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Enantioselective Borylative Dearomatization of Indoles through Copper(I) Catalysis

Koji Kubota, Keiichi Hayama, Hiroaki Iwamoto and Hajime Ito*

Abstract: The first enantioselective borylative dearomatization of a heteroaromatic compound has been achieved using a copper(I) catalyst and a diboron reagent. This reaction involves the unprecedented regio- and enantioselective addition of active borylcopper(I) species to indole-2-carboxylates, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding chiral indolines bearing consecutive stereogenic centers.

Aromatic compounds are ubiquitous in nature and readily available as synthetic materials. The enantioselective dearomatization reactions of heteroaromatic compounds are very powerful transformations because they can be used to provide direct access to a wide variety of chiral-saturated heterocycles, which are important components of pharmaceutical drugs and bioactive molecules. The development of new methods for the formation of consecutive stereogenic centers via the stereoselective dearomatization of multi-substituted aromatic compounds would also have important practical implications for the synthesis of natural products.

Enantioenriched organoboron compounds are recognized as useful chiral building blocks in synthetic chemistry because they can be readily applied to the stereospecific functionalization of stereogenic C–B bonds. Considerable research efforts have recently been devoted to the development of new methods for the metal-catalyzed enantioselective hydro- and protoboration reactions of prochiral C=C double bonds. Despite significant progress in this area, there have been no reports pertaining to the development of C–B bond-forming dearomatization reactions. The lack of research in this area is most likely caused by the high energy barrier encountered during the dearomatization process. The development of an enantioselective C–B bond-forming dearomatization reaction would provide an attractive and complementary approach for the synthesis of complex, functionalized cyclic molecules in combination with the stereospecific transformation of a stereogenic C–B bond.

Ohmura et al. and Weetman et al. independently reported the results of their pioneering studies towards the development of a borylative dearomatization reaction, where pyridines were subjected to a dearomative hydroboration reaction with pinacolborane in the presence of Rh(I) and Mg(II) catalysts. In 2014, Marks et al. reported the development of a similar reaction using La(III) as a catalyst. However, the authors of these studies were only able to demonstrate non-enantioselective N–B bond-forming dearomatization reactions.

Herein, we report for the first time the development of a copper(I)-catalyzed reaction for the highly regio-, diastereo- and enantioselective C–B bond-forming dearomatization of heteroaromatic compounds (Scheme 1). This reaction involves the unprecedented enantioselective addition of an active borylcopper(I) species to an indole-2-carboxylate, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding enantioenriched chiral indoline derivative with excellent diastereo- and enantioselectivities. The stereospecific oxidation of the chiral 3-borylindoline product has also been demonstrated.

During the last decade, our group has been involved in the development of new methods for the copper(I)-catalyzed enantioselective borylation of prochiral alkenes. The results of the related research in this field revealed that electron-deficient substrates with low LUMO levels tend to react efficiently with active borylcopper(I) species. Based on these results, it was envisaged that heteroaromatic systems bearing an electron-withdrawing group could also react with a borylcopper(I) complex in a process involving the formation of a stereogenic C–B bond. With this in mind, a readily available indole-2-carboxylate derivative was selected as a model substrate to investigate the optimum reaction conditions for the enantioselective borylative dearomatization of this substrate using a chiral copper(I) catalyst. This reaction would allow for the synthesis of chiral indolines containing consecutive stereogenic centers at their 2- and 3-positions. Chiral indolines can be found in a wide variety of naturally occurring bioactive compounds and the synthesis of these compounds has consequently attracted considerable interest from researchers working in a number of different fields (Figure 1). The development of an enantioselective dearomatative borylation reaction for indoles would therefore provide an interesting and efficient approach to this class of enantioenriched heterocycles.

Supporting information for this article is given via a link at the end of the document.
The results of an extensive series of optimization experiments revealed that the reaction of carboxybenzyl (Cbz)-protected methyl indole-2-carboxylate (1a) with bis(pinacolato)diboron (2) (2.0 equiv) in the presence of Cu(O-t-Bu)/((R)-L)-L1 (10 mol %), Na(O-t-Bu) (10 mol %) and t-BuOH (2.0 equiv), which was used as a proton source, in THF at 30°C afforded the desired deamidation product (S,R)-3a in high yield (98%), with excellent diastereo- and enantioselectivities (d.r. 97:3, 93% ee) (Table 1, entry 1). Notably, no product was observed when the reaction was conducted in the absence of Cu(O-t-Bu) or ligand L1 (Table 1, entries 2 and 3). A lower yield (74%) of the deamidation product 3a was obtained when Na(O-t-Bu) was omitted from the reaction (Table 1, entry 4), although the omission of t-BuOH led to a significant decrease in the yield and stereoselectivity of the product (33%, d.r. 76:24, 74% ee) (Table 1, entry 5). The use of the less sterically hindered (R,R)-BDPP ligand L2 led to a lower enantioselectivity (74% ee) (Table 1, entry 6). Several other chiral bisphosphine ligands were also tested in the reaction, including (R,R)-QuinoxP*, L3, (R,R)-BenzP* L4 and (R,R)-Me-Duphos L5, but they all showed poor stereoselectivities (Table 1, entries 7–9).

No reaction was observed when the monophosphine-type chiral ligand (R)-MOP L6 was used in the reaction (Table 1, entry 10). A decrease in the loading of the catalyst to 5 mol % did not lead to an erosion in the enantioselectivity (93% ee), although slight decreases were observed in the product yield (76%) and diastereoselectivity (d.r. 92:8) (Table 1, entry 11). The bulkiness of the alcohol was only found to affect the diastereoselectivity of this reaction, because the use of MeOH provided moderate diastereoselectivity (d.r. 75:25, Table 1, entry 12).

Table 1. Copper(I)-catalyzed enantioselective C–B bond-forming deamidation of Indole 1a.54

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)</th>
<th>d.r.</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>standard conditions</td>
<td>98</td>
<td>97:3</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>no Cu(O-t-Bu)</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>no (R,R)-L1</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>no Na(O-t-Bu)</td>
<td>74</td>
<td>89:11</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>no t-BuOH</td>
<td>33</td>
<td>76:24</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-L2 instead of (R,R)-L1</td>
<td>98</td>
<td>89:11</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-L3 instead of (R,R)-L1</td>
<td>93</td>
<td>90:10</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>(R,R)-L4 instead of (R,R)-L1</td>
<td>77</td>
<td>91:9</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>(R,R)-L5 instead of (R,R)-L1</td>
<td>71</td>
<td>97:3</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>(R,R)-L6 instead of (R,R)-L1</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>5 mol % of Cu(O-t-Bu)/(R,R)-L1</td>
<td>76</td>
<td>92:8</td>
<td>93</td>
</tr>
</tbody>
</table>

With an optimized procedure in hand, we proceeded to investigate the scope of the reaction using a variety of indole substrates (Table 2). The introduction of an electron-withdrawing or electron-donating functional group at the 5-position of the indole was well tolerated, with the borylation reaction affording consistently excellent selectivities (3b–e). Indoles bearing a bromo, methoxy or phenyl substituent at their 6-position also reacted with high levels of stereoselectivity (3f–h). The borylation of an indole bearing an ethyl ester group (3i) proceeded with high enantioselectivity (95% ee), but with a lower product yield (52%). The borylation of an indole bearing a bulky isopropyl ester group (1j) failed to provide any of the desired product (S,R)-3j under the optimized conditions. Fortunately, the replacement of (R,R)-L1 with (R,R)-L2 allowed for the borylation of 1j to proceed in good yield (88% NMR) and excellent stereoselectivity (d.r. 95:5, 90% ee). We subsequently proceeded to investigate the scope of the protecting group on the indole. The borylation of tert-butyloxycarbonyl (Boc)-protected indole 1k provided the expected product (S,R)-3k with the highest enantioselectivity (98% ee) observed in the current study, although the yield was significantly decreased (22% NMR). The replacement of (R,R)-L1 with the less sterically hindered (R,R)-L2 led to a significant improvement in the yield (98% NMR) with good stereoselectivity (d.r. 93:7, 86% ee). Unfortunately, the application of the optimized conditions to a fluorenylmethyloxycarbonyl (Fmoc)-protected indole 1l failed to provide any of the desired product, presumably because of the reaction of the acidic proton of the Fmoc group with Na(O-t-Bu), which resulted in the formation of a complex mixture. We also found that Me-protected indoles were not applicable to this protocol.

Table 2. Substrate scope.54

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield</th>
<th>d.r.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>standard</td>
<td>98</td>
<td>97:3</td>
<td>93</td>
</tr>
<tr>
<td>2a</td>
<td>no Cu</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>no (R,R)</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4a</td>
<td>no Na</td>
<td>74</td>
<td>89:11</td>
<td>93</td>
</tr>
<tr>
<td>5a</td>
<td>no t-Bu</td>
<td>33</td>
<td>76:24</td>
<td>74</td>
</tr>
<tr>
<td>6a</td>
<td>(R,R)</td>
<td>98</td>
<td>89:11</td>
<td>74</td>
</tr>
<tr>
<td>7a</td>
<td>(R,R)</td>
<td>93</td>
<td>90:10</td>
<td>27</td>
</tr>
<tr>
<td>8a</td>
<td>(R,R)</td>
<td>77</td>
<td>91:9</td>
<td>61</td>
</tr>
<tr>
<td>9a</td>
<td>(R,R)</td>
<td>71</td>
<td>97:3</td>
<td>37</td>
</tr>
<tr>
<td>10a</td>
<td>(R,R)</td>
<td>&lt;5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11a</td>
<td>5 mol % Cu</td>
<td>76</td>
<td>92:8</td>
<td>93</td>
</tr>
</tbody>
</table>
COMMUNICATION

The chiral borylation product \((S, R)-3d\) generated in this study was subjected to an oxidation reaction, where it was treated with NaBO\(_3\) followed by a silyl protection reaction to give the desired chiral 1,2-aminoalcohol \((S, R)-4\) in a highly stereoselective manner (d.r. >99:1, 94% ee, Scheme 2). It is noteworthy that it would not be possible to synthesize this product using existing dearomative oxidation methods.\(^{[16]}\)

The enantioselective borylation of the 2-methyl indole that does not contain an ester group \((1o)\) resulted in no reaction (Scheme 3a).\(^{[17]}\) Preliminary density functional theory (DFT) calculation (B3PW91/cc-pVDZ) was used to explain the effect of substituents at the 2-position in the substrate (Scheme 3b).\(^{[18]}\) The results show that the LUMO level of \(1a\) (-1.51 eV) was considerably lower than the LUMO+1 level of \(1o\) (-0.68 eV), which is localized in the reactive site, indicating that the electron-withdrawing ester moiety would facilitate the addition of borylcopper(I) intermediate to the indoles.

A mechanism was proposed for the current copper(I)-catalyzed dearomative borylation of indoles (Figure 2a). Cu(O-t-Bu) \(A\) would initially react with diboron reagent \(2\) to form the borylcopper(I) \(B\). The coordination of indole \(1a\) to the copper center would result in the formation of \(\pi\)-complex \(C\). The subsequent 3,4-addition of \(B\) into \(1a\) would give the copper(I) enolate and then transform to the O-enolate with concomitant formation of a stereogenic C–B bond.\(^{[18]}\) After the formation of \(D\), the bulky t-BuOH additive would access \(D\) from the opposite side of the pinacolate boryl group to avoid steric congestion between the B(pin) and t-Bu groups. The subsequent diastereoselective protonation of \(D\) would proceed via a six-membered ring transition state \(E\) to provide the dearomatization product \((S, R)-3a\) and the Cu(O-t-Bu) precatalyst \(A\).

A preliminary DFT calculation (B3PW91/cc-pVDZ) was performed to elucidate the mechanism of the dearomatization step in this reaction (Figure 2b).\(^{[18]}\) The results showed that the activation energy for the addition of borylcopper(I) to indole II to furnish the copper(I) enolate IV was +18.0 kcal/mol, which was in agreement with the proposed pathway (Figure 2a).\(^{[18]}\)

\[\text{NMR yields are shown in parentheses.}\]

\[\text{Isolated yields.}\]

\[\text{[(R)-L1] was used instead of [(R)-L1].}\]

\[\text{Cu(O-t-Bu) would initially react with diboron reagent 2 to form the borylcopper(I) B.}\]

\[\text{The coordination of indole 1a to the copper center would result in the formation of \(\pi\)-complex C.}\]

\[\text{The subsequent 3,4-addition of B into 1a would give the copper(I) enolate and then transform to the O-enolate with concomitant formation of a stereogenic C–B bond.}\]

\[\text{After the formation of D, the bulky t-BuOH additive would access D from the opposite side of the pinacolate boryl group to avoid steric congestion between the B(pin) and t-Bu groups.}\]

\[\text{The subsequent diastereoselective protonation of D would proceed via a six-membered ring transition state E to provide the dearomatization product (S,R)-3a and the Cu(O-t-Bu) precatalyst A.}\]

\[\text{A preliminary DFT calculation (B3PW91/cc-pVDZ) was performed to elucidate the mechanism of the dearomatization step in this reaction (Figure 2b).}\]

\[\text{The results showed that the activation energy for the addition of borylcopper(I) to indole II to furnish the copper(I) enolate IV was +18.0 kcal/mol, which was in agreement with the proposed pathway (Figure 2a).}\]
compounds with potentially interesting biological activities. We envisaged that the results of this study will provide further opportunities for the development of novel stereoselective borylation reactions involving a wide variety of aromatic compounds, such as pyrroles, furans and polyaromatic hydrocarbons. Advances in this area would therefore allow for the efficient synthesis of complex saturated heterocyclic compounds with potentially interesting biological activities.

Acknowledgements

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Keywords: borylation • copper catalyst • enantioselective synthesis • dearomatization • indole

Figure 2. a) Proposed catalytic cycle. b) DFT calculation (B3PW91/cc-pVDZ) of the dearomative insertion step. Relative G value (kcal/mol) at 298 K, 1.0 atm gas phase. Electronic energies are shown in parentheses.

In summary, we have developed the first enantioselective C–B bond-forming dearomatization of heteroaromatic compound using a chiral bisphosphine-copper(Ⅰ) complex catalyst and a diboron reagent. This reaction involved the unprecedented enantioselective dearomative addition of borylcopper(Ⅰ) to methyl indole-2-carboxylate with concomitant formation of a stereogenic C–B bond, followed by the diastereoselective protonation of the copper(Ⅰ) enolate intermediate to deliver the enantioenriched hydrocarbons. Advances in this area would therefore allow for the efficient synthesis of complex saturated heterocyclic compounds with potentially interesting biological activities.


Diastereomeric ratio values of the products were determined by 1H NMR analysis of the crude reaction mixture. The minor diastereomer could be completely separated by silica gel column chromatography. The ee values were determined by HPLC analysis of the isolated products. The configuration of the borylation product was determined by NOE analysis of (S)-3a and X-ray crystallographic analysis of the oxide product (S·B)-3 derived from (S·B)-3c. The details have been provided in the Supporting Information.

The enantioselective borylative dearomatization of methyl indole-2-carboxylate using a copper(I) catalyst and a diboron reagent afforded chiral 3-borylindoline derivatives with excellent regio-, diastereo- and enantioselectivities. The products of this reaction could be transformed to the corresponding chiral 1,2-aminoalcohol with high stereospecificity.

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