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trans-Aminoboration across Internal Alkynes Catalyzed by $B(C_6F_5)_3$ for the Synthesis of Borylated Indoles

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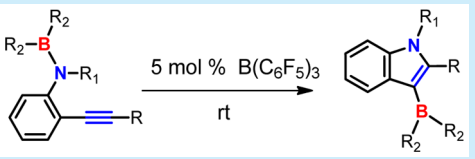
Supporting Information

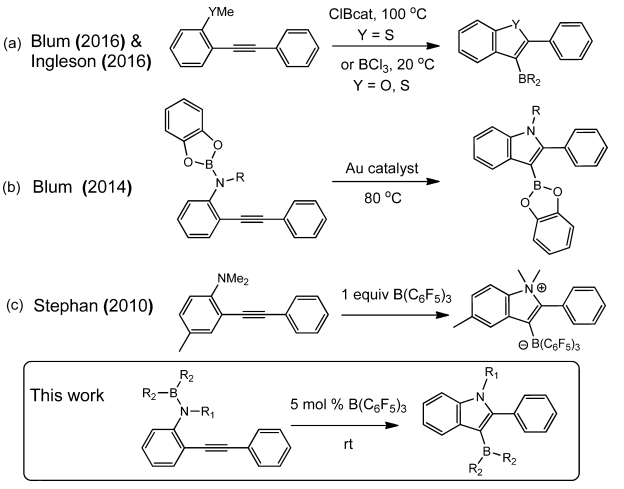
ABSTRACT: We report here a facile $B(C_6F_5)_3$ catalyzed *trans*-aminoboration of internal alkynes, furnishing 3-position borylated indoles at ambient temperature. This reaction proceeds with the breaking of a B−N bond and the formation of N−C and B−C bonds to produce indole and derivatives in one step. It works well for various boron reagents and alkynyl-anilines. The borylated indoles can be further derivatized to give column stable organoboron compounds that can be used for future functionalization.



Indole and its derivatives have important applications in biological systems and materials science.[1] Borylated indoles are of particular interest, as they are versatile building blocks for the construction of functional molecules.[2] Currently, iridium catalyzed borylation represents one of the most powerful methods in obtaining boron derivatized indoles.[3] In addition, electrophilic borylation with borenium species has been demonstrated as an alternative method to introduce boronic acid/boronate ester groups on heterocycles, including indole.[4] Nonetheless, both methods require the preformation of the heterocyclic substrate.

Recently, Lewis acidic boron reagents such as boron trichloride or *B*-chlorocatecholborane (ClBcat) have been shown to be effective in promoting borylative cyclization of alkynes to give borylated species, including borylated heterocyclics (Scheme 1a).[5−7] ClBcat has been successfully applied to the generation of lactones, and thiophenes at high temperature,[6] while borylation with BCl_3 can proceed readily at room temperature to yield borylated benzofurans or benzothiophenes.[7] However, when the same strategy was applied to a dimethylaniline derivative to generate indole with boron trichloride, only a haloboration product was obtained.[7] One known example of borylative cyclization toward indole formation requires the use of gold catalysts for the addition of a B−N σ bond across the C−C triple bond (Scheme 1b).[8] In addition to the catalyst, high temperature (80 °C) is also required for the previously reported borylative cyclization toward indole. Frustrated Lewis pairs (FLPs) have been demonstrated recently to be highly effective in activating small molecules and catalysis.[9] For example, intramolecular FLPs have been successfully used as highly effective catalysts for C−H bond activation and borylation of heteroarenes.[10] The combination of borane and phosphine has also been shown to be effective in activating alkynes intramolecularly or intermolecularly.[11] Similar alkyne activation was also achieved with N, O, or S Lewis bases to form heterocyclic compounds.[12] Borylative cyclization of *o*-(phenylethynyl)-*N*,*N*-dimethyl toluidine with stoichiometric $B(C_6F_5)_3$ was reported previously, which led to the formation of a cyclized zwitterionic product (Scheme 1c),[13] which is not known for use in cross-coupling reactions for further functionalization.

Scheme 1. Borylative Cyclization towards Heterocycles



We report herein a *trans*-aminoboration of internal alkynes catalyzed by a catalytic amount of $B(C_6F_5)_3$ under mild conditions, affording borylated indoles via a straightforward borylative cyclization.

The *trans*-aminoboration reaction was discovered initially from our investigation on whether an internal arylamine unit can facilitate *trans*-hydroboration in a similar manner as pyridine.[14] Instead of hydroboration, the reaction mixture of

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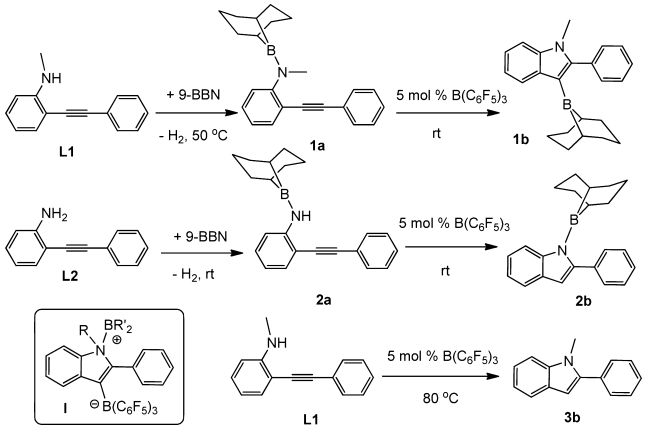
alkynyl arylamine and 9-borabicyclo[3.3.1]nonane (9-BBN) produced the dehydrogenation product **a** readily (Scheme 2).[15]

Scheme 2. Dehydrogenation and $B(C_6F_5)_3$ Catalyzed Aminoboration/Hydroamination of Internal Alkynes



We then considered the possibility of obtaining zwitterionic species **I** similar to that reported by Stephan (Scheme 1c) by reacting **a** with 1 equiv of $B(C_6F_5)_3$. Surprisingly, this attempt led to the isolation of borylated indoles **b**. Most interesting is the observation that the borylated indoles can be obtained in the presence of 5 mol % of $B(C_6F_5)_3$. Since metal-free borylative cyclization of internal alkynes for the synthesis of borylated indoles has not been reported previously, we decided to study this interesting reaction further to establish the scope and to understand the mechanism of this $B(C_6F_5)_3$ promoted borylative cyclization. The results of our investigation are presented here.

First, the reaction of *N*-methyl-2-(phenylethynyl)aniline **L1** with 9-BBN and $B(C_6F_5)_3$ was examined and monitored by NMR spectroscopy. The mixing of **L1** and 9-BBN at 50 °C for 2 days afforded a dehydrogenation product **1a** quantitatively as confirmed by ^1H and ^{11}B NMR spectral data (see Supporting Information (SI)). The characteristic ^{11}B NMR chemical shift (49 ppm) of **1a** indicates a partial double bond character of the B−N bond.[15] **1a** is not stable under ambient conditions and was used for the subsequent reaction without being isolated. Addition of 5 mol % $B(C_6F_5)_3$ into the solution of **1a** in C_6D_6 at ambient temperature immediately leads to the appearance of a sharp ^{11}B peak at −16 ppm, which is similar to that reported for the zwitterionic species by Stephan [Scheme 1c],[13] an indication that the borate compound **I** is likely produced via cyclization (Figure 1). As the reaction proceeds further, a new ^{11}B peak at 77 ppm appears while the peak at 49 ppm decreases in intensity. At the end of the reaction (~5 h), the peak at 49 ppm in the ^{11}B NMR spectrum completely vanishes and is replaced by the peak at 77 ppm while the sharp peak at −16 ppm remains. The combination of ^1H and ^{11}B NMR spectral analysis confirms that the species with a ^{11}B chemical shift at 77 ppm is the 9-BBN borylated 2-phenyl-indole (**1b**), which is formed nearly quantitatively. Considering the relatively strong bond strength of the B−N bond, it is quite remarkable that the borylated cyclization reaction is completed within a few hours at ambient temperature. Unfortunately, due to the high sensitivity of **1b** toward moisture, it cannot be purified by the general purification procedures. Attempts to purify **1b** using a silica column leads to the quantitative isolation of the

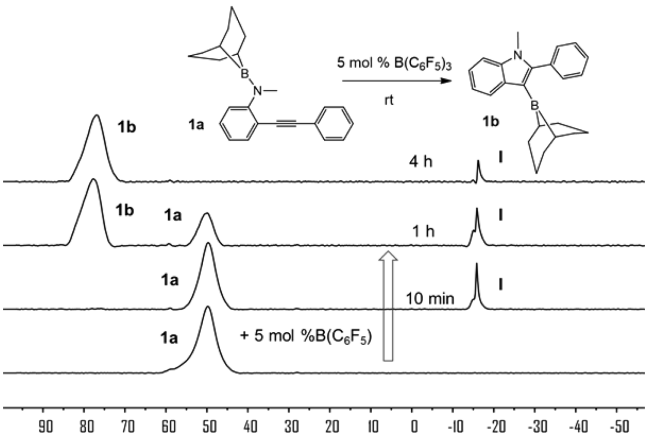


Figure 1. Stacked ^{11}B NMR spectra showing the transformation of **1a** to **1b** in C_6D_6 upon the addition of $B(C_6F_5)_3$ at ambient temperature.

deboronated indole product **3b**, which provides indirect support for the formation of the borylated indole in the reaction. In the absence of $B(C_6F_5)_3$, no cyclization or borylative cyclization is observed for **1a**, which supports the important role of $B(C_6F_5)_3$ in the formation of **1b**.

Next, the reaction of 2-(phenylethynyl)aniline **L2** with 9-BBN and $B(C_6F_5)_3$ was examined. The dehydrogenation occurs at room temperature and was completed within 24 h to give compound **2a** quantitatively, based on ^1H NMR data (see Figure S9). In contrast to **1a**, the addition of a catalytic amount of $B(C_6F_5)_3$ to the solution of **2a** leads to hydroamination and the formation of **2b** exclusively in 95% yield at ambient temperature. Compound **2b** has a ^{11}B peak at 53 ppm, similar to a previously reported chemical shift of ^{11}B with 9-BBN directly bound to the nitrogen in indole.[4b] The exclusive formation of **2b** indicates that the proton transfer is much more favorable than the borinium transfer. We also investigated the reactivity of **L1** in the presence of 5 mol % of $B(C_6F_5)_3$. In contrast to 9-BBN, NMR data indicate that $B(C_6F_5)_3$ forms a simple Lewis acid−base adduct first with **L1**, which is stable at room temperature (see SI, Figures S4 and S5). Heating the mixture of **L1** and its adduct with $B(C_6F_5)_3$ at 80 °C results in the dissociation of the Lewis acid−base adduct and affords 2-phenyl-indole quantitatively, which is mechanistically related to intermolecular hydroamination of terminal alkynes involving arylamines and a catalytic amount of $B(C_6F_5)_3$ reported previously by Stephan and co-workers.[16,17]

These results show consistently that $B(C_6F_5)_3$ can effectively promote *trans*-aminoboration across internal alkynes to afford a borylated indole in the case of secondary amines such as **L1**. However, the sensitivity of 3-position borylated indole **1b** toward moisture makes it difficult in handling and storing the borylated product for further use, even though examples of utilizing 9-BBN derivatized compounds for Suzuki−Miyaura cross-coupling reactions under anhydrous conditions are known in the literature.[18] Thus, we sought to extend the scope of the reaction with an alternative boron reagent such as catecholborane with the aim to achieve stable borylated indoles.

We first attempted to prepare the precursors such as **4a-Bcat**, an analogue of **1a** through dehydrogenation of anilines and catecholborane (HBcat) in a similar manner as the 9-BBN reaction. However, the dehydrogenation of the HBcat reaction requires elevated temperatures, and under this condition not only dehydrogenation occurs but also degradation of

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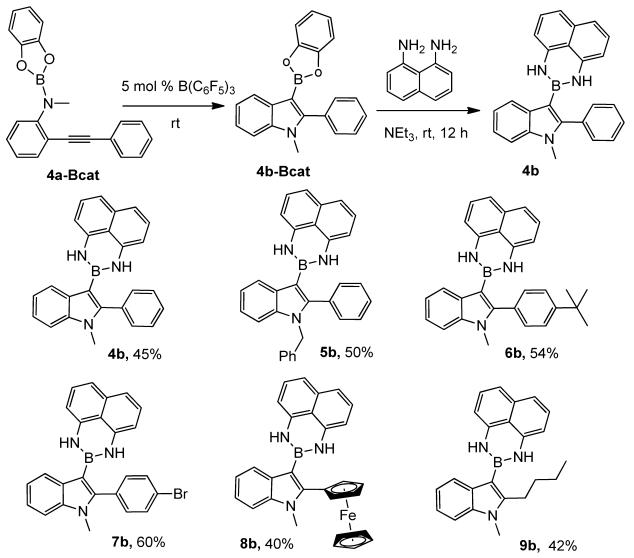
catecholborane arises simultaneously. Thus, we prepared the precursors **4a-Bcat** and related compounds by aminolysis of ClBcat.[8] The resulting aminoboronic esters have a characteristic ^{11}B NMR chemical shift at ∼29 ppm, similar to that reported previously.[8] Upon addition of a catalytic amount of $B(C_6F_5)_3$ into the amino-Bcat compounds, the ^{11}B NMR spectrum displays a similar change as the amino-9-BBN compounds. A borate peak at ∼ −15 ppm appears immediately, and a new ^{11}B peak at ∼32 ppm also appears as the reaction proceeds, which is similar to that observed by Blum and co-workers (Scheme 1b)[8] and assigned to the borylated indole product (e.g., **4b-Bcat** in Scheme 3). NMR data indicated that the Bcat borylated

Scheme 3. Scope of *trans*-Aminoboration Reaction

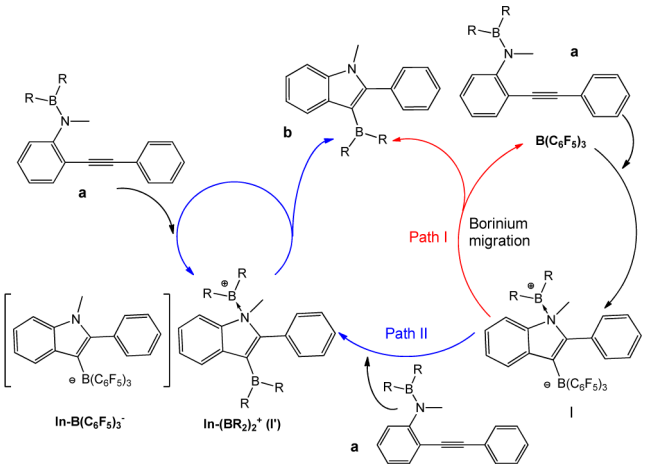


indoles are formed in greater than 90% yield (see Figure S6, for example), and the reaction is completed within 5 h at room temperature.

The Bcat borylated indoles are also highly prone to protodeboronation due to the electron-rich environment, making their isolation and purification difficult. One common strategy to overcome this problem is to convert the Bcat group to more stable boronic esters such as pinacolboronates by transesterification. Another commonly used protecting group for boronic acid is 1,8-diaminonaphthalene (dan), and the resulting B(dan) unit can be used in iterative cross-coupling reactions.[18] We therefore used 1,8-diaminonaphthalene to protect the boron unit in the borylated indoles. The Bcat to B(dan) conversion reaction (e.g., **4b-Bcat** to **4b** in Scheme 3) occurs smoothly at ambient temperature in the presence of triethylamine. The resulting B(dan) borylated indoles have sufficient stability for purification and isolation via standard procedures in good isolated yields as shown in Scheme 3. They can also be fully characterized by NMR and HRMS analyses. To probe the scope of the *trans*-aminoboration reaction, a variety of aniline-alkyne derivatives are examined. The borylative cyclization reaction is in fact applicable to all the secondary arylamine-alkynes we examined. This reaction shows tolerance to not only aryl substituents on the triple bond but also alkyl substituents (**9b**). Alkynes that bear functional groups such as bromo (**7b**) or a bulky ferrocenyl (**8b**) are also compatible with the borylative cyclization.

Mechanistically, we suggest that the borylative cyclization proceeds via a key zwitterionic borate-borenium intermediate **I** based on the NMR data. Two possible reaction pathways based on the intermediate **I** are proposed and shown in Scheme 4. In

Scheme 4. Proposed Mechanism of *trans*-Aminoboration



pathway I, the borenium ion in the intermediate **I** transfers to the 3-position of indole to replace $B(C_6F_5)_3$, forming the product **b**. The freed $B(C_6F_5)_3$ can then promote a second cyclization reaction, continuing the catalytic cycle. In pathway II, the highly electrophilic borenium ion[19] in **I** attacks molecule **a**, promoting cyclization and the formation of a cationic species **I′** and its counterion, $[In{-}B(C_6F_5)_3]^-$. The borenium ion in **I′** could attack another molecule of **a**, releasing the product **b**, while the reproduced **I′** continues the catalytic cycle until all starting material **a** is consumed. To support our hypothesis, attempts were made to react the aminoboronic ester **4a-Bcat** with borenium generated from the reaction of ClBcat, $AlCl_3$, and triethylamine as reported by Ingleson and co-workers.[4c] However, no borylative cyclization was observed from this reaction even at 90 °C. Based on this observation, the catalytic pathway I is most likely for the room temperature borylative cyclization reported herein.

In summary, we have established a facile *trans*-aminoboration reaction catalyzed by $B(C_6F_5)_3$ under ambient temperature. The scope of the reaction is quite general with different boron reagents and alkynyl-aniline derivatives. This borylative cyclization reaction provides an efficient strategy for the construction of boron derivatized indoles. Future work will be focused on the synthesis of other heterocycles employing a similar strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00437.

Experimental details for the synthesis of all compounds, NMR and HRMS data (PDF)

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Notes

The authors declare no competing financial interest.

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