Dearomatization

International Edition: DOI: 10.1002/anie.201502964
German Edition: DOI: 10.1002/ange.201502964

Enantioselective Borylative Dearomatization of Indoles through Copper(I) Catalysis**

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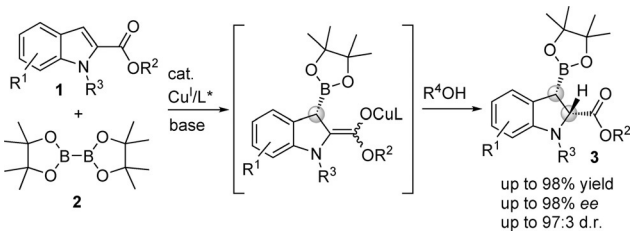
Abstract: *The enantioselective borylative dearomatization of a heteroaromatic compound has been achieved using a copper(I) catalyst and a diboron reagent. This reaction involves the regio- and enantioselective addition of active borylcopper(I) species to indole-2-carboxylates, followed by the diastereoselective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

Aromatic compounds are ubiquitous in nature and readily available as synthetic materials. Enantioselective dearomatization reactions of heteroaromatic compounds are very powerful transformations because they provide direct access to a wide variety of chiral saturated heterocycles, which are important components of pharmaceutical drugs and bioactive molecules.[1] The development of new methods for the formation of consecutive stereogenic centers through the stereoselective dearomatization of multisubstituted aromatic compounds would also have important practical implications for the synthesis of natural products.[2]

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.[3] 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 bonds.[4,5] Despite significant progress in this area, there have not been any 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.[1] 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.[6] and Weetman et al.[7] independently reported the results of their pioneering studies toward the development of a borylative dearomatization reaction, in which 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.[8] reported the development of a similar reaction using La^{III} as a catalyst. However, the authors of these studies were only able to demonstrate nonenantioselective N–B bond-forming dearomatization reactions.[9,10]

Herein, we report 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 enantioselective addition of an active borylcopper(I) species to an indole-2-carboxylate **1**, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding enantioenriched chiral indoline derivative **3** with excellent diastereo- and enantioselectivities. The stereospecific oxidation of the chiral 3-borylindoline product **3** has also been demonstrated.



Scheme 1. Copper(I)-catalyzed diastereo- and enantioselective C–B bond forming dearomatization of indoles.

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.[11] The results of the related research in this field showed that electron-deficient substrates with low LUMO levels tend to react efficiently with active borylcopper(I) species.[12] Based on these results, we 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 objective 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 the synthesis of chiral indolines containing consecutive stereogenic centers at their 2 and

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[**] This work was financially supported by the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University. This work was also supported by JSPS KAKENHI (grant numbers 15H03804 and 15K13633). K.K. thanks JSPS for scholarship support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201502964.

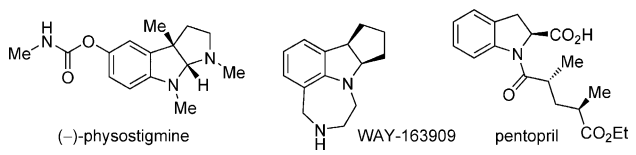


Figure 1. Chiral indoline-based bioactive molecules.

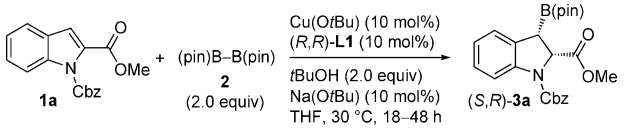
3 positions. Chiral indolines can be found in a wide variety of naturally occurring bioactive compounds and the synthesis of these compounds has consequently attracted considerable interest from researchers working in a number of different fields (Figure 1).[13,14] The development of an enantioselective dearomative borylation reaction for indoles would therefore provide an interesting and efficient approach to this class of enantioenriched heterocycles.

The results of an extensive series of optimization experiments showed that the reaction of Cbz-protected methyl indole-2-carboxylate (**1a**) with bis(pinacolato)diboron (**2**; 2.0 equiv) in the presence of Cu(O*t*Bu)/(*R*,*R*)-**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 dearomatization product (*S*,*R*)-**3a** in high yield (98%), with excellent diastereo- and enantioselectivities (d.r. 97:3, 93% *ee*; Table 1, entry 1).[15] 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 dearomatization 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 sterically less 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 resulted in 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 of the enantioselectivity (93% *ee*), but 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 led to moderate diastereoselectivity (d.r. 75:25, Table 1, entry 12).

With the optimized procedure in hand, we proceeded to investigate the scope of the reaction using a variety of indole substrates (Scheme 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 the borylation of **1j** to proceed in good yield (88%, determined by NMR analysis) 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 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 sterically less 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 Fmoc-protected indole group failed to provide 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.

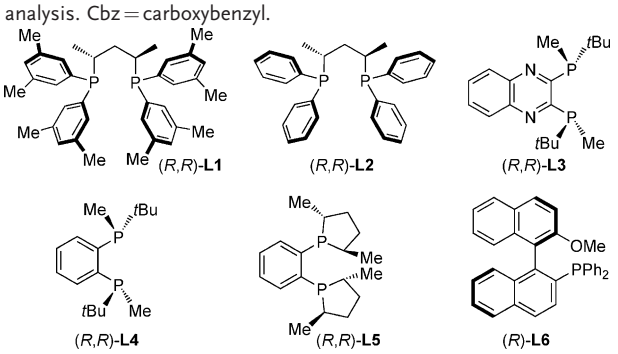
The chiral borylation product (*S*,*R*)-**3d** generated in this study was subjected to an oxidation reaction, in which it was

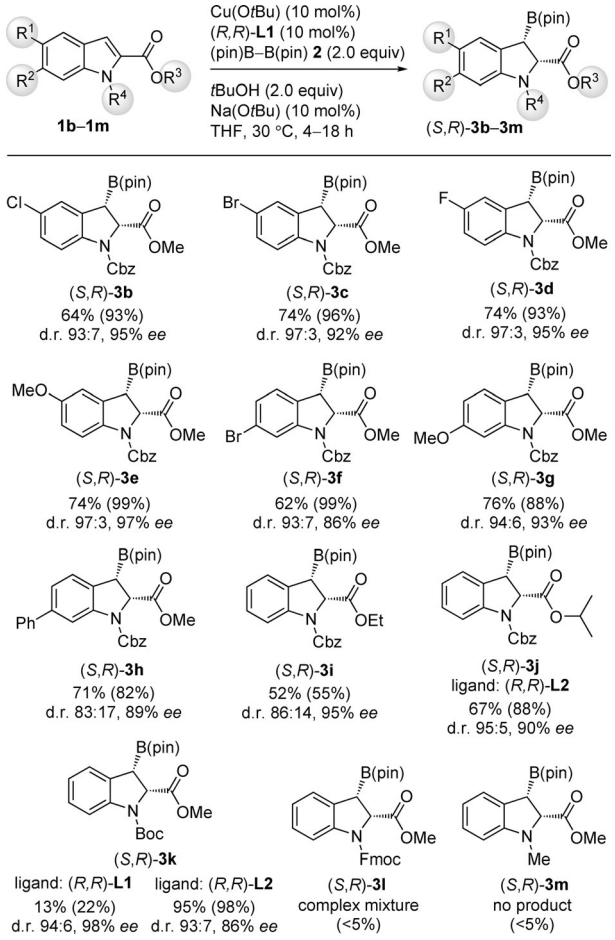
Table 1: Copper(I)-catalyzed enantioselective C–B bond-forming dearomatization of Indole **1a**.[a]



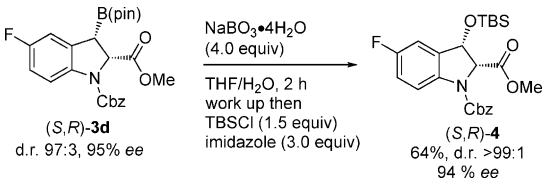
Entry	Conditions	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	standard conditions	98	97:3	93
2	no Cu(O*t*Bu)	<5	–	–
3	no (*R*,*R*)-**L1**	<5	–	–
4	no Na(O*t*Bu)	74	89:11	93
5	no *t*BuOH	33	76:24	74
6	(*R*,*R*)-**L2** instead of (*R*,*R*)-**L1**	98	89:11	74
7	(*R*,*R*)-**L3** instead of (*R*,*R*)-**L1**	93	90:10	27
8	(*R*,*R*)-**L4** instead of (*R*,*R*)-**L1**	77	91:9	61
9	(*R*,*R*)-**L5** instead of (*R*,*R*)-**L1**	71	97:3	37
10	(*R*)-**L6** instead of (*R*,*R*)-**L1**	<5	–	–
11	5 mol% of Cu(O*t*Bu)/(*R*,*R*)-**L1**	76	92:8	93
12	MeOH instead of *t*BuOH	94	75:25	94

[a] Reactions were performed with **1a** (0.5 mmol), Cu(O*t*Bu) (0.05 mmol), chiral ligand (0.05 mmol), bis(pinacolato)diboron **2** (1.0 mmol), Na(O*t*Bu) (0.05 mmol), and alcohol (1.0 mmol) in THF (1.0 mL), unless otherwise stated. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis. Cbz = carboxybenzyl.





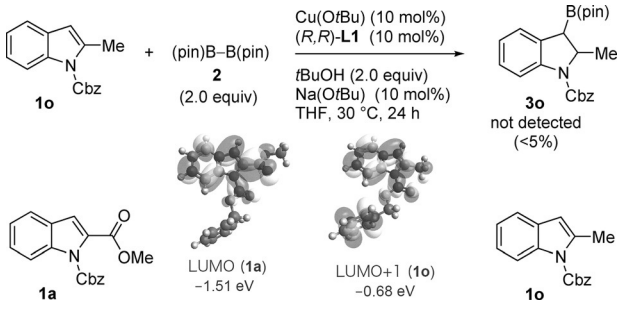
Scheme 2. Substrate scope. Reaction conditions: Cu(O*t*Bu) (0.05 mmol), (*R*,*R*)-**L1** (0.05 mmol), **1** (0.5 mmol), bis(pinacolato)diboron **2** (1.0 mmol), Na(O*t*Bu) (0.05 mmol), and *t*BuOH (1.0 mmol) in THF (1.0 mL). Yields of isolated products are reported. Yields determined by NMR analysis are shown in parentheses. Boc = *tert*-butyloxycarbonyl, Fmoc = fluorenylmethyloxycarbonyl.



Scheme 3. Stereospecific oxidation of chiral 3-borylindoline (*S*,*R*)-**3d**.

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 3). 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 4a).[17] A 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 4b).[18] The results show that the LUMO



Scheme 4. a) Borylative dearomatization of Cbz-protected 2-methyl indole **1o**. b) The reactive vacant orbital levels of **1a** and **1o** (B3PW91/cc-pVDZ).

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).

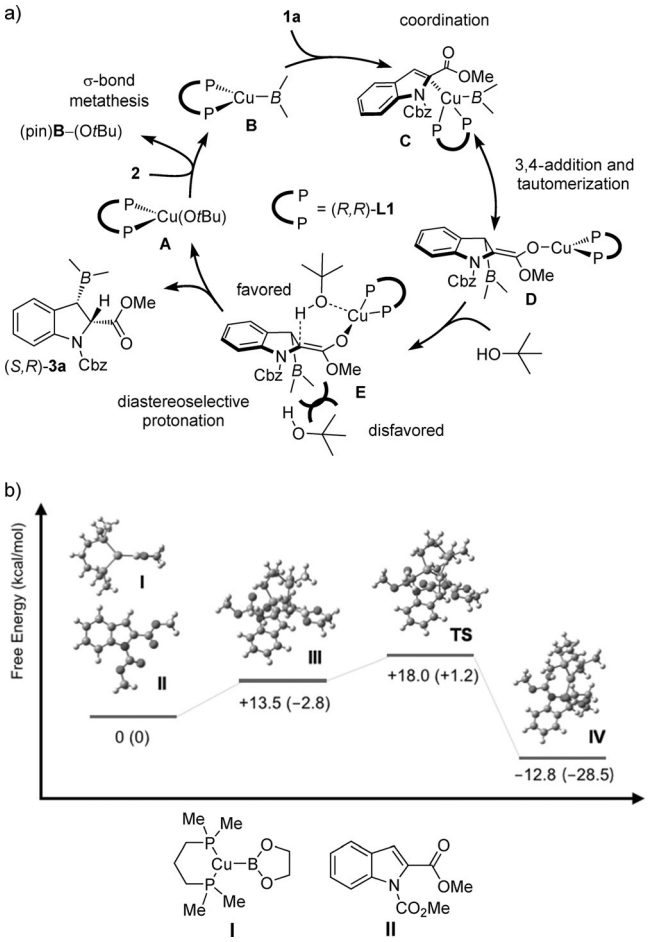


Figure 2. a) Proposed catalytic cycle. b) DFT calculation (B3PW91/cc-pVDZ) of the dearomative insertion step. Relative *G* value (kcal mol^{-1}) at 298 K, 1.0 atm gas phase. Electronic energies are shown in parentheses.

Cu(O*t*Bu) species **A** would initially react with diboron reagent **2** to form the borylcopper(I) species **B**. The coordination of indole **1a** to the copper center would result in the formation of π-complex **C**. The subsequent 3,4 addition of **B** into **1a** would give the copper(I) C enolate and then transform to the O enolate **D** 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) **I** to indole **II** to furnish the copper(I) C enolate **IV** was + 18.0 kcal mol^{-1}, which was in agreement with the proposed pathway (Figure 2a).[18]

In summary, we have developed the enantioselective C–B bond-forming dearomatization of heteroaromatic compounds using a chiral bisphosphine-copper(I) complex as catalyst and a diboron reagent. This reaction involved the 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 chiral indoline bearing consecutive stereogenic centers with excellent regio-, diastereo-, and enantioselectivities. We envisage that the results of this study will provide further opportunities for the development of novel stereoselective dearomative borylation reactions involving a wide variety of aromatic compounds, such as pyrroles, furans, and polyaromatic hydrocarbons. Advances in this area would therefore allow the efficient synthesis of complex saturated heterocyclic compounds with potentially interesting biological activities.

Keywords: borylation · copper · dearomatization · enantioselective synthesis · indoles

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8809–8813
Angew. Chem. **2015**, *127*, 8933–8937

[1] For a review of catalytic enantioselective dearomative transformations, see: a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686; *Angew. Chem.* **2012**, *124*, 12834–12858; b) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807–4815; c) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558–2573.

[2] For a review about the application of dearomatization strategies to the synthesis of natural products, see: a) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093; *Angew. Chem.* **2011**, *123*, 4154–4179.

[3] a) D. G. Hall, *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*, 2nd revised ed., Wiley-VCH, Weinheim, **2011**; b) S. N. Mlynarski, C. H. Schuster, J. P. Morken, *Nature* **2014**, *505*, 386–390; c) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188.

[4] For selected examples of the rhodium(I)-catalyzed enantioselective hydroboration reactions, see: a) T. Hayashi, Y. Matsumoto, Y. Ito, *J. Am. Chem. Soc.* **1989**, *111*, 3426–3428; b) C. M. Crudden, Y. Hleba, A. Chen, *J. Am. Chem. Soc.* **2004**, *126*, 9200–9201.

[5] For selected examples of the copper(I)-catalyzed enantioselective protoboration reaction, see: a) V. Lillo, A. Prieto, A. Bonet, M. M. Diaz-Requejo, J. Ramirez, P. J. Pérez, E. Fernández, *Organometallics* **2009**, *28*, 659–662; b) Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161; c) D. Noh, H. Chea, J. Ju, J. Yun, *Angew. Chem. Int. Ed.* **2009**, *48*, 6062–6064; *Angew. Chem.* **2009**, *121*, 6178–6180; d) J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894–899; e) Z. T. He, Y. S. Zhao, P. Tian, C. C. Wang, H. Q. Dong, G. Q. Lin, *Org. Lett.* **2014**, *16*, 1426–1429; f) A. Parra, L. Amenós, M. Guisán-Ceinos, A. López, J. L. G. Ruano, M. Tortosa, *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836; g) H. Lee, B. Y. Lee, J. Yun, *Org. Lett.* **2015**, *17*, 764–766.

[6] K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 3699–3702.

[7] M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Kohn, C. Weetman, *Organometallics* **2011**, *30*, 5556–5559.

[8] A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro, T. J. Marks, *Nat. Chem.* **2014**, *6*, 1100–1107.

[9] For a report about the palladium-catalyzed nonenantioselective silaborylative dearomatization of pyridines, see: K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2011**, *133*, 7324–7327.

[10] For a report about an organocatalytic N–B bond-forming dearomatization, see: T. Ohmura, Y. Morimasa, M. Suginome, *J. Am. Chem. Soc.* **2015**, *137*, 2852–2855.

[11] For selected examples of copper(I)-catalyzed enantioselective borylation reactions from our group, see: a) H. Ito, S. Ito, Y. Sasaki, K. Matsuura, M. Sawamura, *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857; b) Y. Sasaki, C. Zhong, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227; c) H. Ito, S. Kunii, M. Sawamura, *Nat. Chem.* **2010**, *2*, 972–976; d) K. Kubota, E. Yamamoto, H. Ito, *Adv. Synth. Catal.* **2013**, *355*, 3527–3531; e) E. Yamamoto, Y. Takenouchi, T. Ozaki, T. Miya, H. Ito, *J. Am. Chem. Soc.* **2014**, *136*, 16515–16521.

[12] For experimental and theoretical studies on the copper(I)-catalyzed borylation of activated alkenes, see: a) D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, *25*, 2405–2408; b) L. Dang, H. Zhao, Z. Lin, T. B. Marder, *Organometallics* **2007**, *26*, 2824–2832; c) L. Dang, Z. Lin, T. B. Marder, *Organometallics* **2008**, *27*, 4443–4454.

[13] a) S. Kobayashi, G. Peng, T. Fukuyama, *Tetrahedron Lett.* **1999**, *40*, 1519–1522; b) J. L. Pinder, S. M. Weinreb, *Tetrahedron Lett.* **2003**, *44*, 4141–4143; c) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151–161; d) Y. Sasaki, D. Kato, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 13533–13544.

[14] For a review and selected examples of the synthesis of the indoline scaffold, see: a) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702–711; b) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615.

[15] The diastereomeric ratios of the products were determined by ^{1}H NMR analysis of the crude reaction mixture. The minor diastereomer could be completely separated by column chromatography on silica gel. 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*,*R*)-**3a** and X-ray crystallographic analysis of the oxidation product (*S*,*R*)-**5** derived from (*S*,*R*)-**3c**. The details have been provided in the Supporting Information.

[16] F. Kolundzic, M. N. Noshi, M. Tjandra, M. Movassaghi, S. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 9104–9111.

[17] 2-Methyl indole was selected as a substrate to avoid deprotonation at the 2 position by Na(O*t*Bu). We also confirmed that the

borylation of nonsubstituted Cbz-protected indole resulted in no reaction.

[18] Although the current substrate is aromatic indole-2-carboxylate, we found that the C2=C3 bond contributes more than that of carbonyl moiety to the LUMO orbitals, indicating that the boryl cupration of the indoles proceeds through a 3,4-addition pathway in a similar manner to the borylation of α,β-unsaturated carbonyl compounds (Ref. [12]). The details have been provided in the Supporting Information.

Received: April 1, 2015
Published online: June 11, 2015

