

# Synthesis of Highly Functionalized Chiral 3,3'-Disubstituted Oxindoles via an Organocatalytic Enantioselective Michael Addition of Nitroalkanes to Indolyldenecyanoacetates

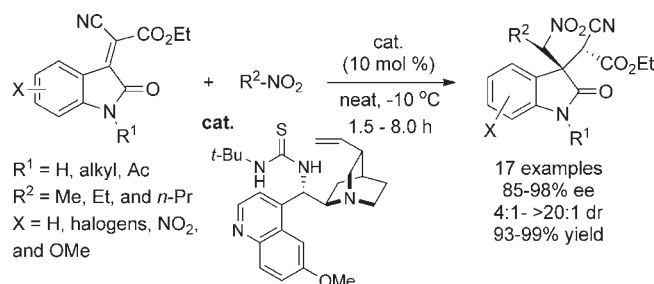
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## ABSTRACT



An efficient bifunctional cinchona alkaloid derived thiourea-promoted enantioselective conjugate addition of nitroalkanes to indolyldenecyanoacetates has been developed under neat conditions. The process leads to synthetically interesting densely functionalized 3,3'-disubstituted oxindoles with creation of up to three stereogenic centers.

Given the broad spectrum of attractive biological properties of oxindole alkaloids,<sup>1</sup> their structures have been a driving force for developing new synthetic reactions. Notably, a number of elegant synthetic strategies have been developed recently, particularly organocatalyzed asymmetric versions.<sup>2</sup> Despite the significant advances made, an organocatalytic enantioselective conjugate addition of nitroalkanes to oxindole-derived Michael acceptors has not been reported to our knowledge.<sup>3–5</sup> The rich chemistry of the resulting nitro-containing products<sup>6</sup> enabled facile

elaboration to structures of interest, important aspects in diversity-oriented synthesis (DOS).<sup>7</sup>

In continuation of our efforts to create structurally diverse oxindole compounds with potentially interesting biological properties<sup>8</sup> and with a view to fashioning the quaternary stereogenic center<sup>9</sup> of a large array of oxindole natural products,<sup>1</sup> we envisioned studying the reaction shown in Scheme 1. The successful realization of a catalytic asymmetric process would enable the generation of 3,3'-disubstituted oxindoles bearing three versatile nitro-, nitrile, and ester functionalities, which could allow convenient synthetic elaboration.<sup>1</sup> Moreover, up to three stereogenic centers including one full carbon quaternary chiral center could be potentially created in this operation.

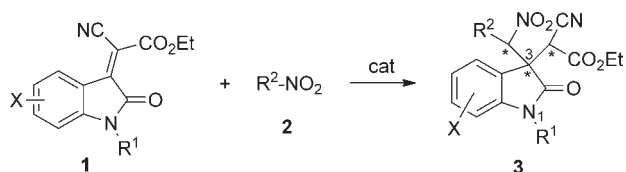
In this paper, we disclose a new, efficient organocatalytic enantioselective Michael addition of nitroalkanes to

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**Scheme 1.** Organocatalytic Enantioselective Michael Addition of Nitroalkanes to  $\alpha,\beta$ -Unsaturated Cyanoacetate Oxindoles



indolylidencyanoacetates to generate 3,3'-disubstituted chiral oxindoles in high yield and with good to high enantioselectivity (85–98% ee) and good to high dr (1:4 to > 20:1 dr ratio) under neat conditions. Furthermore, as demonstrated, the adducts can be readily transformed to chiral spiro-oxindoles as potential CRTH2 (DP2) receptor antagonists.<sup>10</sup>

In the initial study, a variety of bifunctional amine thiourea catalysts (10 mol %)<sup>11,12</sup> were screened for the proposed catalytic enantioselective Michael addition of nitromethane **2a** to indolylidene-cyanoacetate **1a** without a solvent (Table 1). We found that the reaction proceeded smoothly to afford the desired product **3a** in high yields (92–99%, entries 1–8) with moderate dr, but the enantioselectivities varied. Among the catalysts probed, catalyst **IV**<sup>13</sup> gave the highest ee value (77% ee, entry 4). Therefore, it was selected for further optimization of the reaction conditions. It appeared that when the reaction was carried out in a solvent, regardless of polarity (entries 4 and 9–16), they were detrimental to the enantioselectivity and longer reaction times were required. Lowering the reaction

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temperature improved the enantioselectivity and diastereoselectivity significantly, while still preserving high yields and short reaction times (entries 17–19).

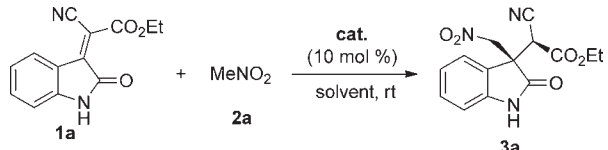
Having established an optimal reaction protocol, we next probed a variety of indolylidencyanoacetates (**1**) with nitroalkanes (**2**) to determine the scope of the **IV**-catalyzed enantioselective Michael addition transformation (Table 2). We found that the process served as a general approach to enantioenriched 3,3'-disubstituted oxindoles **3** with a significant structural variation. Notably, in all cases, the processes proceeded efficiently (1.5–8 h) in high yield (93–99%) and with good to high enantioselectivity (85–98% ee) and diastereoselectivity (4:1 to > 20:1 dr). It appeared that the electronic effect was limited. The benzene ring of **1** bearing electron-neutral (entry 1), electron-withdrawing (entries 2–6), electron-donating groups (entry 7) gave 85–98% ee and diastereoselectivity (9:1 to > 20:1). Nevertheless, it was found that derivatization of the nitrogen moiety in **1** (entries 8–15) had an influence on the diastereoselectivity of products; in general, the dr was decreased while the reaction yields and enantioselectivities were affected marginally. Finally, we also probed the structural features of nitroalkanes that included nitroethane and -propane (entries 16 and 17) as Michael donors for the conjugate addition reaction. They smoothly underwent the reaction with high efficiency, and three stereogenic centers were generated.

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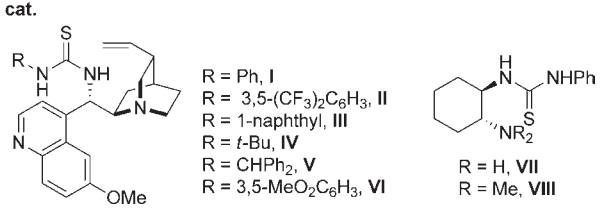
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**Table 1.** Optimization of Reaction Conditions<sup>a</sup>


cat.



| entry           | cat.        | solvent                         | time (h) | % yield <sup>b</sup> | % ee <sup>c</sup> | dr <sup>d</sup> |
|-----------------|-------------|---------------------------------|----------|----------------------|-------------------|-----------------|
| 1               | <b>I</b>    | neat                            | 1/3      | 93                   | 69                | 2:1             |
| 2               | <b>II</b>   | neat                            | 0.5      | 92                   | 69                | 2:1             |
| 3               | <b>III</b>  | neat                            | 1/3      | 90                   | 62                | 3:1             |
| 4               | <b>IV</b>   | neat                            | 5/6      | 99                   | 77                | 3:1             |
| 5               | <b>V</b>    | neat                            | 5/6      | 95                   | 75                | 3:1             |
| 6               | <b>VI</b>   | neat                            | 3        | 90                   | 70                | 2:1             |
| 7               | <b>VII</b>  | neat                            | 2        | 93                   | 46                | 2:1             |
| 8               | <b>VIII</b> | neat                            | 0.5      | 94                   | 60                | 2:1             |
| 9               | <b>IV</b>   | CH <sub>2</sub> Cl <sub>2</sub> | 7        | 96                   | 70                | 3:1             |
| 10              | <b>IV</b>   | DMF                             | 14       | 95                   | 28                | 3:1             |
| 11              | <b>IV</b>   | THF                             | 24       | 94                   | 52                | 3:1             |
| 12              | <b>IV</b>   | toluene                         | 3.5      | 96                   | 62                | 3:1             |
| 13              | <b>IV</b>   | MeCN                            | 8        | 95                   | 72                | 3:1             |
| 14              | <b>IV</b>   | EtOAc                           | 6        | 92                   | 65                | 4:1             |
| 15              | <b>IV</b>   | dioxane                         | 6        | 91                   | 48                | 3:1             |
| 16              | <b>IV</b>   | MeOH                            | 8        | 90                   | 51                | 3:1             |
| 17 <sup>e</sup> | <b>IV</b>   | neat                            | 2.5      | 97                   | 82                | 9:1             |
| 18 <sup>f</sup> | <b>IV</b>   | neat                            | 3.5      | 99                   | 87                | 9:1             |
| 19 <sup>g</sup> | <b>IV</b>   | neat                            | 7        | 98                   | 88                | 9:1             |
| 20 <sup>h</sup> | <b>IV</b>   | neat                            | 40       | 95                   | 87                | 9:1             |

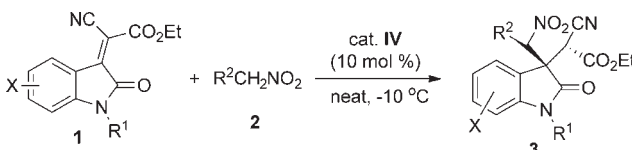
<sup>a</sup> Reaction conditions: unless specified, a mixture of **1a** (121 mg, 0.5 mmol) and a catalyst (0.05 mmol) in nitromethane (1.0 mL) was stirred at rt for a specified time. After concentration in vacuo, the residue was purified by silica gel chromatography, eluting with EtOAc and hexanes (1/2 v/v ratio). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC (Chiralpak AD-H). <sup>d</sup> Determined by <sup>1</sup>H NMR. <sup>e</sup> Reaction carried out at 0 °C. <sup>f</sup> Reaction carried out at -10 °C. <sup>g</sup> Reaction carried out at -25 °C. <sup>h</sup> 5 mol % of catalyst used.

The Michael adducts **3** hold great potential in DOS and therapeutic agent development. Toward this end, we

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**Table 2.** Generality of **IV**-Catalyzed Conjugate Addition of Nitroalkanes **2** to Indolyldienecyanoacetates **1**<sup>a</sup>


| entry           | X, R <sup>1</sup> , R <sup>2</sup> , <b>3</b>          | time (h) | % yield <sup>b</sup> | % ee <sup>c</sup> | dr <sup>d</sup>  |
|-----------------|--|----------|----------------------|-------------------|------------------|
| 1               | H, H, H, <b>3a</b>                                     | 3.5      | 99                   | 87                | 9:1              |
| 2               | 5-Br, H, H, <b>3b</b>                                  | 3        | 95                   | 98                | 12:1             |
| 3               | 5-Cl, H, H, <b>3c</b>                                  | 3        | 94                   | 85                | >20:1            |
| 4               | 7-Cl, H, H, <b>3d</b>                                  | 5        | 96                   | 85                | >20:1            |
| 5               | 5-NO <sub>2</sub> , H, H, <b>3e</b>                    | 1.5      | 94                   | 92                | 12:1             |
| 6               | 5-I, H, H, <b>3f</b>                                   | 3        | 95                   | 89                | 11:1             |
| 7               | 5-MeO, H, H, <b>3g</b>                                 | 2        | 93                   | 85                | >20:1            |
| 8               | H, CH <sub>2</sub> CO <sub>2</sub> Me, H, <b>3h</b>    | 4        | 95                   | 88                | 4:1 <sup>f</sup> |
| 9               | H, Me, H, <b>3i</b>                                    | 4        | 96                   | 97                | 6:1 <sup>g</sup> |
| 10              | H, Ac, H, <b>3j</b>                                    | 6        | 94                   | 96                | 6:1 <sup>h</sup> |
| 11              | 5-Br, Me, H, <b>3k</b>                                 | 6        | 98                   | 92                | 8:1              |
| 12              | 5-Br, CH <sub>2</sub> CO <sub>2</sub> Me, H, <b>3l</b> | 6        | 97                   | 85                | 10:1             |
| 13              | 5-Br, Bn, H, <b>3m</b>                                 | 8        | 97                   | 85                | 4:1              |
| 14              | 5-I, Me, H, <b>3n</b>                                  | 6        | 94                   | 91                | 10:1             |
| 15              | 5-OMe, Me, H, <b>3o</b>                                | 4        | 95                   | 90                | >20:1            |
| 16 <sup>e</sup> | H, H, Me, <b>3p</b>                                    | 3        | 95                   | 88                | 7:1 <sup>i</sup> |
| 17 <sup>e</sup> | H, H, Et, <b>3q</b>                                    | 3        | 97                   | 97                | 6:1 <sup>j</sup> |

<sup>a</sup> Reaction conditions: unless specified, see footnote a in Table 1. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (Chiralpak AD-H or AS-H). <sup>d</sup> Determined by <sup>1</sup>H NMR. <sup>e</sup> Major isomer with *R*-configuration determined by NOESY (see the Supporting Information for details). <sup>f</sup> 14% ee for minor isomer. <sup>g</sup> 84% ee for minor isomer. <sup>h</sup> 73% ee for minor isomer. <sup>i</sup> 25% ee for minor isomer. <sup>j</sup> 98% ee for minor isomer.

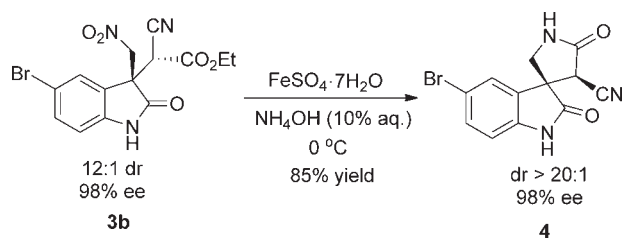
showed that, for example, product **3b** could be readily transformed into a spirooxindole **4** (Scheme 2). Selective reduction of the nitro group by ferrous sulfate to an amine was followed by spontaneous lactamization to give product **4** in 85% yield whose diastereoselectivity was improved (dr > 20:1). It is noteworthy that the racemic spirooxindoles have been reported as CRTH2 (DP2) receptor antagonists of potential use for the treatment of allergic inflammatory diseases.<sup>10</sup> The asymmetric method reported here could be employed for the preparation of the

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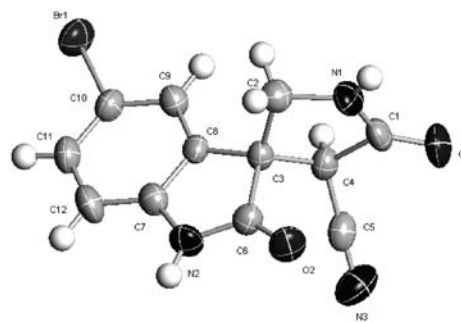
**Scheme 2.** Synthesis of Spirooxindole via Reduction-Lactamization Cascade



enantiomers for biological studies. The absolute configuration of product **3b** was determined by the single-crystal X-ray analysis of compound **4** (Figure 1).<sup>14</sup>

In summary, we have developed a new enantioselective Michael addition of nitroalkanes to indolyldenecyanoacetates, catalyzed by a bifunctional cinchona alkaloid thiourea **IV** under neat, mild reaction conditions. Notably, up to three stereogenic centers and one quaternary chiral center are generated in good to high enantio- and diastereoselectivity. The reaction provides alternative access to synthetically and biologically interesting, structurally diverse, enantioenriched 3,3'-disubstituted oxindoles.

(14) See the Supporting Information for the CIF. The structure of the compound derived from molecule **4** was determined by X-ray crystal analysis. CCDC-851133 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk) and see the Supporting Information.



**Figure 1.** X-ray structure of compound **4**.

Efforts toward application of the densely functionalized Michael adducts in DOS and expanding the strategy for new organic transformations are being pursued in our laboratory.

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**Supporting Information Available.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR and HRMS data and experimental procedures and characterization of the products **3** and **4**. X-ray data for compound **4** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.