Enantiodivergence by minimal modification of an acyclic chiral secondary aminocatalyst

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The development of enantiodivergent catalysis for the preparation of both enantiomers of a chiral compound is of importance in pharmaceutical and bioorganic chemistry. With the design of a class of reactive and stereoselective organocatalysts, acyclic chiral secondary amines, a method for achieving the enantiodivergence is developed simply by changing the secondary N-i-Bu- to N-Me-group within the catalyst architecture while maintaining the same absolute configuration of the catalysts, which modulates the catalyst conformation. This catalyst-controlled enantiodivergent method not only enables challenging asymmetric transformations to occur in an enantiodivergent manner but also features a high level of stereocontrol and broad scope that is demonstrated in eight different reactions (90 examples), all delivering both enantiomers of a range of structurally diverse products including hitherto less accessible, yet important, compounds in good yields with high stereoselectivities.
Different enantiomers of a biologically active molecule generally have different or even opposite biological activities. For example, (2S,3S)-paclobutrazol is a plant growth regulator while (2R,3R)-paclobutrazol is a fungicide. Enantiodivergent syntheses through catalytic asymmetric transformations are one of the most powerful and economical approaches for the stereo-selective synthesis of both enantiomeric products. Although impressive advances have been made, existing catalytic enantiodivergent methods are still limited in scope and may not be suitable for all desired transformations. Meanwhile, there appears a growing number of challenging transformations that cannot be catalyzed effectively by existing chiral catalysts. Thus the development of chiral catalysts and methods enabling challenging asymmetric transformations to occur in an enantiodivergent manner remains significant challenges.

In asymmetric aminocatalysis, chiral secondary amines employed are usually cyclic. The rationale is that the cyclic strain increases the nucleophilicity of the amine and the cyclic structure limits bond rotation, providing a well-organized chiral environment. In contrast, acyclic chiral secondary amine catalysts with both reactivity and stereocenters comparable to cyclic chiral secondary aminocatalysts remain elusive. Meanwhile, the application of acyclic chiral secondary aminocatalysts in enantiodivergent transformations is not reported.

Herein we describe our studies on designing and engineering acyclic chiral secondary aminocatalysts for enantiodivergent, asymmetric reactions. By strategically changing the (achiral) secondary N-alkyl group (within the catalyst architecture) for modification of secondary amine while maintaining the same absolute configuration of the catalysts, a reversal of the enantioslectivity is achieved. This enantiodivergent strategy not only enables asymmetric transformations to occur in an enantiodivergent manner but also features broad scope and high levels of stereocontrol, as demonstrated by its application to 8 different reactions (90 examples), including 7 reactions generating 2 stereocenters, all delivering both enantiomers of structurally diverse products in good yields with good enantioselectivity and diastereoselectivity.

### Results

**Mannich reaction of \(\beta,\gamma\)-alkynyl-\(\alpha\)-imino esters.** Acyclic chiral secondary amine catalysts, which we designed, were easily prepared from acyclic \(\alpha\)-amino acids (for details, see Supplementary Note 2). First, they were tested to catalyze enantiodivergent Mannich reactions between aldehydes and \(C\)-alkynyl ketimines. The resulting products, \(\alpha\)-imino esters bearing quaternary stereocenters, are of synthetic and biological importance. Although the catalytic asymmetric direct Mannich reactions of aldehydes with \(C\)-alkynyl ketimines have recently emerged, the corresponding catalytic asymmetric direct Mannich reactions of aldehydes with \(C\)-alkynyl ketimines providing quaternary \(\alpha\)-imino esters have not yet been realized.

Treatment of 1a and 2a with the acyclic chiral secondary amine catalyst 1a/0.5TfOH in MeCN at \(-40^\circ\) afforded the corresponding Mannich product 3a in good yield; the major isomer, \(\text{anti-3a}\), with the \((3R,4R)\) configuration, was obtained with >20:1 dr (\(\text{anti/syn}\)) and 98:2 er (Table 1, entry 1). The potential

### Table 1 Optimization of the enantiodivergent Mannich reaction

| Entry | Catalyst | \(t\) [h] | Yield [%] | dr [\(\text{anti/syn}\)] | er |
|-------|----------|----------|-----------|--------------------------|-----|
| 1     | Ia/0.5TfOH | 10       | 82        | >20:1                    | 98.2|
| 2     | Ib/0.5TfOH | 10       | 65        | 7:1                      | 39.5-60.5|
| 3     | Ic/0.5TfOH | 14       | 83        | 14:1                     | 17.83|
| 4     | Id/0.5TfOH | 14       | 87        | 8:1                      | 8.92|
| 5     | Ie/0.5TfOH | 14       | 67        | 5:1                      | 14:86|
| 6a    | Id/0.5TfOH | 10       | 78        | >20:1                    | 3.5-96.5|
| 7     | Id        | 72       | Trace     | —                        | — |
| 8     | II/0.5TfOH | 48       | Trace     | —                        | — |
| 9     | III       | 48       | Trace     | —                        | — |
| 10    | IV        | 48       | Trace     | —                        | — |

1. Unless otherwise specified, the asymmetric direct Mannich reaction of \(\beta,\gamma\)-alkynyl-\(\alpha\)-imino ester 1a (0.1 mmol) and propionaldehyde 2a (0.3 mmol) was conducted in the presence of catalyst (20 mol %) and p-\(\text{NO}_2\)-C\(_6\)H\(_4\)-CO\(_2\)H (20 mol %) in MeCN (0.8 mL) at \(-40^\circ\)
2. Yield of isolated product
3. Determined by chiral HPLC
4. Dichloroethane was used as the solvent
1.4-addition onto the alkynyl ketimines was not observed. When secondary N-i-Bu was changed to N-Me within the catalytic architecture, a reversal of enantioselectivity was observed, and the enantiomERIC Mannich product (R,S)-3a was obtained with 7:1 dr and 39.5:60.5 er (entry 2). Optimization of R1 and R3/R3′ substituents of I (keeping R2 = Me) led us to identify Id/0.5TfOH as the optimal catalyst for the enantioselective Mannich product (R,S)-3a with good enantioselectivity and diastereoselectivity (entry 4). When dichloroethane (DCE) was used as the solvent, the diastereoselectivity and enantioselectivity of (R,S)-3a was further improved to >20:1 dr and 3.5:96.5 er, respectively (entry 6). In order to further evaluate the efficiency of our acyclic chiral secondary amine organocatalysts, we compared the performance of 1a and with both high diastereoselectivity and enantioselectivity, while the use of catalyst Id/0.5TfOH gave anti-Mannich adducts (R,S)-3a with the opposite absolute configuration in good yields with both high diastereoselectivity and enantioselectivity. It is mentioned that catalytic asymmetric direct Mannich reactions of aldehydes with acyclic ketimines have not previously been realized.

**Origin of the reversal of enantioselectivity.** Based on the above observations and combined with density functional theory (DFT) calculations (for the details, see Supplementary Note 12), we propose the following possible transition state models (Fig. 2) to account for the observed absolute configuration of both Mannich products. In the case of 1a (N-i-Bu), the enamine 1a-int-I with s-syn C-N skeleton is energetically favored over the enamine 1a-int-II with s-anti C-N skeleton. The dominant s-syn enamine 1a-int-I is used for the C–C bond forming step via transition state TS-I (with the tertiary ammonium H-bonded to the imine N)31; the Si face of the enamine reacts with the Re face of the imine. TS-II involving s-anti-enamine 1a-int-II is disfavored compared to TS-I due to unfavorable steric repulsion. In contrast, in the case of Id (N-i-Me), the enamine Id-int-II with s-anti C-N skeleton is energetically favored over the enamine Id-int-I with s-syn C-N skeleton. The Re face of the s-anti enamine reacts with the Si face of the imine via the favorable TS-IV, which gives the RS isomer predominantly.

**Mannich reaction of trifuoromethyl alkynyl ketimines.** Our developed enantiodivergent catalysts, 1a/0.5TfOH and Id/0.5TfOH, could also efficiently catalyze the asymmetric direct Mannich reactions between aldehydes and trifluoromethylated alkynyl ketimines (Fig. 3). These reactions provide an enantiodivergent catalytic asymmetric synthesis of quaternary propargylamines bearing trifluoromethyl group. Installing the trifluoromethyl (CF₃) functionality into molecular architectures is an important objective in the pharmaceutical industry32. In order to further evaluate the efficiency of our acyclic chiral secondary amine organocatalysts, we compared the performance of 1a and with cyclic chiral secondary amine catalysts III and IV as well as chiral primary amine catalyst II. We found that II could not promote this reaction, while III and IV afforded poor enantioselectivity and diastereoselectivity with complementary relative configuration (for details, see Supplementary Table 2).

**Mannich reactions of cyclic ketimines.** Next, designed enantiodivergent catalysis was explored in the asymmetric direct Mannich reactions of aldehydes with cyclic ketimines. When the reactions of isatin-derived ketimines 6 with aldehydes 2 were carried out in the presence of 1a/0.5TfOH and Id/0.5TfOH, respectively, both enantiomers of the desired Mannich products, anti-7, were obtained in good yields with both high diastereoselectivity and enantioselectivity (Fig. 4). Thus these reactions provide a highly stereoselective method for the catalytic asymmetric enantiodivergent synthesis of 3-substituted 3-amino-2-oxindoles53.

Designed enantiodivergent catalysis was also applicable to the unknown Mannich reaction between a monocyclic ketimine, 8, and 2a (Fig. 5). Both enantiomers of the functionalized chiral pyrazolone 9 were obtained in good yields with both high diastereoselectivity and enantioselectivity, in the presence of catalyst 1a/0.5TfOH (N-i-Bu) and 1e/0.5TfOH (N-Me), respectively54.
The above Mannich reactions are notable in that catalytic asymmetric enantiodivergent Mannich reactions between aldehydes and ketimines have not previously been reported.\(^55–59\)

Cross-aldol reaction of aldehydes with isatins. Next, we sought to further establish the generality of designed enantiodivergent catalysis to test other classes of reactions. First, we targeted the catalytic asymmetric aldol reactions. Among them, the catalytic asymmetric direct cross-aldol reaction of aldehydes with isatins, which is a potentially useful method for the synthesis of chiral 3-substituted 3-hydroxy-2-oxindoles, was first tested. Only few chiral catalysts have been reported for this reaction, and only 4-halogen-substituted isatin substrates can furnish acceptable levels of diastereoselectivities.\(^60,61,62\) When other isatins were used as substrates, poor diastereoselectivities (1.4:1–1.6:1 dr) were observed.\(^61–63\) Pleasingly, we found that, in the presence of our acyclic chiral secondary amine \(\text{If}^\)
Aldehyde–aldehyde cross-aldol reaction. The designed enantiodivergent catalysis methodology was also applicable to the direct aldehyde–aldehyde cross-aldol reaction.\(^{43,65}\) 1a (N-i-Bu) gave the anti-aldol products (S,R)-11, while 1b (N-Me) afforded the enantiomer products (R,R)-13 (Fig. 7). It should be noted that the chiral primary amine II was previously reported by Luo and co-workers\(^{82}\) for this reaction to give the complementary syn-selective aldon product (S,R)-13. Taken together, these reactions constitute a rare example where both enantiodivergence and diastereodivergence is achieved simply by a modest change within the catalytic architecture while maintaining the same absolute configuration.

\(\text{α-Amination reaction of aldehydes.}\) Finally, we explored the possibility of the designed enantiodivergent catalysis for the formation of single stereocenters and tested the α-amination reaction of aldehydes.\(^{67-69}\) II (N-i-Bu) gave the (S)-configured aminated products, and the switch to 1e (N-Me) resulted in a reversal in enantioselectivity (Fig. 8).

Discussion
In summary, by designing a class of reactive and stereoselective acyclic chiral secondary amines as organocatalysts that are easily available and highly modular, we have developed a method for achieving the enantiodivergence, especially in challenging asymmetric transformations. Simple yet strategic modification of the secondary N-substituent (specifically, from \(\text{N-i-Bu-}\) to \(\text{N-Me-}\) group) of secondary amine while maintaining the same absolute configuration of the catalyst led to a reversal of the enantioselectivity through conformation modulation of the catalyst. Besides the high level of stereoselectivity achieved, this designed approach to enantiodivergent catalysis displays broad scope that is demonstrated in eight different transformations including seven reactions involving two prochiral reactants with simultaneous control of diastereoselectivity, all delivering both enantiomers of a range of structurally diverse products including hitherto less accessible yet important compounds in good yields with good stereoselectivities. The present study has made an advance in enantiodivergent organocatalysis. Also it showcases the potential of acyclic chiral secondary aminocatalysts in enantiodivergent catalysis as well as the unusual reactivity and stereoselectivity of acyclic chiral...
Methods

Mannich reaction of \(\beta,\gamma\)-alkylnyl-\(\alpha\)-imino esters by la. To a solution of \(\beta,\gamma\)-alkylnyl-\(\alpha\)-imino ester 1 (0.1 mmol), 4-nitrobenzoic acid (3.3 mg, 0.02 mmol), and catalyst la/0.5TfOH (6.7 mg, 20 mol%) in anhydrous MeCN (0.8 mL) was added aldehyde 2 (0.3 mmol) at \(-40^\circ C\). The reaction mixture was stirred at this temperature until 1 disappeared via thin-layer chromatography (TLC) detection. Then NaBH\(_4\) (19.2 mg, 0.5 mmol) and MeOH (0.5 mL) were added at \(-20^\circ C\). The resulting mixture was stirred for 0.5 h, then recovered to room temperature and kept stirring for 1 h. Finally, the resulting mixture was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/10–1/5) to afford the Mannich product (S,R)-3.

Mannich reaction of \(\beta,\gamma\)-alkylnyl-\(\alpha\)-imino esters by ld. To a solution of \(\beta,\gamma\)-alkylnyl-\(\alpha\)-imino ester 1 (0.1 mmol), 4-nitrobenzoic acid (3.3 mg, 0.02 mmol), and catalyst Id/0.5TfOH (5.6 mg, 20 mol%) in anhydrous DCE (0.8 mL) was added aldehyde 2 (0.3 mmol) at \(-40^\circ C\). The reaction mixture was stirred at this temperature until 1 disappeared via TLC detection. Then NaBH\(_4\) (19.2 mg, 0.5 mmol) and MeOH (0.5 mL) were added at \(-20^\circ C\). The resulting mixture was stirred for 0.5 h, then recovered to room temperature and kept stirring for 1 h. Finally, the resulting mixture was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/10–1/5) to afford the Mannich product (R,S)-3.

Secondary aminocatalysts, which are not observable with existing chiral amine catalysts.

Fig. 5 Enantiodivergent Mannich reaction of monocyclic ketimines. Reaction conditions for the formation of (S,R)-9: 8 (0.1 mmol), MNBA (0.02 mmol, 20 mol %), la/0.5TfOH (20 mol %), 2a (0.3 mmol), MeCN (0.8 mL), \(-40^\circ C\). Reaction conditions for the formation of (R,S)-9: 8 (0.1 mmol), MNBA (0.02 mmol, 20 mol %), le/0.5TfOH (20 mol %), 2a (0.3 mmol), MeCN (0.8 mL), \(-40^\circ C\).

Fig. 6 Enantiodivergent cross-aldol reaction of isatins. Reaction conditions for the formation of (S,S)-11: 10 (0.1 mmol), H/0.5TfOH (20 mol %), 2 (0.3 mmol), THF (0.8 mL), \(-40^\circ C\). Reaction conditions for the formation of (S,S)-11: 10 (0.1 mmol), MNBA (0.02 mmol, 20 mol %), Ig/TfOH (20 mol %), 2 (0.3 mmol), i-PrOH (0.8 mL), \(-20^\circ C\). Single asterisk (*): Run at \(-20^\circ C\). Double asterisks (**) Run at 0°C in DMF (N,N-dimethylformamide).

Fig. 7 Enantiodivergent aldehyde–aldehyde cross-aldol reaction. Reaction conditions for the formation of (S,S)-13: 12 (0.1 mmol), MNBA (0.02 mmol, 20 mol %), la/0.5TfOH (20 mol %), 2a (0.3 mmol), THF (0.8 mL), \(-40^\circ C\). Reaction conditions for the formation of (R,R)-13: 12 (0.1 mmol), MNBA (0.02 mmol, 20 mol %), lh/0.5TfOH (20 mol %), 2a (0.3 mmol), THF (0.8 mL), \(-40^\circ C\). Single asterisk (*): lh/0.5TfOH (20 mol %) was used as the catalyst. The absolute and relative configuration of 13 was determined by comparison with the reported ref. 65.
Aldol reaction of isatins by If. To a solution of isatin 10 (0.1 mmol) and catalyst If/0.5TfOH (7.9 mg, 20 mol%) in anhydrous THF (0.8 mL) was added aldehyde 11 (0.3 mmol) at −40 °C. The reaction mixture was stirred at this temperature until 10 disappeared via TLC detection. Then NaBH4 (19.2 mg, 0.5 mmol) and MeOH (0.4 mL) were added at −20 °C, and the resulting mixture was stirred for 0.5 h. Finally, the resulting mixture was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/5–1/1) to afford the Mannich product (R,R)-11.

Aldol reaction of isatins by Ig. To a solution of isatin 10 (0.1 mmol), 3-nitrobenzoic acid (3.3 mg, 0.02 mmol), and catalyst Ig/0.5TfOH (6.7 mg, 20 mol%) in anhydrous i-PrOH (0.8 mL) was added aldehyde 12 (0.3 mmol) at −20 °C. The reaction mixture was stirred at this temperature until 10 disappeared via TLC detection. Then NaBH4 (19.2 mg, 0.5 mmol) and MeOH (0.4 mL) were added at −20 °C, and the resulting mixture was stirred for 0.5 h. Finally, the resulting mixture was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/5–1/1) to afford the Mannich product (S,S)-11.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and the Supplementary Information as well as from the authors upon reasonable request. The X-ray crystallographic coordinates for structures (S,R)-3a, (S,R)-5d, (S,R)-9, and (R,R)-11a reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under CCDC 1893083, CCDC 1893081, CCDC 1893084, and CCDC 1857209, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
Z.S. conceived and directed the project. J.D. and Z.W. performed the experiments. L.Z. and Y.L. performed DFT calculations. Y.D., F.P., and Z.S. analyzed the results. Z.S. wrote the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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