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Highly stereoselective anti-aldol reactions catalyzed by simple chiral diamines and their unique application in configuration switch of aldol products

Lei Li [a], Shaohua Gou [a,b,*], Fei Liu [a]

[a] Pharmaceutical Research Center and School of Chemistry and Chemical Engineering, Southeast University, Nanjing 211189, China
[b] Jiangsu Province Hi-Tech Key Laboratory for Bio-medical Research, Southeast University, Nanjing 211189, China

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ABSTRACT

Chiral derivatives of *trans*-1,2-diaminocyclohexane with different *N*,*N*-dialkyl groups in well-defined orientations have been synthesized, and applied as catalysts for the asymmetric aldol reaction between a variety of aldehydes and ketones. Enantiomeric catalyst **1j** catalyzed the reaction in ethanol and provided excellent diastereoselectivity and enantioselectivity. Significantly, simple replacement of organic solvents with water switched the products of the aldol reactions from *anti* to *syn* configuration. Such catalytic reactions led to the products with *anti* to *syn* diastereoselectivity up to 99:1 in ethanol, while in water gave the products with *syn* to *anti* diastereoselectivity up to 99:1.

The aldol reaction is one of the most fundamental tools for the construction of carbon–carbon bonds, it can produce β-hydroxyl carbonyl compounds, which are key intermediates or synthetic building blocks for many natural products and drugs.[1]

Asymmetric aldol reactions of ketones with aldehydes usually offer chiral compounds with one or multiple stereocenters, and such highly enantio- and diastereo-selective reactions generating two stereocenters in one step are valuable for asymmetric synthesis. Generally, four products with different mirror images derived from the reaction of symmetric ketone and aromatic aldehyde can be obtained as shown in Scheme 1. According to the previous reports, chiral catalysts would generate the relevant products for each pair of ketones and aldehydes, either *syn*[2] or *anti* enantiomers.[3] So far, in the reaction between cyclohexanone and aldehydes, almost all of the organocatalyts are known to provide *anti*-aldol adducts predominantly, albeit with a few limited exceptions which afford *syn*-products. Thus, employing one single chiral catalyst to control the relative stereochemical configuration of aldol products in such reactions is still challenging.

Since List and Barbas reported the direct aldol reaction of acetone with aryl aldehydes catalyzed by L-proline[4], many kinds of proline-derivated catalysts have been developed for asymmetric aldol reactions.[3a,3b,3d,5] Recently, the application of chiral *trans*-1,2-diaminocyclohexane (abbreviated as DACH) derivatives, which are stable and easy to obtain and modify, has received rapidly growing attention. However, most successful DACH based catalysts are involved with the modification of the monoamines, for example lactamization, sulfonamidization, and thioureation,[6] mimicking enzymatic activities.[1h,6a,6b,7]

Chiral *N*,*N*-dialkyl diamines have been successfully applied by Cheng[2b,8] to catalyze a series of asymmetric aldol reactions. In their reactions of cyclohexanone with aldehydes,[8c] the results with main products in *anti*-configuration were fairly good (up to 95% yield, 10:1 *anti*/*syn*, 98% ee). However, no compounds in *syn* configuration as major products were mentioned. To our knowledge, only Gao and his co-workers[9] recently reported a configuration switch in asymmetric aldol reactions. In their experiments, a chiral diamine combined with succinic acid could catalyze the *syn*-aldol reaction of both cyclohexanone and cycloheptanone with five aromatic aldehydes (up to 94% yield, 1.8:1–5:1 *syn*/*anti*, 53–88% *ee*), either by increasing the size of the additive acids or by introducing a hydrogen-bond donor into the additive acids.

Herein reported is a series of modified diamine catalysts derived from DACH that exhibit excellent diastereoselectivity and enantioselectivity in aldol reactions in ethanol, and their application in the challenging *syn*-aldol reaction.

Modified diamine catalysts were synthesized starting from the commercial chiral diamine **2**. All catalysts except **1a** and **1k** were easily prepared from **2** in a 4-step sequence as shown in Scheme 2, whereas **1a** was obtained by omitting step (c) and **1k** was prepared

* Corresponding author.
E-mail address: sgou@seu.edu.cn (S. Gou).

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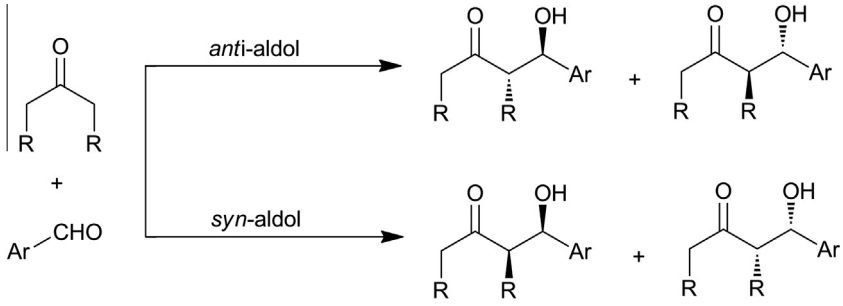
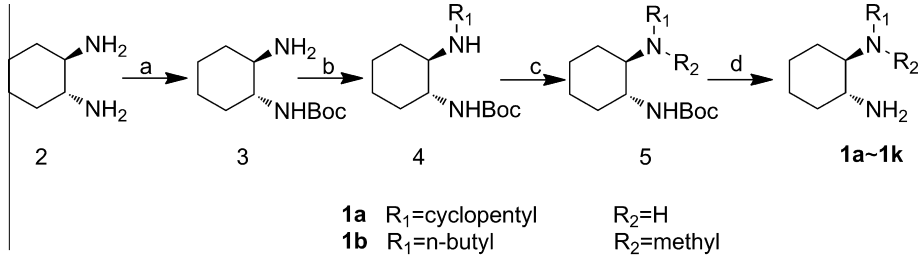


Scheme 1. Four stereoisomeric products of asymmetric aldol reactions between symmetric alkanone and aryl aldehyde.



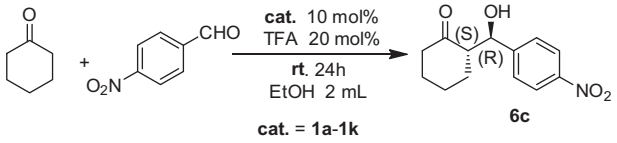
1a R_1=cyclopentyl R_2=H
1b R_1=n-butyl R_2=methyl
1c R_1=i-butyl R_2=methyl
1d R_1=t-pentyl R_2=methyl
1e R_1=cyclohexyl R_2=methyl
1f R_1=cyclopentyl R_2=methyl
1g R_1=cyclopentyl R_2=ethyl
1h R_1=cyclopentyl R_2=n-propyl
1i R_1=cyclopenyl R_2=n-butyl
1j R_1=cyclopentyl R_2=n-pentyl
1k R_1=cyclopentyl R_2=cyclopentyl

Scheme 2. Synthesis of catalysts. Reagents and conditions: (a) Boc_2O, CH_3OH; (b) alkyl aldehyde or ketone, $NaBH_4$, CH_3OH; (c) alkyl aldehyde or ketone, $NaBH_3CN$, CH_3OH; (d) HCl, H_2O.

by a literature method.[10] To probe the activity of different catalysts, asymmetric aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde was firstly carried out as a model experiment (shown in Table 1). The poor catalytic performances observed for **1a** and **1k** (entries 1 and 11) highlighted the importance of the *N*, *N*-dialkylated DACH structure. Among catalysts **1b**–**1f** (entries 2–6), which have different R_1 but the same R_2 group, **1f** had the best effect (R_1 = cyclopentyl). This result confirmed that spatial hindrances would create specific interactions between the organocatalyst and their substrates.[8a,11] Catalyst **1g** with the same R_1 as **1f** and a little long alkyl group (R_2 = ethyl) afforded better diastereoselectivity than **1f** (entry 6 vs 7). This result inspired us looking for the longer alkyl carbon chain of R_2 (entries 6–10). And finally, in consideration of the catalytic effect and the difficulty of synthesis, **1j** gave the optimal results. This result may be due to the two dialkyl substituents on the monoamine, since the cyclopentyl group is one of the most stable rigid aliphatic rings, and meanwhile the pedant-armed group increases the hindrance additionally.

Additionally, auxiliary acids were evaluated by catalyzing the reaction between cyclohexanone and *o*-nitrobenzaldehyde in alcohol (shown in Table 2). It was observed that the ratio of *syn*-product had a slight increase with *anti*/*syn* of the product reaching 35:1 from 48:1 (Table 2, entry 6 vs Table 1, entry 10), but the reaction time was extended to 3 days when the temperature was decreased to 0 °C. This result demonstrated that the formation of *syn*-product could be controlled by the temperature. Five different acids were tested, but only TFA gave the best result (entries 1–5). It is significantly noted that the increase of the size of the additive acid was not an effective way to improve the *syn*/*anti* ratio. This fact was also confirmed in Gao's work[9], though they attributed the increased ratio of *syn*-/*anti*- aldol products to the increasing size of the acids. The amount of auxiliary acid seemed to be an important factor (entries 5–9) in the reaction. The highest amount of *anti*-product was observed by increasing the TFA amount to

Table 1
Screening of catalysts



Entry[a]	Cat.	Yield[b] (%)	Anti/syn[c]	*ee*[d] (%)
1	1a	5	3:1	23
2	1b	37	5:1	96
3	1c	34	14:1	97
4	1d	67	7:1	94
5	1e	58	14:1	96
6	1f	82	27:1	>99
7	1g	74	34:1	>99
8	1h	73	43:1	>99
9	1i	78	48:1	>99
10	1j	95	49:1	>99
11	1k	Trace	—	—

[a] The reaction of *p*-nitrobenzaldehyde (0.5 mmol) with cyclohexanone (1.5 mmol) in ethanol (2 mL) was carried out in the presence of cat. (0.05 mmol) and TFA (0.1 mmol) at room temperature.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Determined by HPLC analysis of the *anti* product.