

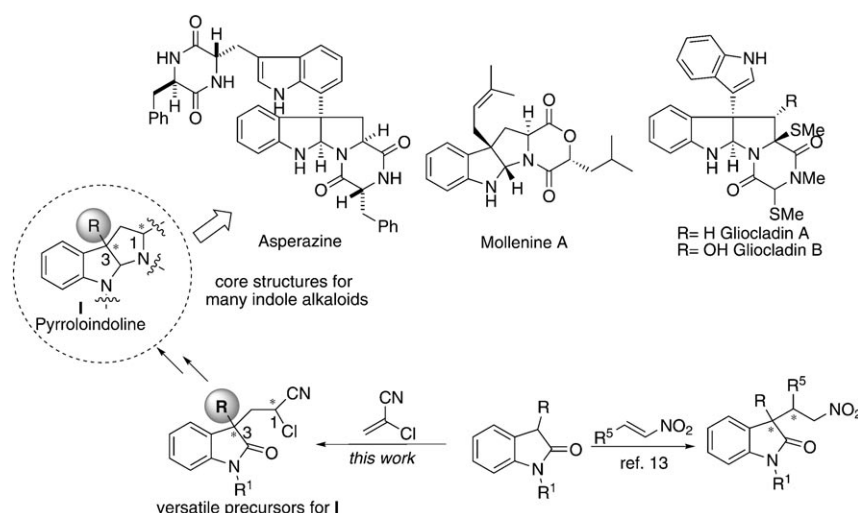
# Asymmetric Conjugate Addition of Oxindoles to 2-Chloroacrylonitrile: A Highly Effective Organocatalytic Strategy for Simultaneous Construction of 1,3-Nonadjacent Stereocenters Leading to Chiral Pyrroloindolines

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The chiral pyrroloindoline core **I** with 1,3-nonadjacent carbon stereocenters (Scheme 1) is a key structural element found in a wide range of indole alkaloids exhibiting diverse bioactivity profiles.<sup>[1]</sup> For instance, biologically active natural products, such as the Gliocladins A–C,<sup>[2]</sup> Molleneine A,<sup>[3]</sup> As-

perazine,<sup>[4]</sup> Brevianamide E,<sup>[5]</sup> and a great number of dimeric diketopiperazine alkaloids,<sup>[6]</sup> are all based on structure **I** (Scheme 1). Accordingly, these natural products have attracted a great deal of attention in the pursuit of their total synthesis and meanwhile still pose significant synthetic chal-

lenges due to their structural complexity and unique bond connections. One widely explored strategy for the synthesis of these natural products is to utilize the intramolecular ring-closure reaction from tryptophan derivatives. Notable contributions along this line include those from the groups of Hino,<sup>[7]</sup> Crich,<sup>[8]</sup> Overman,<sup>[9]</sup> Danishefsky,<sup>[10]</sup> and Movassaghi.<sup>[11]</sup> Though quite straightforward, these methods lack the flexibility to generate substituted pyrroloindolines, particularly for those with 3-substituted quaternary full-carbon stereocenters. To develop a new catalytic methodology for the effective construction of such asymmetrical structural motifs is thus highly important and re-



Scheme 1. Natural products with the pyrroloindoline core containing 1,3-nonadjacent stereocenters and our synthetic strategy.

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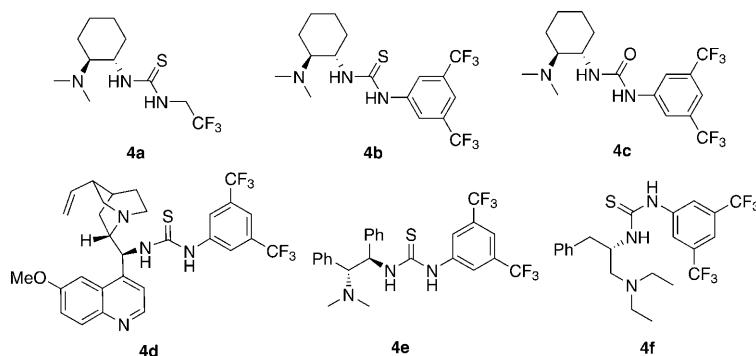
mains an elusive and fundamental goal in this area.

As one of the most versatile C–C bond transformations, asymmetric conjugate addition reactions with carbon nucleophiles have been very successful in creating molecular complexity with high stereocontrol.<sup>[12]</sup> In a particularly valuable context, such a process using 3-substituted oxindoles as nucleophiles would serve as the key chiral transformations leading to complex structural motifs that are ubiquitous in a number of biologically active indole alkaloids.<sup>[13]</sup> For example, Barbas and co-workers reported a novel total synthesis of (+)-physostigmine, in which they used an orga-

nocatalytic 1,4-addition of oxindoles to nitroolefins as the key step.<sup>[13e]</sup> Analogous asymmetric catalysis, which generated one quaternary stereocenter or two 1, 2-adjacent stereocenters of chiral oxindole compounds have also been documented recently.<sup>[13,14]</sup> Despite these advances, highly diastereo- and enantio- stereoselective synthesis of chiral oxindoles containing 1,3-nonadjacent stereocenters, which serve as versatile precursors for pyrroloindoles **1**, has not been achieved so far. One conceivable strategy towards this end could be to use conjugate addition reaction of 3-substituted oxindoles with  $\alpha$ -branched Michael acceptors, such as 2-chloroacrylonitrile.<sup>[15]</sup> Catalytic process of this type would be a significant challenge, however, particularly with regard to the stereocontrol of both the absolute and relative configurations, as the whole catalysis is a tandem conjugate addition–protonation with simultaneous control of two separated stereocenters.

Herein, we present the first catalytic diastereo- and enantioselective conjugate addition reaction of 3-substituted oxindoles to 2-chloroacrylonitrile, which generates chiral oxindoles as direct precursors for pyrroloindoles **1** with excellent stereocontrol. This process was made possible by the use of a chiral alkyl thiourea, which we previously developed by electronic tuning and has since been successfully applied in catalytic reactions featuring all-carbon quaternary stereocenter formations.<sup>[16,17]</sup>

The Michael addition reaction of oxindole **1a** to 2-chloroacrylonitrile (**2**) served as the testing reaction. Six widely used bifunctional tertiary amine thioureas or urea catalysts **4a–4f**<sup>[18]</sup> (Scheme 2) with different scaffolds were screened



Scheme 2. Bifunctional tertiary amine thiourea (urea) catalysts tested in this study.

in the model reaction at 4°C. To our delight, most of the catalysts exhibited high catalytic activities and the Michael products were isolated with good to excellent yields and moderate stereoselectivities (2:1–4:1 d.r. and 64–77% *ee*) except for **4e** (Table 1, entry 5). Among the six bifunctional hydrogen-bonding catalysts examined, our previously developed alkyl thiourea **4a** was found to give the optimal stereoselectivity (Table 1, entry 1, 98% yield, 4:1 d.r. and 77% *ee*).

The reaction was then optimized by screening solvent, temperature, and additive in the presence of **4a** (10 mol %).

Table 1. Catalyst Screening.<sup>[a]</sup>

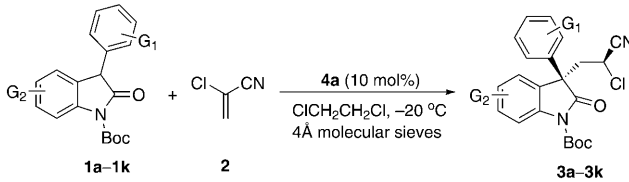
| Entry | Cat.                     | Solvent                         | <i>t</i> [h] | Yield [%] <sup>[b]</sup> | d.r. <sup>[c]</sup> | <i>ee</i> [%] <sup>[d]</sup> |
|-------|--------------------------|---------------------------------|--------------|--------------------------|---------------------|------------------------------|
| 1     | <b>4a</b>                | toluene                         | 12           | 98                       | 4:1                 | 77                           |
| 2     | <b>4b</b>                | toluene                         | 12           | 97                       | 3:1                 | 76                           |
| 3     | <b>4c</b>                | toluene                         | 12           | 99                       | 3:1                 | 75                           |
| 4     | <b>4d</b>                | toluene                         | 12           | 96                       | 2:1                 | 64                           |
| 5     | <b>4e</b>                | toluene                         | 12           | 51                       | 1:2                 | –69                          |
| 6     | <b>4f</b>                | toluene                         | 12           | 80                       | 3:1                 | 76                           |
| 7     | <b>4a</b>                | CH <sub>2</sub> Cl <sub>2</sub> | 12           | 80                       | 4:1                 | 83                           |
| 8     | <b>4a</b>                | CHCl <sub>3</sub>               | 12           | 70                       | 4:1                 | 75                           |
| 9     | <b>4a</b>                | DCE                             | 12           | 96                       | 4:1                 | 84                           |
| 10    | <b>4a</b>                | benzene                         | 12           | 97                       | 4:1                 | 77                           |
| 11    | <b>4a</b>                | xylene                          | 12           | 99                       | 3:1                 | 77                           |
| 12    | <b>4a</b>                | THF                             | 12           | 40                       | 2:1                 | 76                           |
| 13    | <b>4a</b> <sup>[e]</sup> | DCE                             | 36           | 92                       | 11:1                | 93                           |
| 14    | <b>4a</b> <sup>[f]</sup> | DCE                             | 36           | 95                       | 12:1                | 94                           |

[a] The reaction was carried out on a 0.1 mmol scale in the solvent (200  $\mu$ L) at 4°C, and the molar ratio of oxindole **1a**/**2** is 1:3. [b] Yield of the isolated product. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out on a 0.1 mmol scale in ClCH<sub>2</sub>CH<sub>2</sub>Cl (200  $\mu$ L) at –20°C. [f] The reaction was carried out on a 0.1 mmol scale in ClCH<sub>2</sub>CH<sub>2</sub>Cl (200  $\mu$ L) with 4 Å molecular sieves at –20°C.

As illustrated in Table 1, 1, 2-dichloroethane (DCE) gave the best result among a range of screened solvents (Table 1, entries 1 and 7–12). Further improvement could be achieved by lowering the reaction temperature (Table 1, entry 13). Addition of 4 Å molecular sieves to the reaction mixture slightly increased both the diastereoselectivity and enantioselectivity (Table 1, entry 14). Collectively, the best results with respect to yield and stereoselectivity were obtained by performing the reaction at –20°C in DCE in the presence of 4 Å molecular sieves. Under these conditions, the reaction provided the desired product in 95% yield with 12:1 d.r. and 94% *ee* (Table 1, entry 14).

To investigate the scope of the reaction, we first examined the reactions of a range of 3-aryl oxindoles **1a–1k** with **2** under the optimized conditions. As shown in Table 2, oxindoles with 3-aryl groups containing either electron-withdrawing or electron-donating moieties could be converted into the desired products with excellent yields (81–95%), good diastereoselectivity (up to 19:1) and enantioselectivity (86–95% *ee*) (Table 2, entries 1–10). Slightly lower stereoselectivity was obtained with *meta*-substituted 3-aryl oxindoles **1c** and **1f** (Table 2, entries 3 and 6). The reaction of a 5-me-

Table 2. Substrate scope of 3-aryl oxindoles.<sup>[a]</sup>



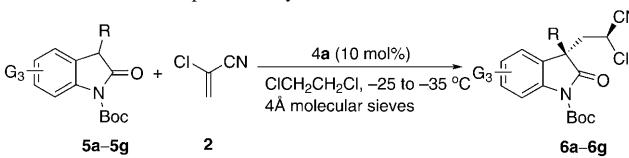
| Entry | G <sub>1</sub>                  | G <sub>2</sub>      | t [h] | Product (yield [%] <sup>[b]</sup> ) | d.r. <sup>[c]</sup> | ee [%] <sup>[d]</sup> |
|-------|---------------------------------|---------------------|-------|-------------------------------------|---------------------|-----------------------|
| 1     | <b>1a</b> : H                   | H                   | 48    | <b>3a</b> (95)                      | 12:1                | 94                    |
| 2     | <b>1b</b> : 4-CH <sub>3</sub> O | H                   | 78    | <b>3b</b> (81)                      | 10:1                | 92                    |
| 3     | <b>1c</b> : 3-CH <sub>3</sub> O | H                   | 72    | <b>3c</b> (86)                      | 7:1                 | 86                    |
| 4     | <b>1d</b> : 4-EtO               | H                   | 72    | <b>3d</b> (85)                      | 11:1                | 93                    |
| 5     | <b>1e</b> : 4-CH <sub>3</sub>   | H                   | 48    | <b>3e</b> (93)                      | 8:1                 | 92                    |
| 6     | <b>1f</b> : 3,5-CH <sub>3</sub> | H                   | 72    | <b>3f</b> (85)                      | 6:1                 | 86                    |
| 7     | <b>1g</b> : 4- <i>n</i> Bu      | H                   | 48    | <b>3g</b> (93)                      | 9:1                 | 92                    |
| 8     | <b>1h</b> : 4-F                 | H                   | 80    | <b>3h</b> (81)                      | 19:1                | 95                    |
| 9     | <b>1i</b> : 4-Cl                | H                   | 48    | <b>3i</b> (93)                      | 9:1                 | 93                    |
| 10    | <b>1j</b> : 4-Ph                | H                   | 60    | <b>3j</b> (90)                      | 12:1                | 95                    |
| 11    | <b>1k</b> : H                   | 5-CH <sub>3</sub> O | 48    | <b>3k</b> (85)                      | 14:1                | 93                    |

[a] The reaction was carried out on a 0.1 mmol scale in CH<sub>2</sub>ClCH<sub>2</sub>Cl (200 μL) with 4 Å molecular sieves at -20 °C, and the molar ratio of 3-aryl-1-Boc-2-oxindoles/2-chloroacrylonitrile is 1:3. [b] Yield of the isolated product. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

thoxyl substituted oxindole **1k** also worked very well to give the desired Michael product **3k** with high yield (85 %), good diastereoselectivity (14:1 d.r.) and enantioselectivity (93 % ee) (Table 2, entry 11).

To further expand the substrate scope, 3-alkyl oxindoles were also employed as nucleophiles. The corresponding results are present in Table 3. To our delight, all of the exam-

Table 3. Substrate scope of 3-alkyl oxindoles.<sup>[a]</sup>



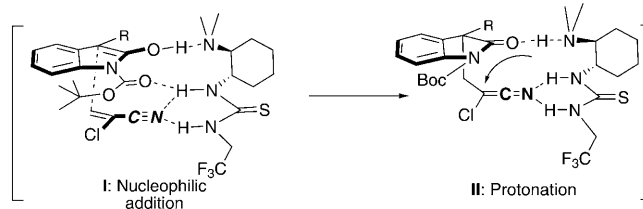
| Entry | R                       | G <sub>3</sub>      | t [h] | Product (yield [%] <sup>[b]</sup> ) | d.r. <sup>[c]</sup> | ee [%] <sup>[d]</sup> |
|-------|-------------------------|---------------------|-------|-------------------------------------|---------------------|-----------------------|
| 1     | <b>5a</b> : Me          | H                   | 48    | <b>6a</b> (93)                      | > 30:1              | 98                    |
| 2     | <b>5b</b> : Me          | 5-CH <sub>3</sub> O | 60    | <b>6b</b> (95)                      | > 30:1              | 97                    |
| 3     | <b>5c</b> : Et          | H                   | 36    | <b>6c</b> (99)                      | > 30:1              | 99                    |
| 4     | <b>5d</b> : Et          | 5-CH <sub>3</sub> O | 48    | <b>6d</b> (92)                      | 19:1                | 97                    |
| 5     | <b>5e</b> : <i>n</i> Pr | H                   | 48    | <b>6e</b> (91)                      | > 30:1              | 99                    |
| 6     | <b>5f</b> : Bn          | H                   | 48    | <b>6f</b> (94)                      | > 30:1              | 97                    |
| 7     | <b>5g</b> : allyl       | H                   | 36    | <b>6g</b> (97)                      | > 30:1              | 98                    |

[a] The reaction was carried out on a 0.1 mmol scale in CH<sub>2</sub>ClCH<sub>2</sub>Cl (400 μL) with 4 Å molecular sieves at -25–35 °C, and the molar ratio of 3-aryl-1-Boc-2-oxindoles/2-chloroacrylonitrile is 1:3. [b] Yield of the isolated product. [c] Determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

ined 3-alkyl oxindoles **5a–5f** smoothly reacted with **2** to afford the corresponding Michael products **6a–6f** with very good yields (91–99 %), excellent diastereoselectivities (up to > 30:1 d.r.) and enantioselectivities (97–99 % ee). 3-Allyl oxindole **5g** can also be used in the current Michael strategy

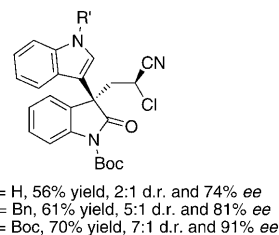
presenting very good activity and stereoselectivity (Table 3, entry 7, 97 % yield, > 30:1 d.r. and 98 % ee).

The absolute configurations of both adducts **3** and **6** have been determined by X-ray crystallographic analysis of compound **3a** and **6a** (for details see the Supporting Information).<sup>[19,20]</sup> The observed stereocontrol can be rationalized by considering transition states **I** and **II** wherein effective multi-hydrogen bonding plays a critical role in nucleophilic addition (**I**) and subsequent protonation (**II**), which generate the quaternary and tertiary stereocenters, respectively (Scheme 3).



Scheme 3. Proposed transition states.

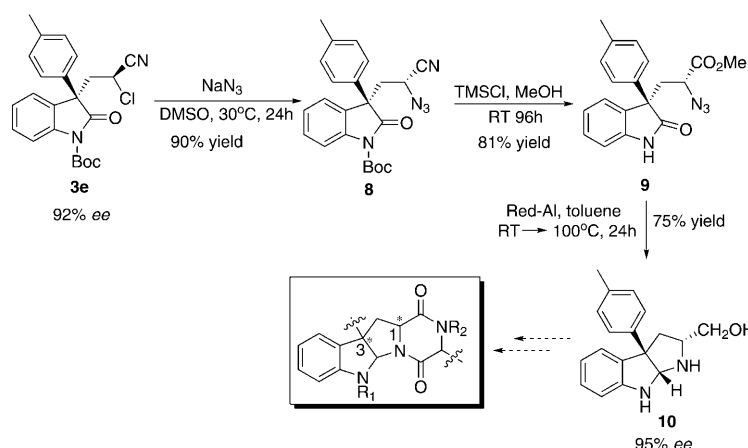
To widen the applications of this Michael strategy, the reactions between 3-(3'-indolyl)oxindoles and 2-chloroacrylonitrile have also been investigated (Scheme 4). The obtained



Scheme 4. Catalytic result with 3-indolyl oxindoles as Michael donors.

chiral oxindoles **7** contain all the skeleton carbon atoms of Gliocladin A, B, and C and can thus serve as a very promising and quick starting point for the total synthesis of Glioclalidins.<sup>[2,21]</sup> An initial attempt with an unprotected 3-indolyl group gave the corresponding conjugated product with moderate yield (56 %) and stereoselectivity (2:1 d.r., 74 % ee). Subsequent N-protection of the 3'-indolyl moiety led to considerable improvement of both the reactivity and stereoselectivity, and the best results were obtained with the *N*-Boc protected starting material. In this case, the desired product **7c** was obtained in 70 % yield, 7:1 d.r., and 91 % ee in the presence of **4a** (10 mol %).

To demonstrate the potential of the current Michael strategy in the context of chiral pyrroloindole synthesis, a large scale synthesis of **3e** was carried out. As shown in Scheme 5, catalytic asymmetric Michael addition of 3-(4-methyl)-phenyl-*N*-Boc oxindole **1e** with 2-chloroacrylonitrile **2** was accomplished with good results by using **4a** (10 mol %). Compound **3e** can be easily converted to **8** by nucleophilic



Scheme 5. Synthesis of pyrroloindole.

substitution of the chloride with sodium azide. Treatment of **8** with trimethylsilyl chloride (TMSCl) in methanol cleanly transformed the cyano group to a methyl ester moiety with concomitant deprotection of the Boc group, to give **9** in 81 % yield. Finally, compound **9** can be readily transformed into the chiral pyrroloindole **10** by reductive amination with Red-Al in toluene. With the pyrroloindole core structure, compound **10** can be readily converted into pyrazino-pyrroloindole-1,4-dione type natural products such as Gliocaldins.<sup>[21]</sup> Meanwhile, this type of structure can also be used as a novel type of asymmetric aminocatalyst.<sup>[22]</sup>

To summarize, in this work we have developed a highly enantioselective conjugate addition reaction of 3-substituted oxindole to 2-chloroacrylonitrile with a readily accessible alkyl bifunctional tertiary amine thiourea as the catalyst. The reactions demonstrated high efficiency and excellent stereoselectivity (up to >30:1 d.r. and up to 99 % ee) while simultaneously generating two separated all-carbon stereocenters. We believe the current reaction provides a long sought-after catalytic stereoselective approach for the synthesis of chiral pyrroloindole structures, which are widely distributed in indole alkaloids. Further investigation of the scope and synthetic utility of this chemistry is underway, and will be reported in due course.

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**Keywords:** Michael addition • natural products • organocatalysis • oxindoles • quaternary center

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