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# Organocatalytic Asymmetric Michael–Michael Cascade for the Construction of Highly Functionalized N-Fused Piperidinoindoline Derivatives

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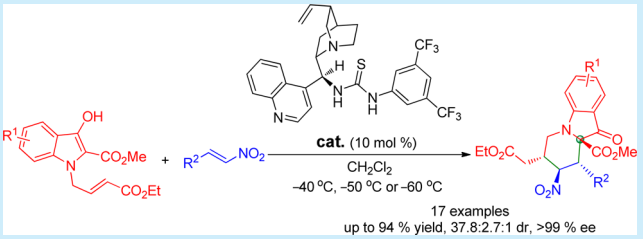
Supporting Information

**ABSTRACT:** Application of indolin-3-one derivatives in a cascade reaction for efficient assembly of complex molecules is a much less explored research area. It is demonstrated that structurally interesting polysubstituted piperidino[1,2-*a*]-indoline compounds containing four contiguous stereocenters including one tetrasubstituted carbon center can be readily obtained with good yields (up to 94% yield) and excellent enantioselectivities (up to >99% ee) by employing indolin-3-one derivatives as substrates via bifunctional catalysis.




Piperidino[1,2-*a*]indoline represents an important class of structural motifs that is frequently found in a large family of natural products and biologically active molecules (Figure 1).[1] For example, indole alkaloids mersicarpine, secoleuconox-

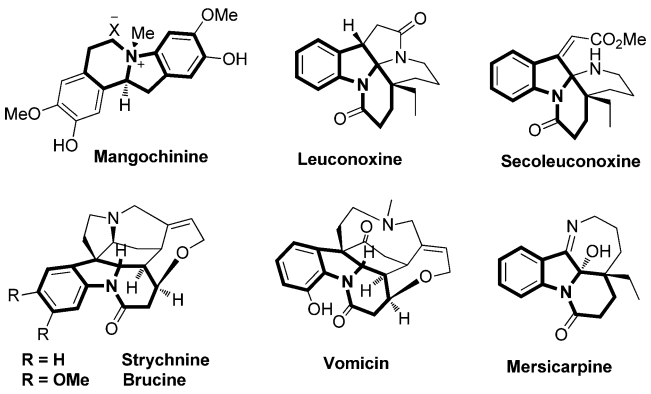



**Figure 1.** Representative natural products containing a piperidino[1,2-*a*]indoline scaffold.

ine, and leuconoxine were isolated from the *Kopsia* species.[1a] Strychine, brucine, and vomicin are representative examples of *Strychnos* alkaloids.[1b] Mangochinine is a main component of the traditional Chinese medicine plant *Manglietia chingii* Dandy (Magnoliaceae) which has antiulcer, muscle relaxant, and antibacterial effects.[1c] Because of its interesting structure and biological activity, the piperidino[1,2-*a*]indoline scaffold has attracted extensive attention from both synthetic and medicinal chemists. A few elegant methods have been developed for the synthesis of the piperidino[1,2-*a*]indoline core structure in the past several years.[2] However, despite these significant advances, it should be noted that most of these established methods are based on metal-catalyzed racemic syntheses and asymmetric catalytic versions are challenging and generally lacking.[2i,j] Therefore, the development of efficient and concise catalytic approaches for the enantioselective construction of highly functionalized piperidino[1,2-*a*]indoline derivatives is highly desired.

The research area involving the use of 2-oxindole derivatives has attracted a great deal of attention from the synthetic community.[3] This class of compounds has been extensively used as privileged substrates and demonstrated to be very reliable for the construction of a large number of pharmaceutical candidates and natural products. However, contrary to the significant progress in the development of 2-oxindole chemistry, indolin-3-one derivatives, which could also potentially serve as good substrates for developing a diverse array of reactions, have received very little attention.[4] Therefore, it is highly desirable to apply these substrates in asymmetric catalysis as a complement to the current 2-oxindole chemistry. We have worked in this area for a while and developed several asymmetric catalytic reactions using this scaffold.[4a−c]

The development of asymmetric organocatalytic cascade reactions has served as a powerful tool for the quick construction of complex molecules with multiple chiral centers.[5,6] Again, the application of indolin-3-one derivatives in cascade reactions for the efficient assembly of complex molecules is still an underdeveloped research area.[4g] With our ongoing interest in the design and development of catalytic cascade reactions[6] and indolin-3-one chemistry,[4a−c] we would like to further expand the scope of indolin-3-one reactivity to cascade reactions for quickly assembling some interesting

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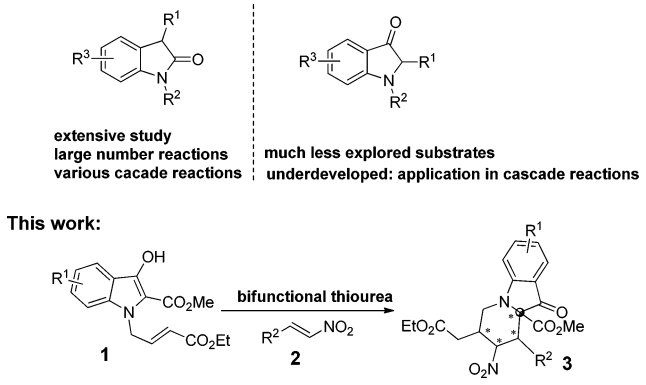
scaffolds. We envisaged that piperidino[1,2-*a*]indoline skeletons possessing four contiguous stereocenters including one chiral tetrasubstituted carbon center could be created via a single Michael−Michael cascade sequence between indolin-3-one derivatives **1** and nitroolefins **2** (Scheme 1).

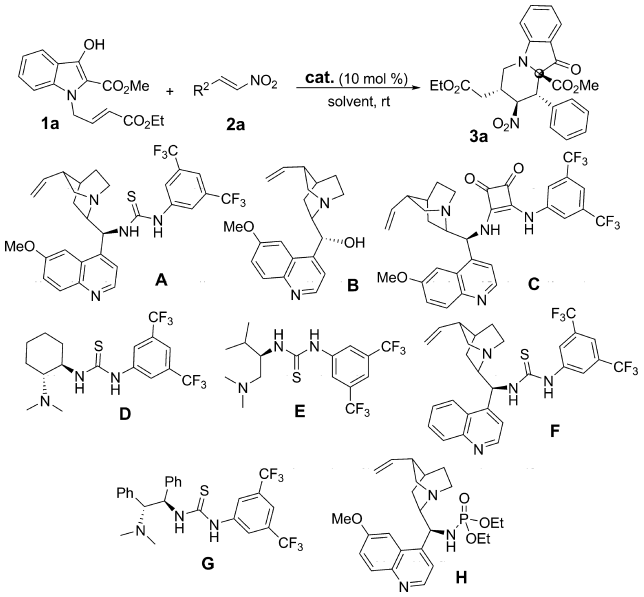
**Scheme 1. Organocatalytic Asymmetric Michael−Michael Cascade To Form Complex Polysubstituted Piperidino[1,2-*a*]indoline Derivatives**




Initially, a feasibility study of our hypothesis revealed that indolin-3-one derivatives **1a** and nitroolefin **2a** reacted smoothly in the presence of catalyst **A** (10 mol %) in $CH_2Cl_2$ at room temperature to furnish the desired product **3a** in 87% yield, 3.6:1.9:1 dr, and 93% ee (Table 1, entry 1). Then, different solvents such as $CH_3CN$, THF, *i*-PrOH, toluene, and dioxane were tested to see how they would affect this cascade reaction (Table 1, entries 2−6). The results showed that $CH_2Cl_2$ was the optimal choice (Table 1, entry 1). However, in the absence of catalyst, the cascade process did not proceed even in $CH_2Cl_2$ (Table 1, entry 7). Next, several bifunctional catalysts were investigated, and bifunctional catalyst **F** was found to be the most promising catalyst for this cascade reaction (Table 1, entry 12). For catalyst **E** and **H**, no expected product was obtained (Table 1, entries 11 and 14). Finally, we examined the temperature effect on this cascade reaction and found it could affect the diastereoselectivities significantly. By lowering the temperature, the diastereoselectivities were improved. (Table 1, entries 12 and 15−19). When the reaction temperature was dropped to −60 °C, the desired product was obtained with high yield and stereoselectivity (89% yield, 43.4:9.2:1 dr and 99% ee) (Table 1, entry 18).

With the reaction conditions optimized, the substrate scope was then investigated to show the generality of this cascade reaction (Table 2). In most cases, the reactions afforded the corresponding polysubstituted piperidino[1,2-*a*]indoline products with moderate to excellent yields (49−94%), moderate to good diastereoselectivities(8.2:3.9:1 to 37.8:2.7:1), and excellent enantioselectivities (up to >99% ee). The structural variation of nitroalkenes **2** could be well tolerated in this reaction irrespective of the electronic nature or position of the substituents on the aromatic ring. Compared with the electron-donating nitroalkenes (**3c**−**e**), the electron-withdrawing nitroalkenes (**3l**,**m**) gave higher yields and required shorter reaction time. Generally speaking, due to the steric effect of the ortho substituents, the ratio of the two major diastereomers increased significantly in **3e**, **3h**, **3k**, and **3r** vs **3a**. It is noteworthy that this cascade process could also be successfully extended to an aliphatic substituted nitroalkene **3o**, albeit with lower

**Table 1. Optimization of Reaction Conditions**[a]




| entry | cat. | solvent | time (h) | % yield[b] | dr[c] | % ee[d] |
|---|---|---|---|---|---|---|
| 1 | A | $CH_2Cl_2$ | 48 | 87 | 3.6:1.9:1 | 97 |
| 2 | A | THF | 48 | <20 | nd | nd |
| 3 | A | dioxane | 48 | <20 | nd | nd |
| 4 | A | *i*-PrOH | 48 | 75 | 2.2:1.5:1 | 93 |
| 5 | A | $CH_3CN$ | 48 | 82 | 4.0:2.7:1 | 94 |
| 6 | A | toluene | 48 | 69 | 3.6:1.5:1 | 96 |
| 7 | none | $CH_2Cl_2$ | 48 | trace | nd | nd |
| 8 | B | $CH_2Cl_2$ | 72 | 70 | 1.2:2.7:1 | nd |
| 9 | C | $CH_2Cl_2$ | 48 | 82 | 1.2:2.4:1 | 82 |
| 10 | D | $CH_2Cl_2$ | 48 | 83 | 2.8:3.2:1 | nd |
| 11 | E | $CH_2Cl_2$ | 72 | trace | nd | nd |
| 12 | F | $CH_2Cl_2$ | 48 | 89 | 4.6:1.8:1 | 98 |
| 13 | G | $CH_2Cl_2$ | 48 | 36 | 2.4:1.1:1 | 97 |
| 14 | H | $CH_2Cl_2$ | 80 | trace | nd | nd |
| 15[e] | F | $CH_2Cl_2$ | 48 | 87 | 7.8:2.9:1 | 98 |
| 16[f] | F | $CH_2Cl_2$ | 48 | 87 | 26.4:7.2:1 | 98 |
| 17[g] | F | $CH_2Cl_2$ | 48 | 85 | 35.9:8.8:1 | 98 |
| 18[h] | F | $CH_2Cl_2$ | 72 | 89 | 43.4:9.2:1 | 99 |
| 19[i] | F | $CH_2Cl_2$ | 100 | 54 | 6.1:1 | >99 |

[a]Unless otherwise specified, all reactions were carried out with catalyst (10 mol %), **1a** (0.10 mmol), and **2a** (0.20 mmol) in the indicated solvent (1.0 mL) at room temperature. [b]Combined yields of all diastereomers after flash column chromatography. [c]Determined by $^1$H NMR analysis of the crude products. [d]ee value of major compound **3a**; determined by chiral-phase HPLC analysis (OD-H column). [e]Reaction performed at 0 °C. [f]Reaction performed at −40 °C. [g]Reaction performed at −50 °C. [h]Reaction performed at −60 °C. [i]Reaction performed at −70 °C.

selectivities. The variation on the indolin-3-one scaffold could also be tolerated in this cascade reaction and afforded the desired products **3p**−**r** with good results. The only exception was 2-furyl-substituted nitroalkene; under the optimal reaction conditions, the reaction using it (**3n**) as a substrate was not successful and resulted in a complex mixture.

The absolute configuration of the major products in this Michael−Michael cascade reaction was determined by X-ray crystal diffraction of compound **3q** (Figure 2).[7] As shown in Scheme 2, a possible reaction mechanism was also proposed. The electrophilicity of nitroolefin **2** is enhanced by the


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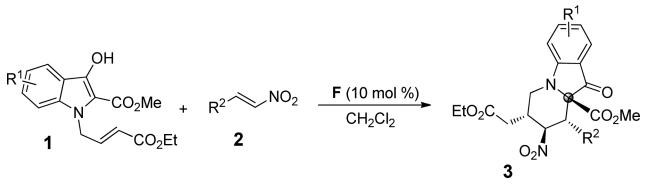
**Table 2. Substrate Scope of Michael–Michael Cascade**[a]




| entry | $R^1$ | $R^2$ | % yield[b] | dr[c] | % ee[d] |
|---|---|---|---|---|---|
| 1 | H | $C_6H_5$ | 89 (**3a**) | 43.4:9.2:1 | 99/nd |
| 2[f] | H | 2-naphthyl | 78 (**3b**) | 17.6:5.3:1 | >99/90 |
| 3[g] | H | 4-Me$C_6H_4$ | 72 (**3c**) | 29.3:8.5:1 | 99/>99 |
| 4[g] | H | 4-MeO$C_6H_4$ | 51 (**3d**) | 8.2:3.9:1 | 99/>99 |
| 5[g] | H | 2-MeO$C_6H_4$ | 64 (**3e**) | 14.7:2.5:1 | 99/nd |
| 6[g] | H | 4-F$C_6H_4$ | 91 (**3f**) | 14.8:5.2:1 | 99/nd[e] |
| 7[g] | H | 4-Cl$C_6H_4$ | 89 (**3g**) | 17.8:6.2:1 | >99/99 |
| 8 | H | 2-Cl$C_6H_4$ | 92 (**3h**) | 39.7:4.3:1 | 99/nd |
| 9 | H | 4-Br$C_6H_4$ | 86 (**3i**) | 19.2:6.9:1 | 99/>99 |
| 10 | H | 3-Br$C_6H_4$ | 89 (**3j**) | 39.5:9.4:1 | >99/>99 |
| 11 | H | 2-Br$C_6H_4$ | 94 (**3k**) | 37.8:2.7:1 | 99/nd |
| 12 | H | 4-$NO_2C_6H_4$ | 87 (**3l**) | 18.0:6.3:1 | 98/nd[e] |
| 13 | H | 4-$CF_3C_6H_4$ | 92 (**3m**) | 33.7:11.5:1 | 98/nd[e] |
| 14[g] | H | 2-furyl | nd (**3n**) | complex | nd |
| 15[f] | H | *n*-propyl | 71 (**3o**) | 4.2:1.8:1 | 88/59 |
| 16 | 6-Cl | $C_6H_5$ | 76 (**3p**) | 25.4:7.1:1 | 98/>99 |
| 17 | 5-Br | $C_6H_5$ | 49 (**3q**) | 11.2:4.4:1 | 99/nd[e] |
| 18 | 5-Br | 2-Br$C_6H_4$ | 69 (**3r**) | 26.2:3.9:1 | 99/>99 |

[a]Unless otherwise specified, all reactions were carried out with catalyst **F** (10 mol %), **1** (0.10 mmol), and **2** (0.20 mmol) in $CH_2Cl_2$ (1.0 mL) at −60 °C, and the reaction time was determined by TLC (see the Supporting Information). [b]Combined yields of all diastereomers after flash column chromatography. [c]Determined by $^1$H NMR analysis of the crude products. [d]ee values of major compound **3** and major minor diastereomer ; determined by chiral-phase HPLC analysis (AD-H and OD-H column). [e]The major minor diastereomer could not be separated by chiral-phase HPLC analysis. [f]Reaction performed at −40 °C. [g]Reaction performed at −50 °C.

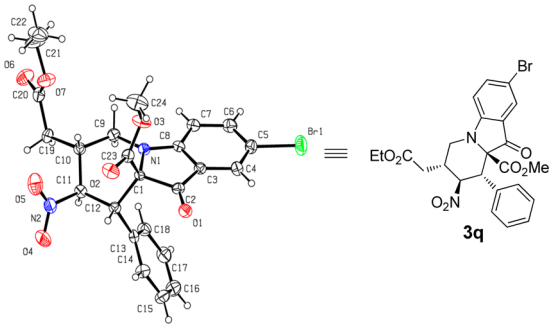
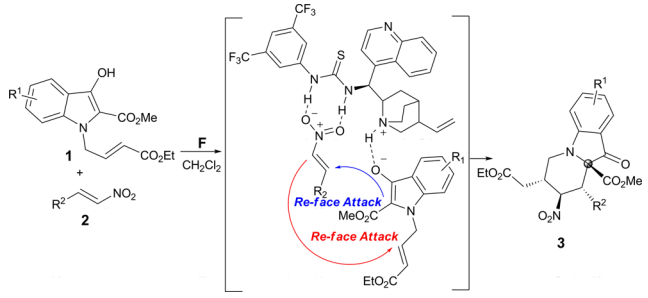



**Figure 2.** X-ray structure of compound **3q**.

hydrogen-bonding interaction with the thiourea moiety of bifunctional catalyst while a highly nucleophilic enolate species is generated by the interaction of tertiary amine group and indolin-3-one **1**. As a consequence, a Michael addition of the enolate to the nitroolefin via a *Re*-face attack followed by a *Re*-face attack of the in situ generated carbanion intermediate on the double bond of $\alpha,\beta$-unsaturated ester occurs to generate products **3**.

In conclusion, we have developed an effective strategy employing much less explored indolin-3-one derivatives for the construction of highly functionalized N-fused piperidinoindoline derivatives via a bifunctional thiourea-catalyzed asymmetric

**Scheme 2. Proposed Mechanism for Michael–Michael Cascade**




Michael–Micheal cascade. The complex polysubstituted piperidino[1,2-*a*]indoline derivatives containing four contiguous stereocenters, including one chiral tetrasubstituted carbon center were obtained with good yields, good diastereoselectivities, and excellent enantioselectivities. This work not only provides a new method for the synthesis of chiral N-fused piperidinoindoline derivatives but also is an important complement to existing oxindole chemistry. Further investigation and application of activated indolin-3-one derivatives are ongoing in our laboratories.

## ■ ASSOCIATED CONTENT

### Supporting Information

Additional optimization of reaction parameters, experimental procedure, and characterization data for all new compounds, X-ray crystal structure data (CIF) for compound **3q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(7) CCDC 987092 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.