Copper-Catalyzed Highly Enantioselective Cyclopentannulation of Indoles with Donor−Acceptor Cyclopropanes

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Supporting Information

ABSTRACT: A highly diastereo- and enantioselective BOX/Cu(II)-catalyzed C2,C3-cyclopentannulation of indoles with donor−acceptor cyclopropanes has been developed on the basis of asymmetric formal [3 + 2] cycloaddition of indoles. This reaction provides rapid and facile access to a series of enantioenriched cyclopenta-fused indoline products and can be further extended to the construction of tetracyclic pyrroloindolines. The synthetic potential of the reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

C2,C3-fused indolines are widely present as core structures in a large number of natural products and biologically active molecules and have been the focus of extensive synthetic efforts for a long time.1 Recently, catalytic asymmetric transformations of indoles have been emerging as a powerful enantioselective strategy for the synthesis of these products, featuring the rapid assembly of the multicyclic skeleton in a cascade fashion using readily available indole feedstocks.2−4 The key step in these transformations is the generation of the chiral electrophilic indoleniminium intermediate, which is susceptible to intramolecular attack by a pendant group to close the ring. The asymmetric organocatalytic Friedel−Crafts reaction is the most studied approach for generating chiral incipient indoleniniums,5 while asymmetric metal-catalyzed reactions such as palladium-catalyzed C3 allylation of indoles,6a copper-catalyzed arylation,6e and gold-catalyzed alkenylation4f have also proved to be effective. Recently, Barluenga and co-workers6b reported the use of tungsten Fischer carbenes in the asymmetric C2−C3 annulation reaction of indoles, and Lian

Table 1. Reaction Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>t (h)</th>
<th>Yield (%)b</th>
<th>de (%)c</th>
<th>ee (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-DBFOX</td>
<td>24</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ph-PyBOX</td>
<td>24</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>L4a</td>
<td>24</td>
<td>86</td>
<td>7.5/1</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>L4b</td>
<td>2</td>
<td>93</td>
<td>10/1</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>L4c</td>
<td>30</td>
<td>76</td>
<td>7/1</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>L5a</td>
<td>2</td>
<td>88</td>
<td>7/1</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>L5b</td>
<td>2</td>
<td>94</td>
<td>10/1</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>L5c</td>
<td>2</td>
<td>93</td>
<td>14/1</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>L5c</td>
<td>5</td>
<td>95</td>
<td>20/1</td>
<td>91</td>
</tr>
</tbody>
</table>

Notes: 1a/2a = 1.2/1 and [2a] = 0.3 mmol in toluene (3 mL) under N2. bIsolated yields. cDetermined by 1H NMR analysis. dDetermined by chiral HPLC. 1a/2a = 1/1.5 and [2a] = 0.3 mmol in toluene (3 mL) at 0 °C.

Figure 1. Cyclopenta-fused indolines in natural products.
and Davies established a rhodium-catalyzed version with vinyldiazoacetates. The two works represent the few enantioselective examples of the synthesis of cyclopenta-fused indoline, which is a common structure in many natural products such as kopsane, vindolinine, and dasyrachine (Figure 1). Within this scenario, here we report a new entry to this arsenal, a highly diastereo- and enantioselective Lewis acid-catalyzed formal [3 + 2] cycloaddition of indoles with donor-acceptor (D-A) cyclopropanes. In particular, pyrroloindoles can also participate in this annulation reaction, providing the core structure in borreverines.

We initiated our study with the ligand screening, using indole 1a and cyclopropane 2a as the model substrates and Cu(OTf)2 as the copper source. The tridentate bis(oxazoline) (BOX) ligands Ph-DBFOX and Ph-PyBOX, which have shown good selectivity in cycloadditions of cyclopropanes with nitrones and aldehydes or imines, did not show any activity in the current reaction (Table 1, entries 1 and 2). Indane-BOX ligand L4a gave the desired cyclopentannulation product 3a in 86% yield with a promising 55% ee (entry 3). To our delight, modification of the bridging carbon by the introduction of a benzyl group (L4b) not only increased the catalytic activity but also significantly improved the enantioselectivity to 80% ee (entry 4). However, the coordinating oxazoline side-arm group in L4c retarded the reaction rate and decreased the enantioselectivity by 12%, perhaps because of the weakened Lewis acidity due to the ligation of the additional oxazoline to copper (entry 5). Further elaboration of the ligand was thus focused on using benzyl side-arm groups. Unfortunately, both steric and electronic alterations of the benzene ring failed to provide an obvious improvement in the enantioselectivity.

Recently, we found that a type of cage-like BOX ligand...
containing two aryl side-arm groups (L5a, L5b) can significantly improve the enantioselectivity in the cyclopropanation reaction of alkenes compared with ligands having only one aryl side-arm group or without this side-arm modification.10 Though initial replacement of L4b with L5a led to a significant drop in selectivity (entry 6), introduction of a tert-butyl group at the para position or the two meta positions of the pendant phenyl group improved both the diastereo- and enantioselectivity (entries 7 and 8), and the new ligand L5c was identified as the best (the crystal structure of L5c/CuBr2 is shown in Table 1).9 Varying the substrate ratio and lowering the temperature to 0 °C further improved the stereoselectivity to a decent level (20/1 dr and 91% ee; entry 9).

Under the optimized conditions, the reaction scope was examined (Table 2). The reaction worked well with a range of indoles. Compared with 5-methyl-substituted indole 1b, the reactions of 5-bromo- and 5-chloro-substituted indoles 1c and 1d were slower, but the electronic effect on the enantioselectivity was negligible (entries 2 and 5 vs 3 and 4). 4-Methyl-substituted indoles were converted with slightly higher diastereo- and enantioselectivity (>50/1 dr and 95% ee; entry 6) than 5-, 6-, or 7-substituted ones (entries 2, 7, and 9). It is noteworthy that indole C3 substituents other than methyl1b,c are also compatible with the current reaction (entries 10−14), allowing additional functionalities such as hydroxy, amino, and allyl groups to be introduced into the final products. In the case of 1k, the pendant carbamate group may also act as a donor group for further modifications (entry 22), while alkylcyclopropanes (R3 = H, Me) were inert under the current reaction conditions and formed no product even after 2 days at 50 °C. In general, except for 1o and 2g, all of the reactions proceeded with excellent diastereoselectivity (from 12/1 to >50/1 dr). The absolute configuration of 3ha was assigned by X-ray crystallography,9 and the configurations of the other products were assigned by analogy. For less reactive cyclopropanes, the present reactions could proceed with a concurrent kinetic resolution of the cyclopropanes, though the reactions were normally slower. At ca. 50% conversion, both the [3 + 2] annulation products and the recovered (S)-cyclopropanes 2h and 2i were obtained in high yields with high enantioselectivities (entries 23 and 24).

On the basis of the crystal structure of the L5c/CuBr2 complex, the square-planar geometry of Box/Cu2+ dicarbonyl complexes,12 and the stepwise annulation mechanism,5 a working model (Figure 2) was tentatively proposed to explain the enantioselection in the present reaction. In view of the steric demand in the nucleophilic attack of C3-substituted indoles at an sp3 carbon and the donor-group stabilization effect, the cyclopropane C2 carbon must have a significant carbocation character.6a,13 The approach of the Si face of the indole to the transient (R)-cyclopropane (left) should be more favored, experiencing less steric interaction with the ligand indanyl substituent. The preference for the (R)-cyclopropane is in line with the kinetic resolution results (Table 2, entries 23 and 24), in which (S)-cyclopropanes were recovered.

Inspired by the beneficial electronic effect of the electron-donating groups and the good enantioselectivity in the reaction of penta-fused indole 1o, a synthetic route for the synthesis of the tetracyclic core of borreverinee based on the cyclopentannulation of pyrroloindole 9 was designed (Scheme 1). Gratifyingly, the [3 + 2] annulation of 9 with 10 could even be carried out at −40 °C, and only a single diastereoisomer was observed with high enantioselectivity (95% ee). The four-step synthesis starting from tryptamine 6 gave the desired product 11 in 23% overall yield. The success with pyrroloindole-type substrates provides a novel and rapid access to tetracyclic pyrroloindole structures.

In summary, a highly diastereo- and enantioselective cyclopentannulation reaction of indoles with cyclopropanes has been successfully developed. The reaction performed well with a series of indoles and D−A cyclopropanes under mild conditions, giving penta-fused indoline products with excellent diastereoselectivities (up to >50/1 dr) and enantioselectivities (up to 96% ee). The application of this reaction to pyrroloindoles established an unprecedented approach to...
tetraacyclic pyrroloindoline compounds. The synthetic potential of the current reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

**ASSOCIATED CONTENT**

1 Supporting Information

Experimental procedures, characterizations and analytical data of ee values of products, and a zip file containing CIFs for 11, 3ha, 3oa, and L5c/CuBr2. 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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**REFERENCES**


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(9) For details, see the Supporting Information.


(11) In the reactions of N-benzyl-2-methylindole, only Friedel—Crafts alkylation products were isolated, and with 2.0 equiv of cyclopropane 2b, good enantioselectivity (92% ee) was also achieved.
