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Transition-Metal-Free Direct *anti*-Carboboration of Alkynes with Boronic Acids To Produce Alkenylheteroarenes

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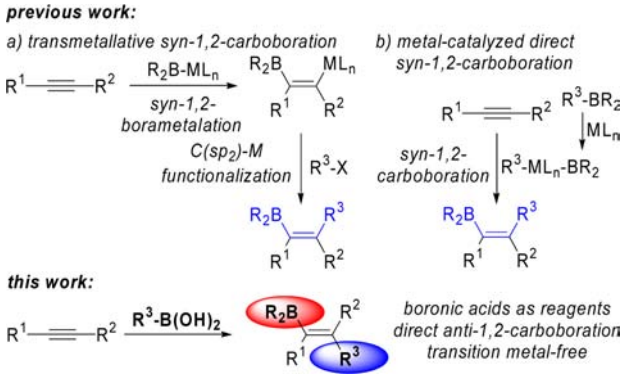
Supporting Information

ABSTRACT: The transition-metal-free intermolecular direct 1,2-carboboration reaction of heteroarylacetylenes using boronic acids as reagents is achieved by utilizing tartaric acid as promoter. The reaction proceeds with excellent regioselectivity and *anti* stereoselectivity to afford boroxole frameworks. The resulting compounds are of use for the stereoselective preparation of polysubstituted alkenylheteroarenes.

The carboboration of alkynes constitutes a useful strategy for the synthesis of polysubstituted alkenylboronic acid derivatives. These boron derivatives are of general utility as intermediates in important organic transformations that lead to the regioselective formation of tri- and tetrasubstituted alkenes, which are relevant organic compounds otherwise difficult to prepare as single isomers.[1] Their engagement in metal-catalyzed reactions such as the Suzuki–Miyaura[2] or the Chan–Lam[3] couplings, and in conjugate additions,[4] can give rise to complex molecules. Additionally, their reactions under metal-free conditions constitute a new, rapidly expanding area.[5−7] Either protolytic[8] or metal-catalyzed deborylation[9] of these intermediates may convert terminal alkynes into disubstituted alkenes and internal alkynes into trisubstituted alkenes. Consequently, the development of new ways to synthesize functionalized, polysubstituted alkenylboronic acids and boronates constitutes a valuable addendum to all these important synthetic procedures. Current means toward this end are significantly limited.[10] Most popular approaches rely on the hydroboration of alkynes,[11] the electrophilic trapping with borates of alkenylmetal intermediates generated from alkenyl halides, and the direct transition-metal-catalyzed coupling of the latter with diboronyl reagents. Control of the regio- and stereochemistry is crucial in these transformations, and this is not always easy to achieve by the previously reported methods.

More recently, the metal-catalyzed 1,2-carboboration of alkynes has attracted great interest for the synthesis of trisubstituted alkenylboronates (Scheme 1).[12] Transmetalative carboborations have been most amply developed. In these reactions, the carbon and boron moieties arise from two different reagents. These transformations take place by the intermediacy of 1,2-borylmetal species which add *syn* across alkynes.[13,14] The *syn*-β-borylalkenylmetal intermediates thus generated can be exploited synthetically by functionalization of their C(sp_2)–metal bond with several types of carbon reagents. However, these intermolecular *syn*-1,2-borylmetalation reactions become challenging when dealing with nonsymmetrical internal alkynes, as internal alkynes are less reactive than terminal alkynes and the regiochemistry of the addition is not easy to control.

Scheme 1. Carboboration of Alkynes



Some other transition-metal-catalyzed procedures have been developed, in which a direct carboboration of an alkyne can be accomplished. In these reactions, a boron compound delivers both the carbon and boron moieties to an alkyne under activation with a transition-metal catalyst, which adds oxidatively to the B–C bond of the reagent. This has proven useful for cyanoborations and alkynylborations only.[15] Despite these efforts, finding new carboboration reactions is highly desirable. Particularly attractive is the search for *anti* carboborations.[16]

Although various boron sources have been used in carboboration reactions, boronic acids have not been used thus far as reagents for this purpose.[17] These boron compounds have low toxicity and are reasonably stable to air and humidity, and their manipulation does not require subambient temperatures, an inert atmosphere, or anhydrous solvents.

The purpose of this work is the establishment of a new intermolecular direct *anti*-1,2-carboboration reaction using boronic acids as reagents under transition-metal-free conditions. The reaction will be directed toward the synthesis of functionalized alkenylheteroarenes.

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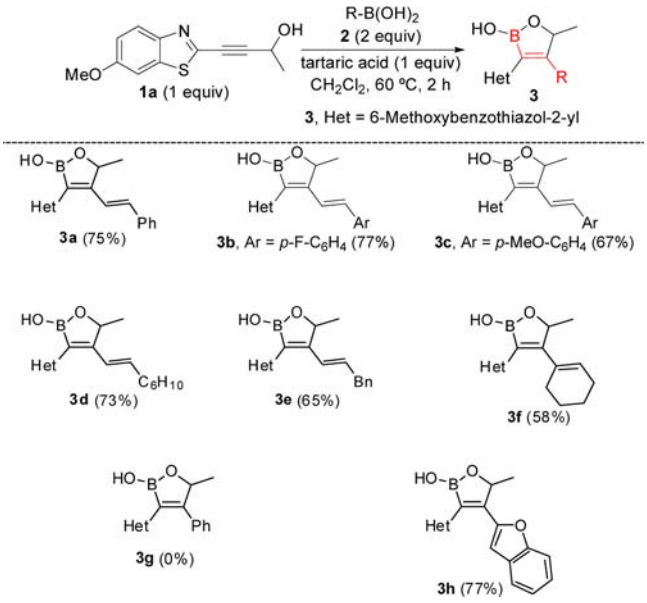
Functionalized alkynes are particularly interesting compounds with regard to further transformation of the resulting reaction products. In this regard, propargylic alcohols constitute valuable starting materials.[18] In addition, the conversion of alkynylheteroarenes into alkenylheteroarenes is of wide interest.[19] Compounds such as oxazoles, thiazoles, and imidazoles are ubiquitous in pharmaceuticals, agrochemicals, and natural products. New functionalizations of these privileged structures pave the way for future applications.

We started our investigation by examining the formation of compound **3a** (Scheme 2) as a model reaction using various

Scheme 2. Scope of Boronic Acids[a]



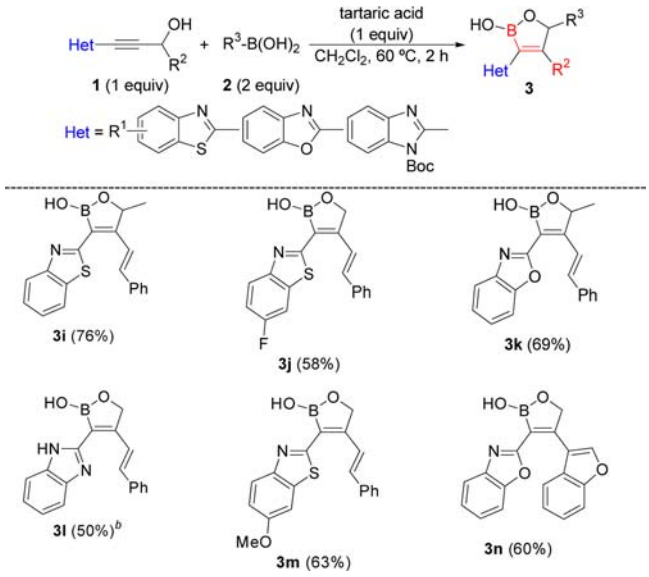
[a]Yield of the isolated product (silica gel chromatography).

nonmetallic additives that have proven of utility in the activation of boronic acids toward addition reactions (see the Supporting Information). However, the use of trifluoroacetic anhydride (TFAA) or boron trifluoride etherate did not afford any reaction product. These reagents are known convert the starting boronic acids into more electrophilic boron species either by acylation (TFAA)[20] or by the transient formation of a difluoroborane (BF_3).[21] This could help coordination of the new electrophilic boron species to the alkyne, the alcohol, or the imine-type nitrogen of **1a** to start off the carboboration process intramolecularly. In light of the lack of reactivity, we assumed that these reagents may coordinate instead with the basic centers of **1a** directly, thus inhibiting an effective activation of the boronic acid. Therefore, we switched to the less aggressive lactic or tartaric acids.[22] The best yield was observed when the reaction was performed in the presence of tartaric acid (1.0 equiv) in CH_2Cl_2 at 60 °C for 2 h.

Having optimized the reaction conditions, we investigated the scope of the reaction with respect to the boronic acid substrate (Scheme 2). 2-Arylalkenylboronic acids bearing electron-donating or electron-withdrawing groups underwent the 1,2-carboboration reaction with benzothiazole **1a** (**3b**, **3c**). Alkylvinylboronic acids were also suitable partners (**3d**, **3e**), including a 1,2-disubstituted compound (**3f**). Although no reaction was observed with phenylboronic acid[23] (**3g**), 2-benzofurylboronic acid coupled smoothly with **1a** (**3h**). The transformation exhibited high regioselectivity and high stereoselectivity: the new C−B bond was formed at the alkyne carbon which was substituted by the heteroarene ring, and the new C−C bond was formed at the alkyne carbon flanked by the alcohol functional group, in an *anti* relative disposition with respect to the C−B bond. This arrangement gave rise to the formation of a boroxole ring. No other coupling products were detected in the reaction mixtures.

Subsequently, we turned our attention to the use of other heteroarenes (Scheme 3). We found that benzothiazoles,

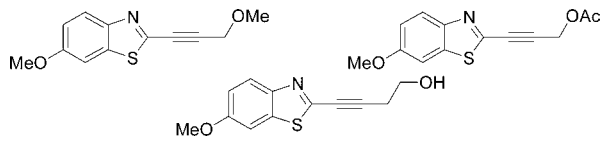
Scheme 3. Alkyne Scope[a]



[a]Yield of the isolated product (silica gel chromatography). [b]Deprotected along with the reaction.

benzoxazoles, and benzimidazoles underwent the direct *trans*-1,2-carboboration reaction. However, no reaction with (*E*)-phenylvinylboronic acid (**2a**) was found when the heterocyclic moiety of the starting alkyne was replaced by phenyl or 2-pyridyl. Several additional reactions were performed to investigate the participation of the alcohol moiety. Both primary and secondary propargylic alcohols were tolerated (Scheme 3). However, no reaction with (*E*)-phenylvinylboronic acid (**2a**) was observed when the OH group was protected as an ester or an ether (Scheme 4). No reaction was found either with a homopropargylic alcohol (Scheme 4).

Scheme 4. Unsuccessful Benzothiazole Substrates



On the other hand, we found that terminal alkynes could also be efficient substrates for the transition-metal-free synthesis of conjugated dienes (Scheme 5).

A possible reaction course for the heteroarylacetylenic alcohols **1** is shown in Scheme 6. The interaction of lactic acid or tartaric acid with the boronic acid may give rise to the formation of a dioxaborolanone (**I**). In this type of cyclic boronate the Lewis acidity of the boron atom is increased with

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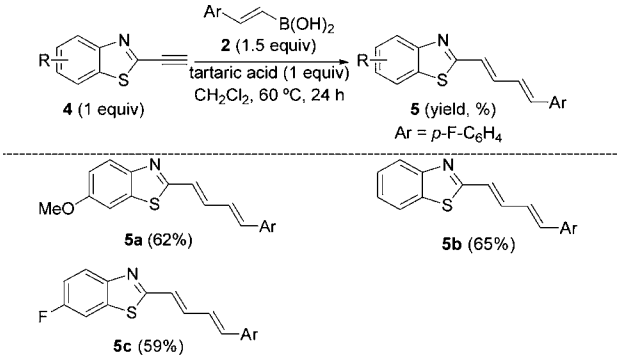
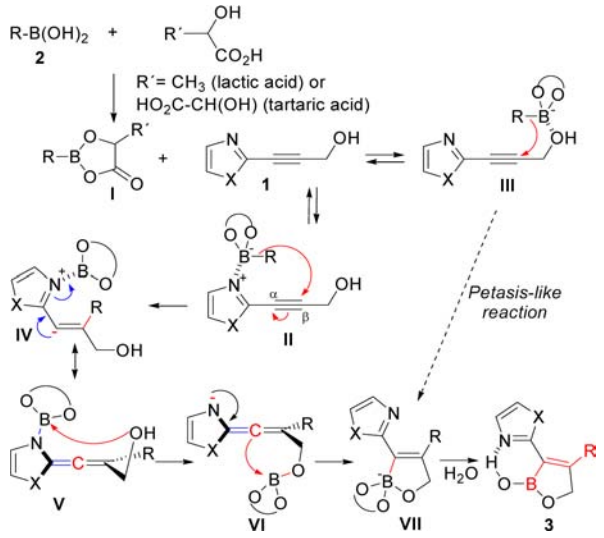
Scheme 5. Reactions with Terminal Alkynes



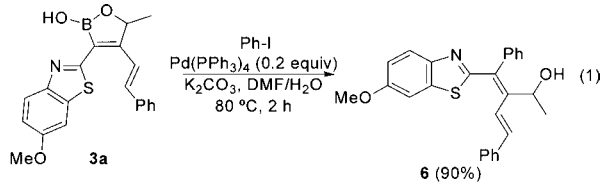
Scheme 6. Plausible Reaction Pathway

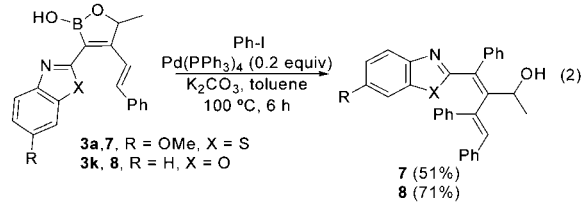


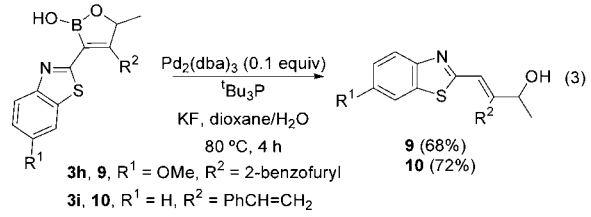
respect to boronic acids or acyclic boronates.[24] This enhancement of the electrophilicity may promote coordination of the boron atom to the lone pair of the imine-type nitrogen of the heteroaromatic substrates (**II**) or to the hydroxyl group (**III**) to give tetracoordinated boron species. Although direct transformation from **III** to **VII** in a Petasis-like reaction[25,26] on the protonated heterocyle is not to be ruled out, we believe that coordination to nitrogen (**II**) will also contribute to increase the electron-withdrawing character of the heteroarene. This effect could explain the regiochemistry of the addition: Transfer of the carbon backbone from boron to the β-carbon of the alkyne will be electronically favored, as it would render a vinyl anion (**IV**) which is resonance-stabilized with the N-quaternized heteroarene moiety (**V**). The key step determinant of the stereoselectivity will be the intramolecular addition of the sp-carbon of intermediate **VI** to the boronate moiety. This step, which may be the driving force of the whole process, generates the new sp_2-carbon with the boron and hydroxyl substituent on the same side of the alkene, permitting the formation of a boroxole ring upon hydrolysis. The final compounds **3** can be stabilized by intramolecular hydrogen bond formation.

In the case of terminal heteroarylacetylenes (Scheme 5), as in this case the formation of an oxaborole is no longer possible, direct N-protonation of the allene intermediate in situ takes place to give an *E*-alkene stereoselectively after rearomatization.

Boroxoles **3** could be used directly in C−C and C−H bond-forming reactions without transformation into other boron derivatives, further illustrating the synthetic potential of this protocol. Thus, compound **3a** was suitable for Pd-catalyzed coupling with 4-iodobenzene to afford the polysubstituted diene **6** (eq 1). Variation of the reaction conditions permitted a







combination of Mizoroki−Heck and Suzuki reactions to afford **7** and **8** (eq 2). Retention of the *E*-stereochemistry was also possible upon metal-catalyzed protodeborylations to give dienes **9** and **10** (eq 3).

In conclusion, the use of tartaric acid as reaction promoter enabled the *anti*-1,2-carboboration reaction of heteroarene-derived propargylic alcohols through the formation of oxaboroles. The current protocol features complete regioselectivity, relatively broad generality for azoles, and the absence of transition-metal catalysis. The transformation is synthetically useful for the stereoselective preparation of densely functionalized alkenes and dienes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. 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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(26) This type of mechanism will not be possible for the examples gathered in Scheme 5.

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