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# Asymmetric Nitroaldol Reactions of Nitroalkanes with Isatins Catalyzed by Bifunctional Cinchona Alkaloid Derivatives

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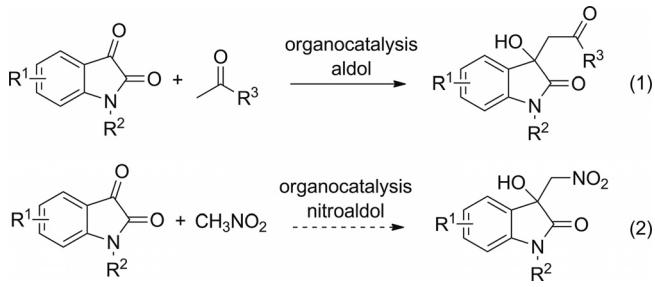
The enantioselective nitroaldol reactions of isatins with nitroalkanes were smoothly carried out by organocatalysis. A C6′-OH cinchona alkaloid derivative bearing a C9-OBn group exhibited outstanding catalytic efficiency as an acid–base bifunctional catalyst for the nitroaldol reaction of isatins with nitromethane, providing 3-hydroxy-3-(nitromethyl)indolin-2-ones in good yields (90–98%) and with good to high enantiomeric excess values (72–95%). The resultant oxindole derivatives are highly important for the synthesis of related natural products and pharmaceutically active compounds.

## Introduction

With continuing efforts in the development of practical methods for the asymmetric catalysis of organic reactions,[1] the nitroaldol (or Henry) reaction has been an important C–C bond-formation protocol in organic synthesis, which provides efficient access to valuable functionalized structural motifs such as 1,2-amino alcohols or amino acids.[2] To date, both chiral metallic complexes and chiral organocatalysts have been developed for the enantioselective catalytic nitroaldol reaction.[3] Among the various chiral Lewis acids reported, Re (La and Yb), Zn, Cu, Co, and Mg metallic complexes are commonly used in asymmetric nitroaldol reactions.[4] However, the search for an organocatalyzed enantioselective nitroaldol transformation has attracted considerable attention over the last few years. Some types of chiral organocatalysts, including quaternary ammonium salts,[5] guanidine,[6] thiourea,[7] and cinchona derivatives,[8] have been developed, and many of these systems have demonstrated powerful efficiency in terms of their reactivities and enantioselectivities.

Many natural products possessing valuable biological properties contain the 3-substituted-3-hydroxy-2-oxindole heterocyclic unit.[2,9] The biological and synthetic importance of this structural motif has stimulated significant activity into its enantioselective variants. Thus, several synthetic methods, such as enantioselective aldol reactions (Scheme 1),[10] asymmetric 1,2-additions,[11] allylation reactions[12] Morita–Baylis–Hillman reactions,[13] Friedel–Crafts reactions,[14] and hydrogenation,[15] have been developed to provide optically active 3-substituted-3-hydroxy-2-oxindoles by using chiral metallic complexes or chiral organic molecules as catalysts. By comparison, the use of isatins as acceptors in direct asymmetric aldol reactions has been extensively explored in recent years, which efficiently furnishes valuable enantiomerically enriched 3-substituted-3-hydroxy-2-oxindole derivatives in high yields and excellent enantioselectivities [Scheme 1, Equation (1)].[10–15] However, there are no reports outlining the use of isatins and nitroalkanes in the enantioselective nitroaldol reaction, which is mediated by organic molecular catalysts [Scheme 1, Equation (2)]. During the preparation of our manuscript, the enantioselective nitroaldol reaction of isatins with nitroalkanes in the presence of cupreine and benzoic acid as catalysts was reported by Wang and co-workers.[16] In this paper, we disclose that the nitroaldol reaction of nitroalkanes with isatins could be smoothly catalyzed by an acid–base bifunctional cinchona derived organocatalyst; the resulting enantiomerically enriched 3-hydroxy-3-(nitromethyl)indolin-2-ones were obtained in high yields (90–98%) and with good to high enantioselectivities (72–95%*ee*).




Scheme 1. Organocatalytic aldol and nitroaldol reactions of isatins.

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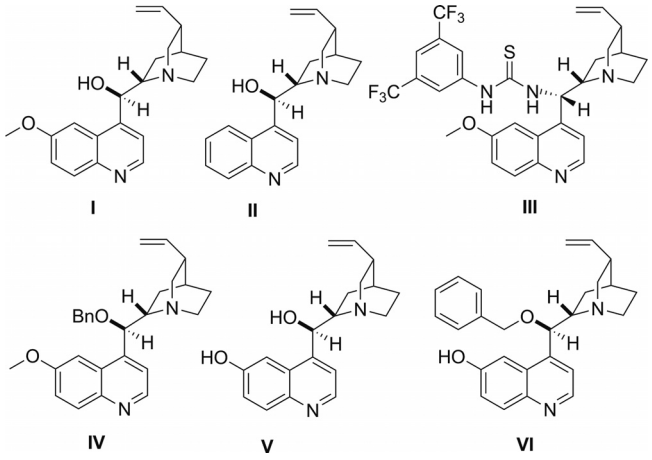
## Results and Discussion

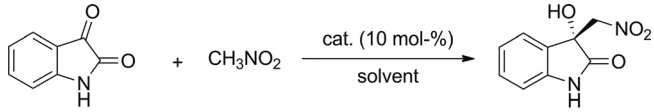
Initially, inspired by the direct aldol reactions of isatins with carbonyl compounds,[10] we examined several cinchona-derived organocatalysts for the catalytic nitroaldol reaction of nitromethane with isatin **1a** in the presence of a catalyst loading of 10 mol-% in THF (Scheme 2). The results are summarized in Table 1. Quinine **I** and cinchonidine **II** were not effective in the enantioselective nitroaldol reaction, although desired **3a** was obtained in 92% and 95% yield, respectively, within 2 h (Table 1, Entries 1 & 2). Subsequently, cinchona alkaloid derivatives **III**–**VI** were investigated (Table 1, Entries 3–6). Promisingly, when C6′-OH cinchona alkaloid **V** was employed as the catalyst, the reaction provided the desired product in 98% yield with 33%*ee* (Table 1, Entry 5). We immediately shifted our attention to C6′-OH cinchona alkaloid derivative **VI** bearing a C9-OBn group,[17] which was established by the Deng group as a type of acid–base bifunctional catalyst. Pleasingly, the reaction proceeded smoothly in the presence of the catalyst (10 mol-%), which afforded the desired product in 98% yield with 87%*ee* (Table 1, Entry 6). Thus, catalyst **VI** proved to be the optimal catalyst for the nitroaldol reaction of nitromethane with isatin in terms of enantioselectivity.




Scheme 2. Screened catalysts.

To further improve the enantioselectivities, the solvent and temperature were optimized. As shown in Table 1, we found that the enantioselectivities were greatly influenced by the reaction media. Dichloromethane was particularly unfavorable for this stereoselective transformation, furnishing the addition product as a nearly racemic mixture (Table 1, Entry 7). The reactions proceeded in the other solvents, including ethyl ether, ethyl acetate, and dioxane, and the desired products were obtained in good to excellent yields (75–96%) with moderate to good enantioselectivities (54–73%*ee*; Table 1, Entries 8–10). Furthermore, when the reaction temperature was dropped to –10 °C, the enantioselectivity slightly increased to 88%, and the yield of the desired product was invariable even if the reaction time was prolonged to 12 h (Table 1, Entry 11). By decreasing the reaction temperature to –20 and –30 °C, enantioselectivities

Table 1. Optimization of reaction conditions.[a]




| Entry | Cat. | Solvent | Temp. [°C] | Time [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **I** | THF | 10 | 2 | 92 | 0 |
| 2 | **II** | THF | 10 | 2 | 95 | 0 |
| 3 | **III** | THF | 10 | 2 | 96 | 10 |
| 4 | **IV** | THF | 10 | 11 | 80 | 21 |
| 5 | **V** | THF | 10 | 2 | 98 | 33 |
| 6 | **VI** | THF | 10 | 3.5 | 98 | 87 |
| 7 | **VI** | DCM | 10 | 6 | 80 | 3 |
| 8 | **VI** | $Et_2O$ | 10 | 6 | 88 | 54 |
| 9 | **VI** | EtOAc | 10 | 1 | 75 | 73 |
| 10 | **VI** | dioxane | 10 | 1 | 96 | 65 |
| 11 | **VI** | THF | –10 | 12 | 96 | 88 |
| 12 | **VI** | THF | –20 | 24 | 94 | 91 |
| 13 | **VI** | THF | –30 | 96 | 93 | 93 |
| 14 | **VI** | THF | –40 | 96 | 80 | 71 |

[a] Reactions were performed with **1a** (0.2 mmol), **2** (2.0 mmol), and catalyst **I**–**VI** (10 mol-%) in solvent (2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

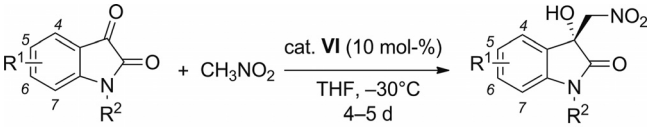
of 91 and 93%*ee*, respectively, could be obtained for this transformation at the cost of reactivity (Table 1, Entries 12 & 13). Unexpectedly, when the reaction temperature was lowered to –40 °C, both the enantioselectivity and the yield were dramatically reduced in comparison to those obtained at –30 °C (Table 1, Entry 14 vs. 13). In pursuit of the optimal reaction conditions, the reaction concentration, the catalyst loading, and the molar ratio of nitromethane were also investigated, and the results are summarized in the Supporting Information (Table S1). Finally, we found that the optimal reaction conditions for this transformation involved the use of THF at –30 °C with nitromethane (10 equiv.) in the presence of the catalyst (10 mol-%).

With the optimized reaction conditions in hand, the substrate scope and limitations of the reaction were subsequently investigated (Table 2). We found that substitutions on the isatins and their positions had a great impact on the enantioselectivities of the desired products (Table 2, Entries 1–10). For 4-Cl- and 4-Br-substituted isatins **1b** and **1c**, the reactions provided desired products **3b** and **3c** in 97 and 96% yield, respectively, with 82 and 78%*ee*, respectively (Table 2, Entries 2 & 3). Pleasingly, 5-Me-substituted isatin **1d** gave the product in 92% yield with 95%*ee* after 5 d (Table 2, Entry 4), whereas 5-halogenated isatins **1e**–**g** furnished the products with the varying level of enantioselectivities (Table 2, Entries 5–7). Among them, substrate **1e** bearing a 5-F group gave the desired product in 90% yield with 79%*ee* (Table 2, Entry 5). Apparently, electron-donating substituents on the isatins give products with higher enantioselectivity, whereas electron-withdrawing substituents on the isatins give products with lower enantioselectivity. Expectedly, for substrates **1g** and **1h** bearing 5-Br and 6-Br substituents, desired products **3g** and **3h** could

be obtained in 94 and 91% yield, respectively, with 91 and 88% *ee*, respectively, which are distinctly better than those obtained with substrates **1e** and **1f** bearing 5-F and 5-Cl substituents (Table 2, Entries 7 and 8 vs. 5 and 6). On the other hand, the use of N–Me and N–Bn protected isatins **1i** and **1j** afforded corresponding products **3i** and **3j** in excellent yields, but with moderate enantioselectivities (Table 2, Entries 9 and 10).

Table 2. Substrates scope in the reaction.[a]




| Entry | Product ($R^1$, $R^2$) | Time [d] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **3a** (H, H) | 4 | 94 | 93 |
| 2 | **3b** (4-Cl, H) | 4 | 97 | 82 |
| 3 | **3c** (4-Br, H) | 4 | 96 | 78 |
| 4 | **3d** (5-$CH_3$, H) | 5 | 92 | 95 |
| 5 | **3e** (5-F, H) | 4 | 90 | 79 |
| 6 | **3f** (5-Cl, H) | 5 | 96 | 81 |
| 7 | **3g** (5-Br, H) | 5 | 94 | 91 |
| 8 | **3h** (6-Br, H) | 4 | 91 | 88 |
| 9 | **3i** (H, $CH_3$) | 4 | 96 | 72 |
| 10 | **3j** (H, $CH_2C_6H_5$) | 4 | 98 | 73 |

[a] Reactions were performed with **1a**–**j** (0.2 mmol), **2** (2.0 mmol), and catalyst **VI** (10 mol-%) in solvent (2.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

Fortunately, single crystals of compounds **3g** and **3h** were obtained by recrystallization from hexane/acetone, and the absolute configurations of **3g** and **3h** were determined by X-ray analyses (Figures 1 and 2). On the basis of the correlation of the spatial configuration of catalyst **VI** and the absolute configurations of adducts **3g** and **3h**, and also inspired by Deng's rational analyses of a *gauche*-open active conformer for C6′-OH cinchona alkaloids (Scheme 3) [17a,17b] we envision that nitromethane is deprotonated by the tertiary amine in the quinuclidine backbone to form the enolate. The isatins could be activated and orientated through hydrogen bonding between the isatin carbonyl groups and the 6′-OH group and the protonated N–H group in the quinuclidine rings. Attack at the *Re* face of the isatin by the nitro enolate results in the observed major *R* enantiomer for **3g** and **3h**, whereas the steric hindrance between the phenyl ring of the isatin and the nitro enolate leads to the disfavored *S* enantiomer as the minor isomer.

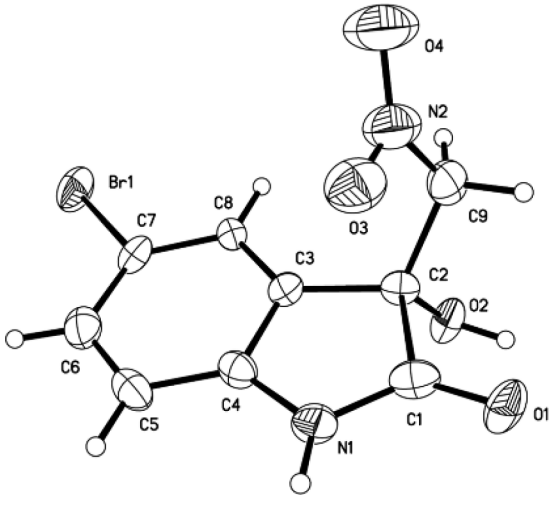



Figure 1. The X-ray crystal structure of **3g**.

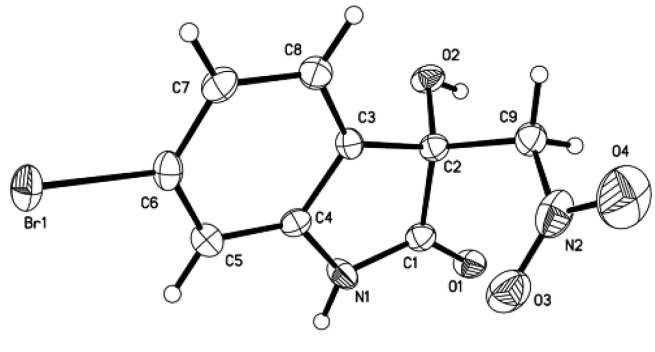
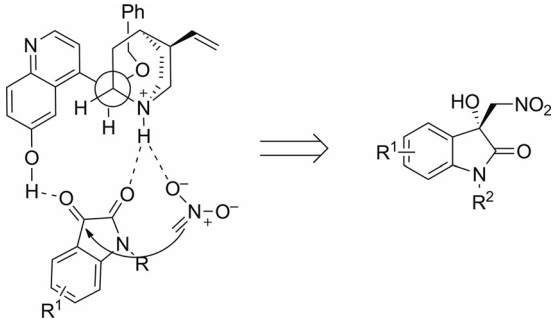



Figure 2. The X-ray crystal structure of **3h**.




Scheme 3. Proposed stereochemical model for the **VI**-catalyzed Henry reaction of nitromethane with isatins.

## Conclusions

In conclusion, we have demonstrated the feasibility of the enantioselective Henry reaction of isatins with nitroalkanes catalyzed by C6′-OH cinchona alkaloid derivative **VI**. This reaction provides a convenient and effective catalytic approach for the synthesis of enantiomerically enriched 3-hydroxy-3-(nitromethyl)indolin-2-ones in good yields (90–98%) and with good to high enantioselectivities (72–95% *ee*). The catalyst screening results and X-ray crystallographic analysis suggest that both the C6′-OH group and the quinuclidine are responsible for stereogenic induction into the nitroaldol products. Further mechanistic studies and synthetic utilities are underway in our laboratory.

## Experimental Section

**General Procedure for the Enantioselective Henry Reaction of Nitroalkane with Isatins:** To a solution of **1** (0.2 mmol) and catalyst **VI** (10 mol-%) in THF (2 mL) was added **2** (2.0 mmol, 10 equiv.). The reaction mixture was kept at –30 °C for 4–5 d. The reaction mixture

was quenched with water (5 mL) and then extracted with ethyl acetate (2× 5 mL). The combined organic layers were washed with brine, dried with $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($SiO_2$; petroleum ether/ethyl acetate, 10:1 to 3:1) to afford desired products **3a**–**j**.

CCDC-827771 (for **3g**) and -827978 (for **3h**) contain 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.

**Supporting Information** (see footnote on the first page of this article): Experimental details and spectroscopic data.

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