Homogeneous Catalysis **Hot Paper**

How to cite:
International Edition: doi.org/10.1002/anie.202103108
German Edition: doi.org/10.1002/ange.202103108

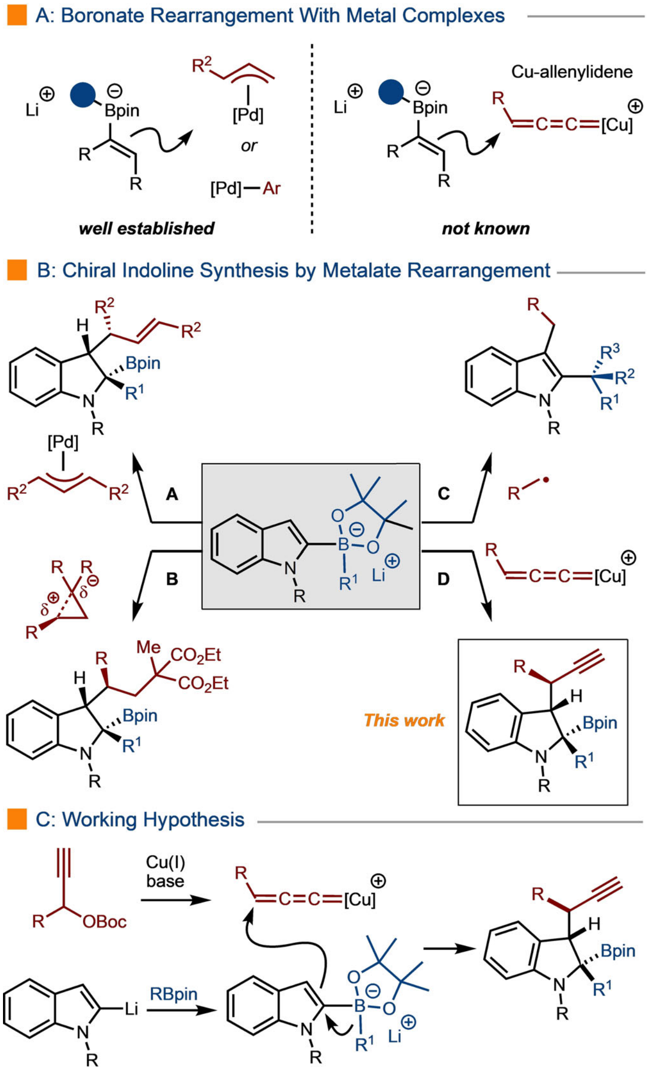
Allenylidene Induced 1,2-Metalate Rearrangement of Indole-Boronates: Diastereoselective Access to Highly Substituted Indolines

*Amit Kumar Simlandy and M. Kevin Brown**

Abstract: *A process to achieve 1,2-metalate rearrangements of indole boronate as a way to access substituted indolines in high diastereoselectivities is presented. The reaction involves the generation of a Cu–allenylidene, which is sufficiently electrophilic to induce the 1,2-metalate rearrangement. The scope of the reaction is evaluated as well as further transformations of the product.*

The 1,2-metalate rearrangements of boronates (e.g., Matteson- or Zweifel-type reactions) have been established as a versatile method for chemical synthesis.[1] Recent studies in this area have led to the introduction of processes that are induced by organometallic complexes (Scheme 1 A).[2] In particular, the Morken,[3,4] Ishikura,[5] and Ready[6] groups have demonstrated that alkenylboronates can be captured by electrophilic Pd-complexes. These methods have greatly expanded the scope of electrophiles that can capture boronates. To expand chemical space and with our interest in Cu-catalyzed transformation we questioned if electrophilic Cu-complexes, in particular a Cu–allenylidene, could induce the rearrangement.

Of the many boronates that can be used in 1,2-metalate rearrangements, indole derivatives are of interest because of the potential to prepare chiral indoline motifs (Scheme 1 B). Chiral indoles and indolines are abundant in natural products and pharmaceutically active molecules.[7] Studies by Ishikura showed that 2-lithioindoles can be coupled with trialkylboranes and allylic acetates in the presence of a palladium catalyst, where a Pd-allyl complex triggers the 1,2-metalate rearrangement to furnish substituted indoles (Scheme 1 B, reaction A).[4] Recently, the Ready group developed the enantioselective variant of this reaction that also allowed for the use of pinacol boronates (Scheme 1 B, reaction A).[6] The Studer group developed a transformation where 1,2-metalate shift from an indole boronate can be achieved by ring opening of an activated donor-acceptor cyclopropane with $Sc(OTf)_3$ followed by trapping with alkyl halides (Scheme 1 B, reaction B).[8] Elegant studies from Aggarwal and co-workers have demonstrated that an alkyl radical can induce an enantiospecific migration event thus allowing straightforward access to substituted indoles (Scheme 1 B, reaction C).[9]



Scheme 1. 1,2-Metalate rearrangements of indole boronates.

On the basis of these studies, we envisioned that electrophilic Cu–allenylidene complexes (generated from propargyl alcohol derivatives and Cu-complexes)[10,11] could prompt the 1,2-metalate rearrangement (Scheme 1 C). If successful, the reaction would allow for the synthesis of chiral indoline products with up to three contiguous stereogenic centers in addition to versatile Bpin and alkyne motifs. To the best of our knowledge, this is the first report of Cu–allenylidene induced 1,2-metalate rearrangements.

Initial efforts led to the result illustrated in Equation (1). Addition of *t*BuLi to N-Me-indole (**1**) led to formation of the known 2-lithioindole. Trapping of this intermediate with

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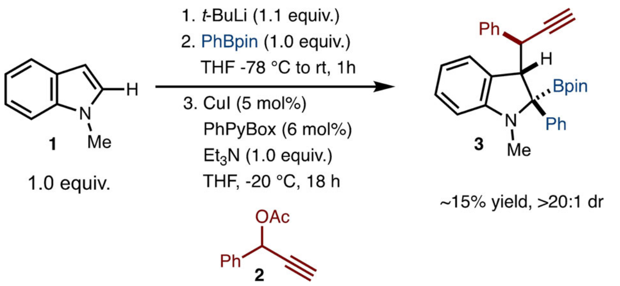
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202103108.

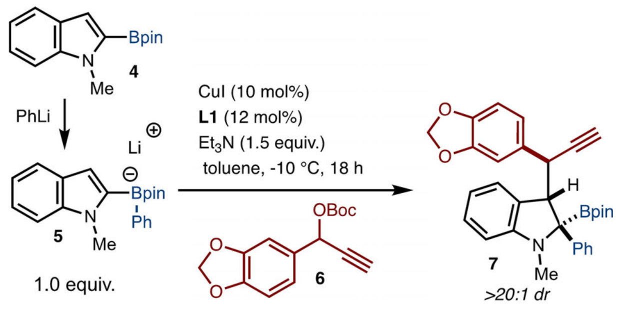
PhBpin followed by addition of Cu–PhPyBox, propargyl acetate **2** and Et_3N led to generation of **3** in ≈15% yield and >20:1 *dr* (55:45 *er*) [Eq. (1)].



(1)

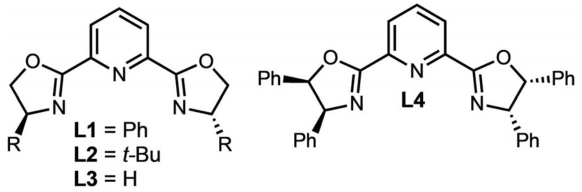
Based on the early results, optimization of the reaction was carried out. Initially the reaction setup was altered such that 2-Bpin-indole (**4**) in combination with PhLi was used (as opposed to lithiation of N-Me-indole (**1**) and treatment with PhBpin), which was operationally simpler. In addition, preliminary studies revealed that use of the OBoc (**6**) vs. OAc (**2**) propargyl electrophile was superior (Table 1, entry 1). Under the adjusted reaction setup, evaluation of solvents let to the finding that toluene was better than THF and led to formation of the product in quantitative NMR yield and >20:1 *dr* (Table 1, entry 2). Other chiral ligands were evaluated and generally worked well, with **L1** and **L2** being optimal (Table 1, entries 2 and 4). Achiral ligand **L3** was not beneficial compared to others. Despite the fact that the reaction was poorly enantioselective, chiral ligand **L2** was chosen for ease of reaction setup (**L2**–CuI is most soluble in toluene). Interestingly, CuI is a competent catalyst in the absence of PyBox ligand (Table 1, entry 7). Since CuI alone is a competent catalyst, this may be, in part, the source of the uniformly low levels of enantioselectivity observed. Other bases such as NaO*t*Bu and Cs_2CO_3 were not compatible in the reaction conditions. However, presence of base is crucial for product formation (Table 1, entry 11). Finally, other reaction parameters were tested, and it was found that the combination of CuI and Et_3N was ideal (Table 1, entry 4).

Table 1: Optimization.



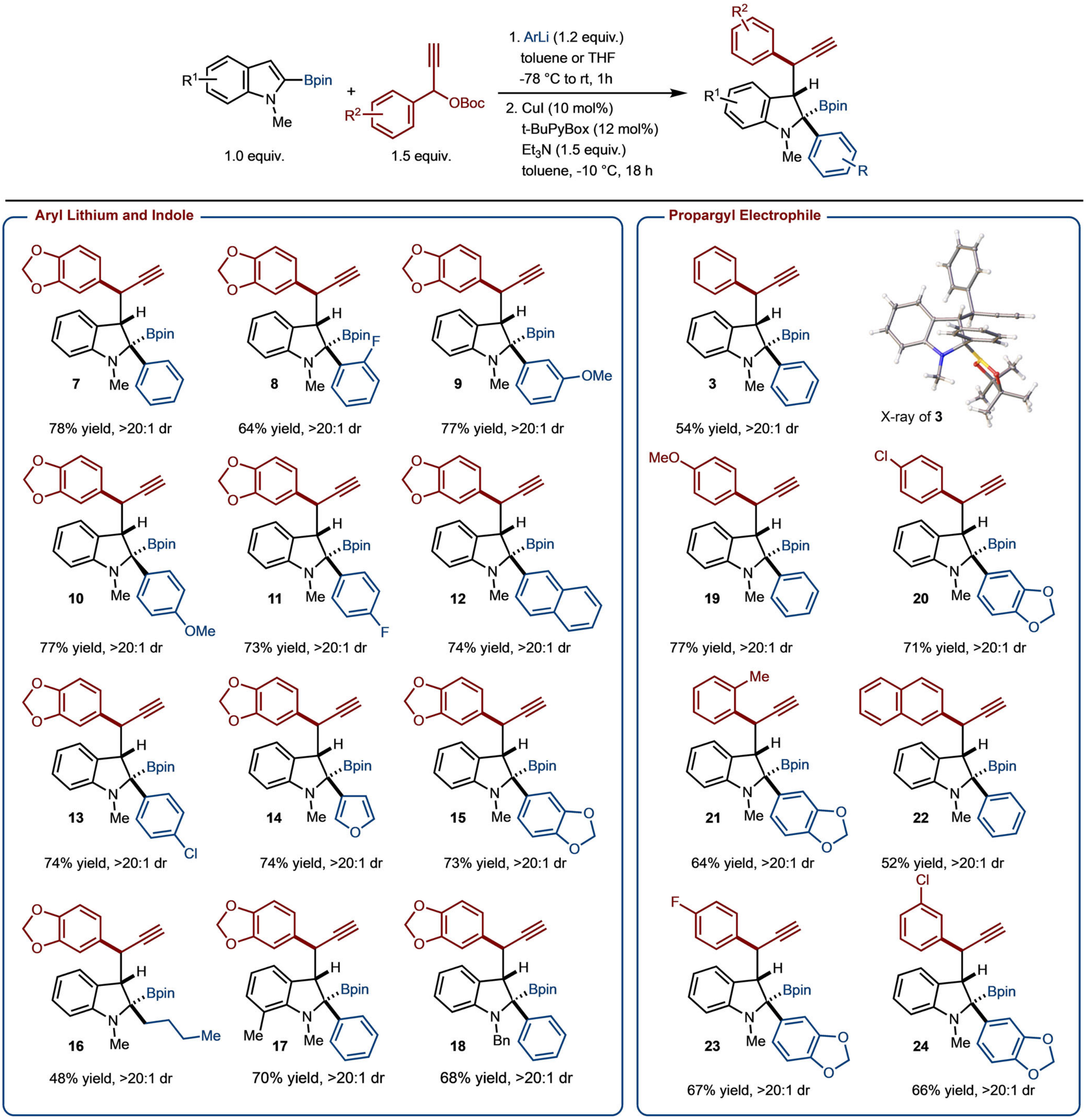
Entry	Change of Conditions	Yield [%][a]
1	THF as solvent	30
2	Toluene as solvent	99
3	$PhCF_3$ as solvent	78
4	**L2** as ligand	99 (78)[b]
5	**L3** as ligand	70
6	**L4** as ligand	97
7	No ligand, only CuI	78
8	NaO*t*Bu as base	<5
9	Cs_2CO_3 as base	25
10	No CuI	<5
11	No Base	<10

[a] Yield and *dr* determined by ^1H NMR analysis of the crude reaction mixture using an internal standard. [b] Isolated yield.



With an optimized set of conditions in hand, the scope of the process was evaluated. With respect to the aryl lithium component, both electron-withdrawing (products **8**, **11**, **13**) and electron-donating groups (products **9**, **10**, **15**) were tolerated. While sterically demanding substituents such as *o*-Br did not react, *o*-F did allow for product formation (product **8**). In general, halogen substituents (product **13**) were well tolerated in the reaction. It should also be noted that a furan ring did not compete for the electrophilic Cu–allenylidene species and product **14** was formed in high yield and *dr*. Simple naphthyl (product **12**) and highly electron-rich piperonyl (product **15**) groups migrated efficiently to deliver the products in high yield. Reaction with *n*BuLi also allowed for formation of **16**, albeit in moderate yield due to instability of the product upon purification. Surprisingly, alkenyl migrating groups remained unproductive under the reaction conditions (see the Supporting Information). The group on indole is not limited to only methyl, as simple benzyl protected indole furnished the product **18** in high yield. Finally, substitution of the indole unit at C6 with a Me-group (product **17**) was tolerated. In the case of the propargyl electrophile, both electron-withdrawing (product **20**) and electron-donating (product **19**) groups worked well, although the latter was superior. Sterically demanding *o*-Me (product **21**) was also tolerated to generate the product in good yield, but aliphatic substituents on the propargyl *Boc*-carbonate did not allow for product formation (see the Supporting Information). In all cases products were obtained as a single observable diastereomer (>20:1 *dr*). The relative stereochemistry of the chiral indoline **3** was determined by single crystal X-ray analysis.

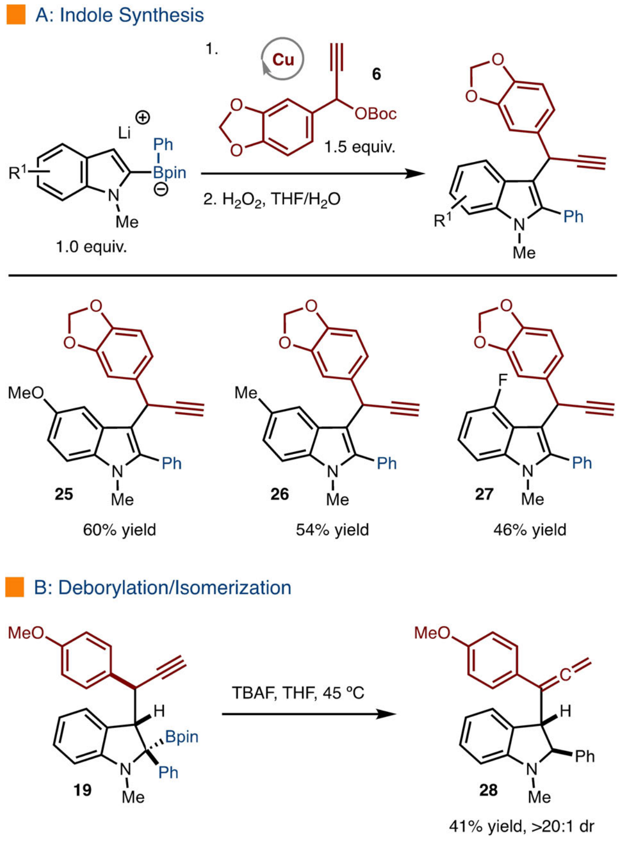
While the reaction to generate the indoline demonstrated in Scheme 2 is significant, preparation of highly substituted indoles is also of high value. As such, after reaction workup, oxidation of the Bpin resulted in formation of disubstituted indoles (Scheme 3A). The scope of this reaction was demonstrated with select substituted indoles (products **25**–**27**). This process is noteworthy as 2,3-disubstituted indoles are easily prepared from simple components in two steps. Finally, treatment of **19** with TBAF also induced a deborylation and double bond isomerization to furnish allene **28** as a single diastereomer (Scheme 3B). Our attempts to prevent the alkyne isomerization by changing temperature or using TBAF·3 H_2O were unsucessful. Base-mediated isomerization of alkynes to allenes is well precedented in literature.[12] The



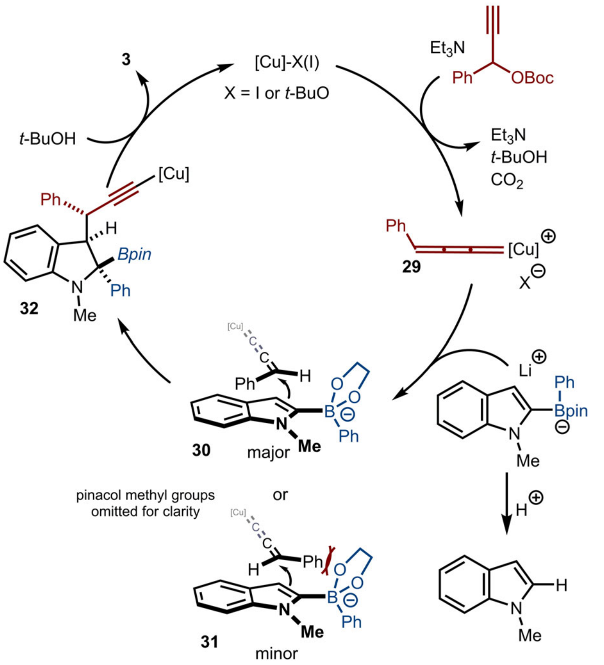
Scheme 2. Cu-catalyzed 1,2-metalate rearrangement. Reactions run on 0.2 mmol scale. Yield is the average of two runs and is of isolated product after alumina column chromatography.[14]

moderate yield is due to the facile elimination of the propargyl unit during deborylation to form 2-phenylindole.

A catalytic cycle for the reaction is illustrated in Scheme 4 and is based on prior work.[10] With the aid of base, the Cu^I-complex undergoes reaction with the propargyl electrophile to generate the Cu–allenylidene.[10,11,13] This highly electrophilic complex then undergoes reaction with the indole boronate to induce 1,2-metalate shift and generate **32**. Turnover of the catalyst is achieved by proton transfer (possibly with *t*BuOH). The rate of reaction between Cu–allenylidene and the indole boronate complex should be sufficiently fast to avoid undesired protonation that forms N–Me indole and PhBpin. This was obsered when 4-$CF_3C_6H_4$ and cyclohexyl-substituted propargyl Boc-carbonate were employed in the reaction. Based on the reaction outcome, models that rationalize the diastereoselectivity are illustrated (**30** and **31**). It is proposed that the Cu–allenylidene approaches such that the Ph-group is positioned over the indole aromatic ring (potential π-π interaction) (**30**) and to avoid steric pressure with the boronate unit (**31**). Finally, the



Scheme 3. Further transformations of product.



Scheme 4. Proposed catalytic cycle.

Cu–allenylidene is positioned opposite to the migrating Ph-group for an *anti*-addition.

In summary, a method for the synthesis of 2,3-disubstuted indolines by a Cu-catalyzed propargylation of 2-indole boronate derivatives was developed. The outlined approach offers a new electrophile class that is capable of inducing 1,2-metalate rearrangement and will have further implications in other classes of rearrangements.

Acknowledgements

We thank Indiana University and the NSF (CAREER award CHE1554760). This project was partially funded by the Vice Provost for Research through the Research Equipment Fund and the NSF MRI program, CHE-1726633 and CHE-1920026. Support for the acquisition of the Bruker Venture D8 diffractometer through the Major Scientific Research Equipment Fund from the President of Indiana University and the Office of the Vice President for Research is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,2-metalate rearrangement · boron · copper · indoles · indolines

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[14] Deposition Number 2060610 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: March 2, 2021
Accepted manuscript online: March 18, 2021
Version of record online: ■■ ■■, ■■■■

Communications

Homogeneous Catalysis

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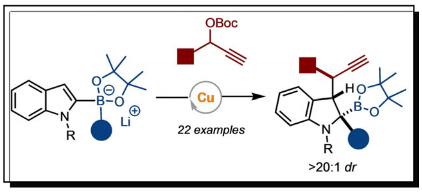
Allenylidene Induced 1,2-Metalate Rearrangement of Indole-Boronates: Diastereoselective Access to Highly Substituted Indolines



A new class of electrophile, Cu–allenylidene has been introduced to induce 1,2-metalate rearrangement. Merger of Cu-catalyzed propargylation and 1,2-boronate shift has allowed access to densely functionalized chiral indolines with up to three contiguous stereogenic centres in highly diastereoselective fashion (>20:1 *dr*). Utility of Bpin and alkyne moieties has been demonstrated by subsequent synthetic elaborations.