Asymmetric synthesis of 2,3-disubstituted indolines via an organocatalytic intramolecular Michael addition†

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An asymmetric synthesis of 2,3-disubstituted indolines has been developed via an organocatalytic intramolecular Michael addition. When a primary amine derived from cinchona alkaloid was used as the catalyst, the intramolecular cyclization reaction of (E)-3-(1-(2-oxopropylamino)aryl)-1-arylprop-2-en-1-ones afforded the corresponding cis-2,3-disubstituted indoline derivatives with high yields, moderate diastereoselectivities, and excellent enantioselectivities (up to 2.7 : 1 dr and 99% ee). Moreover, the catalytic reaction of (E)-3-(1-(2-oxopropylamino)aryl)-1-alkylprop-2-en-1-ones afforded trans-2,3-disubstituted indolines in high yields and with good-to-excellent diastereo- and enantioselectivities (up to 20 : 1 dr and 99% ee).

Optically active indolines are structurally essential elements in biologically active natural alkaloids and chiral pharmaceuticals.⁰ Among various indolines, chiral 2,3-disubstituted indolines are significant building blocks in both synthetic and medicinal chemistry because they are present in numerous natural products and pharmaceuticals including (-)-strychnine, aspidospermidine, WAY-163909, and (-)-physostigmine, as shown in Fig. 1.² They have two chiral centers leading to four possible diastereomers, each of which can exhibit significantly different chemical and biological activities. Therefore, it is challenging and interesting to develop novel synthetic methodologies for constructing enantioenriched 2,3-disubstituted indoline derivatives in synthetic organic chemistry.

Consequently, diverse strategies have been developed for the synthesis of enantioenriched indolines.⁵ Among these, the most powerful tool for the asymmetric synthesis of 2,3-disubstituted indolines is the catalytic hydrogenation of substituted indole derivatives.⁴ Although asymmetric hydrogenation is one of the most straightforward methods in terms of simplicity and atom efficiency, this transformation affords only cis-2,3-disubstituted indolines. Catalytic kinetic resolution is also used to obtain such chiral indolines.⁵ Recently, some significant syntheses of optically active indolines have been achieved using asymmetric intramolecular cyclization reactions such as electrophilic cyclization.⁶ The benefit of these reactions is the easy introduction of various functional groups at the 2- and 3-positions of indoline. Kündig and co-workers reported that the reaction of N-aryl, N-branched alkyl carbamates with a Pd-catalyst bearing chiral N-heterocyclic carbene ligand, giving enantioenriched 2,3-disubstituted indolines.⁶ Xiao and co-workers developed an innovative cycloaddition strategy for the enantioselective synthesis of trans-2,3-disubstituted indolines, involving the Pd-catalyzed decarboxylation-cycloaddition reaction of vinyl benzoxazinanones with sulfur ylides.⁶ More recently, Buchwald and co-workers reported an efficient Cu–H-catalyzed strategy using 2-alkenylimine precursors obtained from alkenylanilines and aromatic aldehydes for the highly diastereo- and enantioselective synthesis of cis-2,3-disubstituted indolines.⁶ However, to the best of our knowledge, the synthesis of chiral 2,3-disubstituted indolines by asymmetric cycloaddition using organocatalyst has not been reported, even though asymmetric organocatalysis has significantly progressed over the past decade.⁶a

Within the framework of our program devoted to the development of stereoselective cascade reactions of o-aminophenyl

Fig. 1 Representative chiral 2,3-disubstituted indoline derivatives.
Although a low diastereoselectivity was obtained, catalyst IIId amine catalyst reomer, respectively (Table 1, entries 3 enantioselectivities of 64, 62, and 77% ee for the major diaste-

Fig. 2 Evaluated bifunctional chiral organocatalysts.

Table 1 Catalyst screening

| Entry | Catalyst | Additive | Time (h) | Yield (%) | cis/trans | ee d,e (%) |
|-------|----------|----------|----------|-----------|-----------|------------|
| 1     | I        | None     | 48       | 92        | 67 : 33   | 41/23      |
| 2     | II       | None     | 168      | 94        | 66 : 34   | 33/31      |
| 3     | IIIa     | AcOH     | 168      | 62        | 15 : 85   | 38/64      |
| 4     | IIIb     | AcOH     | 240      | 76        | 31 : 69   | 52/62      |
| 5     | IIIc     | AcOH     | 168      | 61        | 20 : 80   | 36/77      |
| 6     | IIId     | AcOH     | 120      | 86        | 53 : 47   | 88/85      |
| 7     | None     | 240      | 85       | 41        | 40 : 69   | 69/21      |

a All reactions were performed with 0.1 mmol of 1a, catalyst (10 mol%), and additive (20 mol%) in toluene (0.2 M). b Isolated yield after chromatographic purification. c Determined by 1H NMR analysis. d The ee values were determined by chiral HPLC analysis. e ee values cis/trans diastereomers.

was the best choice for the model reaction in terms of the chemical yield and enantioselectivity of the major diastereomer. In addition, an acid additive was an important factor in this reaction; the reaction without using an additive showed lower reactivity and enantioselectivity than those using an additive (Table 1, entry 6 vs. entry 7).

After confirming primary amine IIId as the optimum catalyst for this Michael reaction, other factors influencing the reaction such as the acid additive, solvent, and reaction temperature were thoroughly investigated (Table 2). First, an acid additive was determined as essential to both the reactivity and enantioselectivity of the reaction. 2-Nitrobenzoic acid gave superior results with respect to reaction rate and enantioselectivity (Table 2, entry 6). Moreover, this Michael reaction was found to be sensitive to the solvent. In toluene, CH2Cl2, CICH2CH2Cl,
Table 2 Optimization of the reaction conditions

| Entry | Additive | Solvent | Time (h) | Yield (%) | cis/trans | ee<sup>d,e</sup> (%) |
|-------|----------|---------|----------|-----------|-----------|----------------------|
| 1     | AcOH     | Toluene | 120      | 85        | 41 : 59   | 88/85                |
| 2     | CF<sub>3</sub>CO<sub>2</sub>H | Toluene | 72       | 91        | 59 : 41   | 91/88                |
| 3     | CCl<sub>3</sub>CO<sub>2</sub>H | Toluene | 48       | 88        | 63 : 37   | 93/88                |
| 4     | PhCO<sub>2</sub>H | Toluene | 24       | 95        | 59 : 41   | 94/88                |
| 5     | 4-NO<sub>2</sub>BzOH | Toluene | 6        | 85        | 40 : 60   | 93/89                |
| 6     | 2-NO<sub>2</sub>BzOH | Toluene | 8        | 94        | 64 : 36   | 96/88                |
| 7     | 2-NO<sub>2</sub>BzOH | CH<sub>2</sub>Cl<sub>2</sub> | 10 | 98 | 56 : 44 | 95/90 |
| 8     | 2-NO<sub>2</sub>BzOH | ClCH<sub>2</sub>CH<sub>2</sub>Cl | 8 | 97 | 51 : 49 | 95/90 |
| 9     | 2-NO<sub>2</sub>BzOH | CHCl<sub>3</sub> | 6 | 96 | 60 : 40 | 96/87 |
| 10    | 2-NO<sub>2</sub>BzOH | EtOAc | 4 | 96 | 60 : 40 | 96/90 |
| 11    | 2-NO<sub>2</sub>BzOH | CH<sub>3</sub>CN | 96 | 41 | 23 : 77 | 51/36 |
| 12    | 2-NO<sub>2</sub>BzOH | THF | 96 | 73 | 52 : 48 | 89/68 |
| 13    | 2-NO<sub>2</sub>BzOH | MeOH | 96 | 50 | 20 : 80 | 48/45 |
| 14<sup>f</sup> | 2-NO<sub>2</sub>BzOH | EtOAc | 24 | 98 | 63 : 37 | 98/94 |
| 15<sup>f</sup> | 2-NO<sub>2</sub>BzOH | EtOAc | 28 | 97 | 62 : 38 | 96/89 |

<sup>a</sup> Unless otherwise specified, the reactions were performed with 0.1 mmol of 1a, catalyst III<sub>d</sub> (10 mol%), and additive (20 mol%) in solvent (0.2 M).<br><sup>b</sup> Isolated yield after chromatographic purification.<br><sup>c</sup> Determined by <sup>1</sup>H NMR analysis.<br><sup>d</sup> The ee values were determined by chiral HPLC analysis.<br><sup>e</sup> ee values cis/trans diastereomers.<br><sup>f</sup> Reaction performed at 0 °C.<br><sup>g</sup> Reaction performed with 10 mol% 2-NO<sub>2</sub>BzOH at 0 °C.

CHCl<sub>3</sub>, and EtOAc, the reaction smoothly proceeded and completed within 10 h, affording the corresponding product 2a in high yields and with excellent enantioselectivities for both diastereomers (Table 2, entries 6–10). In CH<sub>2</sub>CN, THF and MeOH, the reaction was completed in a longer time than in other solvents with moderate yields and enantioselectivities, even though a high enantioselectivity was observed for the major diastereomer in THF (Table 2, entries 11–13). Although a low diastereoselectivity was observed in EtOAc, both the diastereomers were obtained in the highest yields and enantioselectivities (Table 2, entry 10). Therefore, EtOAc was selected as the most suitable solvent for this asymmetric intramolecular Michael addition. A lower reaction temperature provided a better stereocONTrol. The desired product was achieved in an excellent yield and with enantioselectivities (98% ee cis isomer; 94% ee trans isomer) and a moderate diastereoselectivity (cis/trans, 63 : 37) (Table 2, entry 14). In addition, when the amount of 2-nitrobenzoic acid was reduced from 20 mol% to 10 mol%, the enantioselectivity decreased (Table 2, entry 14).

With the optimized reaction conditions in hand (1 equiv. of 1, 10 mol% catalyst III<sub>d</sub>, and 20 mol% 2-nitrobenzoic acid in EtOAc at 0 °C), the substrate scope of the reaction was investigated, and the results are summarized in Table 3. This trans-formation has a broad substrate scope. The reactions of all the substrates smoothly afforded the corresponding indolines in moderate-to-high yields (62–97%) and with excellent enantioselectivities (93–99% ee) for the major diastereomer in all the cases except p-Me-substituted substrate 1m. Gratifyingly, the electronic nature of the R<sup>1</sup> group slightly affected the reaction efficiencies with regard to enantioselectivities and yields. Both electron-withdrawing (Table 3, entries 2–4) and electron-donating (Table 3, entries 5 and 6) groups were well tolerated; the obtained diastereoselectivities were still low in all the cases. For the R<sup>2</sup> group, the reactions proceeded well with electron-withdrawing substituents (Table 3, entries 7–12) and electron-donating substituents (Table 3, entries 12–14). Notably, a substrate bearing an ortho- and para-substituted halogen group on the phenyl R<sup>2</sup> group afforded the corresponding product with a higher diastereoselectivity than the other substrates. A substrate bearing both ortho-substituted chloro group provided trans-2,3-disubstituted indoline 2j in the major diastereomer (cis/trans, 33 : 67) (Table 3, entry 10). Moreover, a heteroaromatic group was introduced at the R<sup>2</sup> position; the reaction proceeded rapidly, affording the corresponding products 2o and 2p in high yields and with good enantiocontrol (over 91% ee, Table 3, entries 15 and 16).

To evaluate the practical applications of this methodology, a gram-scale reaction using the standard conditions was conducted; product 2a was obtained without any significant changes in the yield or stereoselectivity (Scheme 2). The absolute configuration of product cis-2d was determined by X-ray crystallographic analysis and found to be 2S,3R. The configurations of the other products were assigned by analogy.
Furthermore, the reactions of \((E)-3-(2-(2-oxopropylamino)aryl)-1-alkylprop-2-en-1-ones\) bearing an alkyl group at the \(R^2\) position, such as methyl, cyclopropyl and \(\text{t}-\text{butyl}\), smoothly afforded the corresponding 2,3-disubstituted indolines in high yields and with excellent enantioselectivities (Table 4, entries 1–3). To our delight, \(\text{t}-\text{butyl}\) \(\alpha,\beta\)-unsaturated ketone provided the desired \(\text{trans}-2,3\)-disubstituted indoline \(4c\) with an excellent diastereomeric ratio (\(\text{trans}/\text{cis}, 13 : 1\)) and enantioselectivity (98% ee; Table 4, entry 3). Encouraged by the excellent results obtained using \(\text{t}-\text{butyl}\) \(\alpha,\beta\)-unsaturated ketone, the scope of our strategy was further extended. No obvious impact was observed on either the reaction efficiency or stereoselectivity, regardless of the electronic nature, bulkiness, or position of the substituent on the benzene ring of \((E)-3-(2-(2-oxopropylamino)aryl)-1-t\)-butylprop-2-en-1-ones. Both electron-withdrawing groups (Table 4, entries 4–6) and electron-donating groups (Table 4, entries 7 and 8) were well tolerated, and all the products were obtained in good yields and with excellent diastereoselectivities (\(\text{trans}/\text{cis}, 13 : 1\) to >25 : 1) and enantioselectivities (93–99% ee).

On the basis of our experimental results, a plausible transition state for this asymmetric Michael reaction is shown in Scheme 3. The Si-face attack of \text{anti-enamine} to the Re-face of \(\text{t}-\text{butyl} \alpha,\beta\)-unsaturated ketone led to the formation of the \(S,S\)-configured \(\text{trans}-\text{indoline} 4c\).

To further demonstrate the synthetic utility of this methodology, we have illustrated a representative procedure to convert the enantioenriched indoline product into the corresponding alkenyl ester 5 (Scheme 4). The reaction of \(\text{trans}-4c\) with methyl(triphenylphosphoranylidene)acetate provided Wittig product 5 in moderate yield without affecting the enantioselectivity.

**Table 3** Substrate scope of the organocatalytic asymmetric intramolecular Michael addition

| Entry | \(R^1\) | \(R^2\) | Time (h) | 2 | Yield\(^b\) (%) | \(\text{cis}/\text{trans}\) | ee\(^d,e\) (%) |
|-------|--------|--------|----------|---|----------------|----------------|--------------|
| 1     | \(\text{H}\) | Ph     | 28       | 2a | 97             | 63 : 37        | 98/94        |
| 2     | \(4-\text{Cl}\) | Ph     | 36       | 2b | 96             | 58 : 42        | 95/93        |
| 3     | \(5-\text{Cl}\) | Ph     | 48       | 2c | 88             | 58 : 42        | 99/95        |
| 4     | \(4-\text{Br}\) | Ph     | 48       | 2d | 97             | 56 : 44        | 99/95        |
| 5     | \(4-\text{Me}\) | Ph     | 56       | 2e | 91             | 60 : 40        | 99/93        |
| 6     | \(4,5-\text{MeO}\) | Ph     | 72       | 2f | 91             | 58 : 42        | 95/97        |
| 7     | \(\text{H}\) | \(p-\text{ClC}_6\text{H}_4\) | 36       | 2g | 86             | 61 : 39        | 92/76        |
| 8     | \(\text{H}\) | \(m-\text{ClC}_6\text{H}_4\) | 56       | 2h | 93             | 51 : 49        | 92/90        |
| 9     | \(\alpha-\text{ClC}_6\text{H}_4\) | 48     | 2i | 96             | 73 : 27        | 94/92        |
| 10    | \(2,6-\text{ClC}_6\text{H}_3\) | 96     | 2j | 83             | 33 : 67        | 91/90        |
| 11    | \(\text{H}\) | \(p-\text{BrC}_6\text{H}_4\) | 48       | 2k | 82             | 70 : 30        | 98/94        |
| 12    | \(\text{H}\) | \(p-\text{FC}_6\text{H}_4\) | 36       | 2l | 95             | 65 : 35        | 95/86        |
| 13    | \(\text{H}\) | \(p-\text{MeC}_6\text{H}_4\) | 36       | 2m | 85             | 54 : 46        | 90/84        |
| 14    | \(\text{H}\) | \(p-\text{MeOC}_6\text{H}_4\) | 48       | 2n | 91             | 55 : 45        | 96/89        |
| 15    | \(\text{H}\) | 2-Furanyl | 36       | 2o | 92             | 47 : 53        | 92/91        |
| 16    | \(\text{H}\) | 2-Thienyl | 24       | 2p | 86             | 43 : 57        | 94/94        |

\(^a\) All reactions were performed with 0.1 mmol of \(1\), catalyst \(\text{III}d\) (10 mol%), and 2-\(\text{NO}_2\)\(\text{BzOH}\) (20 mol%) in EtOAc (0.2 M) at 0°C. \(^b\) Isolated yield after chromatographic purification. \(^c\) Determined by \(^1\text{H}\) NMR analysis. \(^d\) The ee values were determined by chiral HPLC analysis. \(^e\) ee values \(\text{cis}/\text{trans}\) diastereomers.
Conclusions

In conclusion, we have developed an efficient method for the asymmetric synthesis of 2,3-disubstituted indolines through an organocatalytic intramolecular Michael addition. The reaction of (E)-3-(2-(2-oxopropylamino)aryl)-1-arylprop-2-en-1-ones afforded the corresponding cis-2,3-disubstituted indoline derivatives in high yields and with moderate diasteroselectivities and excellent enantioselectivities (up to 2.7 : 1 dr and 99% ee) using a primary amine derived from a cinchona alkaloid as the catalyst. Moreover, the catalytic reaction of (E)-3-(2-(2-oxopropylamino)aryl)-1-alkylprop-2-en-1-ones helped to develop an unprecedented approach for the synthesis of chiral trans-2,3-disubstituted indolines in high yields and with good-to-excellent diastereo- and enantioselectivities (up to >25 : 1 dr, and 99% ee).

Conflicts of interest

There are no conflicts to declare.

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Table 4 Distereo- and enantioselective synthesis of trans-2,3-disubstituted indoline

| Entry | R¹ | R²     | Time (h) | 4      | Yieldb (%) | trans/cisc | cecd (%) |
|-------|----|--------|----------|--------|------------|------------|---------|
| 1     | H  | Me     | 72       | 4a     | 65         | 1 : 1.5    | 84/87   |
| 2     | H  | Cyclopropyl | 48     | 4b     | 93         | 4 : 1      | 94      |
| 3     | H  | t-Bu   | 18       | 4c     | 98         | 13 : 1     | 98      |
| 4     | 4-Cl | t-Bu   | 12       | 4d     | 97         | 13 : 1     | 95      |
| 5     | 5-Cl | t-Bu   | 48       | 4e     | 78         | >25 : 1    | 93      |
| 6     | 4-Br | t-Bu   | 12       | 4f     | 92         | 15 : 1     | 98      |
| 7     | 4-Me | t-Bu   | 18       | 4g     | 98         | 20 : 1     | 99      |
| 8     | 4,5-MeO | t-Bu   | 18       | 4h     | 85         | >25 : 1    | 99      |

Unless otherwise specified, the reactions were performed with 0.1 mmol of 3, catalyst IIIId (10 mol%), and 2-NO₂BzOH (20 mol%) in EtOAc (0.2 M) at 0 °C. Isolated yield after chromatographic purification. Determined by 1H NMR analysis. The ee values were determined by chiral HPLC analysis.
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The relative stereochernistry of compound 4 (trans-isomer) was established by the distinguished chemical shift in 1H NMR of the trans-isomer and by NOESY.