexanone (0.6 mmol) for 48 h.
[b] Isolated combined yields of *anti*-**14** and *syn*-**14**.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC of major isomer.
[e] Reaction for 72 h.



Scheme 1. Proposed di-iminium activation of both substrates in the aldol reactions of hydroxyacetone with aromatic aldehydes.

group reported that proline derivatives **2** could effectively catalyze this reaction affording the linear isomer with excellent enantioselectivity.[17] Zhao[18] and Luo[19] found that using L-threonine and diaminocyclohexane derivatives as catalysts in this reaction could selectively give the branched isomer *syn*-**14** with excellent enantioselectivity. Even though, it still remained a challenge to find more simple and efficient catalyst.[20] Thus, we further explored the asymmetric reaction of hydroxyacetone **12c** with various aldehydes under our reaction conditions.

As showed in Table 2, in all the cases of hydroxyacetone as the aldol substrate, the branched *syn*-isomer **14** was obtained as major products in good yields (50–85%) and good to excellent enantioselectivity (50–93% ee).[1e,21,22] Such as, 2-cholo-benzyl-aldehyde (**13h**) gave product **14n** in 65% with >20:1 *syn*/*anti* and 89% ee (entry 14, Table 2), which is much better than the Paradowska's result(1:1 *anti*/*syn*, 23% ee).[23] Likewise, *ortho*-substituted aromatic aldehydes also achieved higher diastereoselectivity (up to >20:1 *syn*/*anti*, entries 11, 13, and 14, Table 2) than *para*- or *meta*-substituted aromatic aldehydes (entries 9, 10, and 12, Table 2). The absolute configuration of compounds *syn*-**14k** and *syn*-**14n** was determined by comparing our chiral HPLC result with Gong's results.[1e]

To account for the formation of predominant *syn*-products in the cases of hydroxyacetone **12c** as a substrate, we proposed a possible transition states TS1 and TS2 as shown in B, Scheme 1, in which both substrates could be activated simultaneously by protonated primary amino-groups of 1,2-diaminocyclohexane. It could be seen clearly that TS1 is sterically unfavorable and TS2 is more favorable leading to the formation of the major *syn*-stereoisomer. While for cyclohexanone, TS2 is favorable for the thermodynamic stability to produce the major *anti*-stereoisomer (A, Scheme 1).

In conclusion, we have developed an efficient asymmetric aldol reactions of ketones and aromatic aldehydes using a simple and commercially available chiral 1,2-diaminocyclohexane as catalyst, hexanedioic acid as co-catalyst in MeOH–H_2O. It was found the aromatic aldehydes with electron-withdrawing groups could react with cyclic ketone affording the corresponding product in good yields (40–78%), with high diastereoselectivity (up to >20:1 *anti*/*syn*) and enantioselectivity (up to 94% ee). While for acyclic hydroxyacetone, *syn*-dihydroxyketones as the major products were obtained in good yields with enantioselectivity(up to 85% yield, >20:1 *syn*/*anti*, 93% ee). The proposed transition state model helps to explain the substrate-dependent diastereoselectivity.

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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.2011.04.116.

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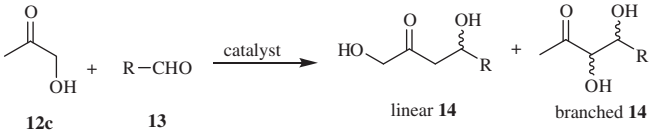
22. Reaction of hydroxyacetone **12c** with various aldehydes could provide linear **14** and/or branched isomers **14**.



12c **13** linear **14** branched **14**

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