Cyclization

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Boron Perturbed Click Reactions Prompt Aromatic C–H Activations**

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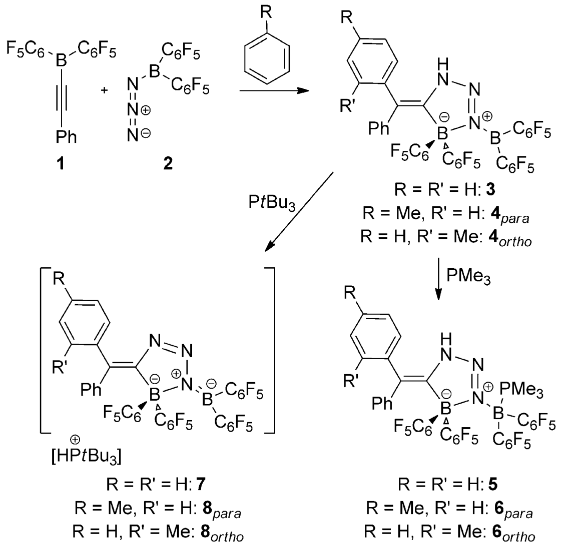
Abstract: *The reaction of boron alkynes and boron azides leads to rare N_3BC heterocycles resulting from aromatic C–H activation of benzene and toluene. While subsequent treatment with PMe_3 gave the P–B adduct with the exocyclic boron, reaction with $PtBu_3$ effected deprotonation of the heterocycle to give the corresponding phosphonium salt.*

Click chemistry, as coined by Sharpless in 2001,[1] refers to a set of reactions which allow the easy formation of molecules in a quick and reliable way. Such reactions are characterized by high yields of the desired product with relatively few by-products, and exhibit a high functional-group tolerance. This strategy is a powerful synthetic tool to generate a large library of compounds and has found application in the pharmaceutical industry, materials science, and other industries.[2] Many different reactions fulfill these criteria, including nucleophilic ring-opening reactions, additions to carbon–carbon multiple bonds, non-aldol carbonyl chemistry, and cycloaddition reactions.[1] The latter includes the model and most prominent example for click chemistry: the 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles. The thermal variant was first described by Huisgen[3] and requires elevated temperatures and often produces mixtures of regioisomers. This disadvantage was overcome with a copper- and, later, ruthenium-catalyzed cycloaddition reaction which provides selectively one regioisomer. In the case of the copper-catalyzed[4] variant, only terminal alkynes can be utilized, whereas both terminal and internal alkynes can be involved in the ruthenium-catalyzed[5] reaction. Although a number of boron-substituted azides (R_2BN_3)[6] and alkynes ($RC{\equiv}CBR_2$, R = alkyl or aryl)[7] have been reported, only a few examples of their application in click chemistry are known. Harrity et al. described the cycloaddition of an alkynylborante with benzyl azide leading to a boron substituted 1,2,3-triazole.[8] The first cycloaddition reaction of a boron azide with C≡C bonds was described by Curran et al. to give N-heterocyclic carbene boryl triazoles.[9] Recently, we extended this scope to the 1,3-dipolar cycloaddition reaction of the boron azide, Cy_2BN_3, with electron-poor acetylenes.[10] Herein, we report the unusual and uncatalyzed reaction of bis(pentafluorophenyl)boron-substituted alkynes and azides leading to an exceptional five-membered BCN_3 heterocycle by the activation of the corresponding aromatic solvent. Moreover, mechanistic considerations for the formation of this remarkable reaction are presented.

The bis(pentafluorophenyl)boron alkyne $(F_5C_6)_2BC{\equiv}CPh$[7g] (**1**) was prepared according to the literature procedure by the reaction of $(PhC{\equiv}C)_2SnMe_2$ and $(F_5C_6)_2BCl$.[11] Alternatively, **1** can also be synthesized directly from in situ generated lithium acetylide and $(F_5C_6)_2BCl$ in 76 % yield. The reaction of the **1** with $(F_5C_6)_2BN_3$[12] (**2**) in benzene and toluene, leads to the formation of the new air- and moisture-sensitive N_3BC-heterocycles **3** and **4**$_{para}$/**4**$_{ortho}$, respectively (Scheme 1). These products are isolated as red or orange powders in 73–77 % yield.



Scheme 1. Reactions of **1** and **2** in benzene and toluene.

The ^{1}H NMR spectrum of **3** shows a broad resonance at $\delta = 12.42$ ppm attributed to an NH fragment as well as multiplets at $\delta = 7.51$, 7.29, 7.22, 7.14, and 6.82 ppm, all of which integrate to a total of ten protons which are assignable to two phenyl groups. ^{1}H/^{1}H COSY, ^{1}H/^{13}C HSQC, and ^{1}H/^{13}C HMBC data confirm this assignment. In the ^{11}B NMR spectrum of **3** a broad and a sharp resonance are observed at $\delta = 48.5$ and -6.0 ppm, respectively while the ^{19}F NMR signals are detected at $\delta = -131.4$ (o-C_6F_5), -132.1 (o-C_6F_5),

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−149.7 (p-C_6F_5), −157.0 (p-C_6F_5), −161.8 (m-C_6F_5), and −164.7 ppm (m-C_6F_5). The separation of resonances attributable to the m- and p-C_6F_5 groups are indicative for the presence of one tricoordinated and one tetracoordinated boron atom.[13]

The NMR spectra of the heterocycle **4** show the presence of two isomeric species; the major isomer being a symmetrical substituted toluene isomer, $\mathbf{4}_{para}$, and a minor species with an unsymmetrical substitution pattern at toluene ($\mathbf{4}_{ortho}$). The ^1H NMR spectrum exhibits two broad NH resonances for the two isomers at $\delta = 12.53$ ($\mathbf{4}_{para}$) and 12.16 ppm ($\mathbf{4}_{ortho}$), in a ratio of 1:0.56. The toluene methyl groups of the two isomers were detected as singlets at $\delta = 2.41$ and 2.05 ppm. ^{13}C and two-dimensional NMR spectral data (^1H/^1H-COSY, ^1H/^{13}C-HSQC, ^1H/^{13}C-HMBC, and HSQC TOCSY) correspond with this assignment. The ^{11}B NMR spectrum of **4** exhibits two signals similar to those of **3** at $\delta = 48.6$ and −6.0 ppm while the ^{19}F NMR spectrum shows two sets of signals in regions similar to those seen for **3**. Again the intensity was consistent with the $\mathbf{4}_{para}$ and $\mathbf{4}_{ortho}$ isomers in a ratio of 1:0.56.

Subsequent treatment of **3** and **4** with the Lewis base PMe_3 in toluene led to the formation of the Lewis acid-base adducts **5** and **6**, respectively (Scheme 1). These compounds were isolated in 92–93 % yield as yellow solids. The ^1H NMR spectrum shows resonances attributable to the NH fragment of **5**, $\mathbf{6}_{para}$, and $\mathbf{6}_{ortho}$, and are shifted upfield to $\delta = 10.76$, 10.78, and 10.37 ppm, respectively. The Lewis adducts **5**, $\mathbf{6}_{para}$, and $\mathbf{6}_{ortho}$ show broad signals in the $^{31}P\{^1H\}$ NMR spectra at $\delta =$ −5.7, −5.7, and −5.9 ppm, respectively. In the ^{11}B NMR spectrum resonances for **5** and **6** are observed at $\delta = -4.3$ (for **5** and **6**) and $\delta = -5.2$ (for **5**) and $\delta = -5.1$ ppm (for **6**) with the latter signals exhibiting a P–B coupling constant of 86 and 77 Hz for **5** and **6**, respectively. The ^{19}F NMR spectra of **5** and **6** exhibit very broad signals for the fluorine atoms of the pentafluorophenyl groups, at ambient temperature (25 °C). These broad signals are attributed to restricted rotation of the C_6F_5 groups around the P−B bond. In the case of **6** decreasing the temperature to −40 °C slows this molecular motion, thus revealing three sets of signals in a ratio of 1:0.4:0.16. These signals are assigned to the major isomer $\mathbf{6}_{para}$, and the two rotamers of the minor isomer $\mathbf{6}_{ortho}$.

The nature of the adducts of the heterocycles were subsequently confirmed with X-ray crystallographic studies of **5** and $\mathbf{6}_{para}$ as single crystals were obtained from a CH_2Cl_2 solution (Figure 1). These compounds feature a rare N_3BC framework, as only a handful of heterocycles, fused with an icosahedral carborane anion, have been described in the literature.[14] In the case of **5** the N_3BC framework is essentially planar with the N(1)-B(1)-C(1)-N(3) torsion angle being 2.3°. In contrast, the corresponding N_3BC core in $\mathbf{6}_{para}$ deviates slightly from this planarity with a N(1)-B(1)-C(1)-N(3) torsion angle of 8.2°. The N(1)-N(2) and N(2)-N(3) bonds exhibit similar lengths of 1.307(4) and 1.301(4) Å in **5** and 1.310(3) and 1.291(3) Å in $\mathbf{6}_{para}$. These values are larger than a typical N–N double bond (1.20 Å)[15] and shorter than a typical N–N single bond (1.48 Å).[15] These observations are consistent with a delocalized bonding pattern at the three nitrogen atoms. The B(1)-N(3) bond lengths within the heterocycles are found to be 1.634(5) (in **5**) and 1.640(4) Å (in $\mathbf{6}_{para}$), whereas the exocyclic B(2)-N(3) single bond lengths are 1.573(5) (in **5**) and 1.577(4) Å (in $\mathbf{6}_{para}$). The C(1)-N(1) bonds within the heterocycle **5** and $\mathbf{6}_{para}$ have a length of 1.417(4) and 1.414(4) Å, respectively, thus suggesting some degree of delocalization. The B(1)-C(1) distances in **5** and $\mathbf{6}_{para}$ of 1.632(5) and 1.626(5) Å, are typical of B–C single bonds.[15] The C(1)-B(1)-N(3) bond angles in **5** and $\mathbf{6}_{para}$ are 95.6(3) and 95.3(2)°, respectively, and reflect the impact of the constrained five-membered ring.

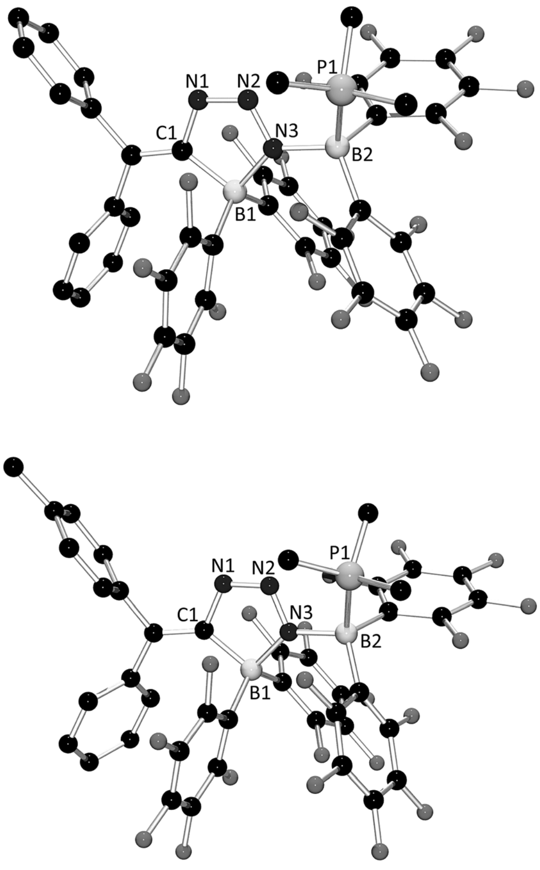
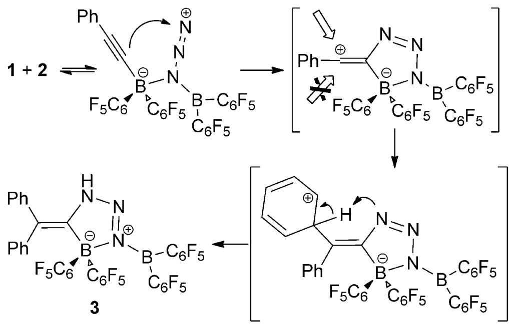


Figure 1. POV-ray depiction of **5** (top) and $\mathbf{6}_{para}$ (bottom). Hydrogen atoms are omitted for clarity.

The mechanism for the formation of **3** and **4** is thought to involve initial coordination of the boron azide to the boron alkyne (Scheme 2). This coordination is consistent with inhibition of the formation of **3** by the addition of BCl_3, as BCl_3 competes with **1** effectively and precludes reaction of **1** with **2**. Following coordination of **1** and **2**, nucleophilic addition of the α-alkynyl carbon atom to the terminal azide nitrogen atom leads to the mesomeric carbocation (Scheme 2). This prompts electrophilic aromatic substitution of the solvent, thus resulting in C−C and N−H bond formation, ultimately yielding the heterocycles **3** and $\mathbf{4}_{para}$ and $\mathbf{4}_{ortho}$. The regiochemistry of the aromatic substitution to the exocyclic carbon atom results in C−C bond formation *trans* to the $B(C_6F_5)_2$ fragment. It is thought that this regiochemistry is guided by the proximity of the proton accepting nitrogen atom. In the case of toluene, electrophilic aromatic substitution proceeds at either the *para* or *ortho* positions, thus affording the two isomers. Performance of the



Scheme 2. Proposed mechanism for formation of **3**.

reaction of **1** and **2** in a 1:1 mixture of C_6H_6 and C_6D_6 showed formation of 50% product of the protio product **3**. The absence of an isotope effect infers the rate-determining step in the formation of **3** is not the C–H activation. This data suggests cyclization from the adduct of **1** and **2** is rate determining. It is also noteworthy that the corresponding reaction of $(F_5C_6)_2BC{\equiv}CtBu$[7g] with **2** led only to decomposition, presumably a result of the inability of a corresponding carbocation.

The compounds **3** and **4** also react with P*t*Bu$_3$ to give the yellow powders **7** and **8**, respectively, in almost quantitative yield (Scheme 1). The ^{1}H NMR spectrum of **7** shows a doublet at $\delta = 5.18$ ppm with a characteristic P–H coupling of 437 Hz. The ^{31}P{^{1}H} signal at $\delta = 58.18$ ppm is consistent with the formation of the cation [HP*t*Bu$_3$]$^+$. In the ^{11}B NMR spectrum two resonances are observed at $\delta = 39.2$ and -11.2 ppm. The ^{19}F NMR spectrum of the phenyl-substituted compound (**7**) shows signals at $\delta = -132.1$ (o-C_6F_5), -162.6 (p-C_6F_5), and -167.5 ppm (o-C_6F_5), which are attributable to the tetracoordinated boron atom. Furthermore, ^{19}F signals for the two C_6F_5 groups at the tricoordinated boron atom are observed at $\delta = -131.7$ (o-C_6F_5), -132.9 (o-C_6F_5), -156.3 (p-C_6F_5), -156.6 (p-C_6F_5), and -164.3 ppm (2-m-C_6F_5). The corresponding data for the toluene-substituted salt **8** are similar. These spectra show additional signals attributable to the *para* and *ortho* isomers in a ratio of 1:0.47.

Crystals of **7**, obtained from a concentrated benzene solution, allowed confirmation of the nature of this salt by X-ray crystallography (Figure 2). The N(1)-N(2) bond within the five-membered ring system has a length of 1.260(3) Å while the N(1)-N(2) is 1.420(2) Å. The boron–nitrogen bond length within the heterocycle has a value of 1.587(3) Å, which is clearly shorter than the corresponding bond in the neutral **4**. The exocyclic N(3)-B(2) bond has some double bond character typical of an aminoborane with a length of 1.390(3) Å [cf. 1.372(2) Å in $(C_6F_5)_2BNMe_2$.[16]] The parameters of the cation [HP*t*Bu$_3$] are unexceptional.

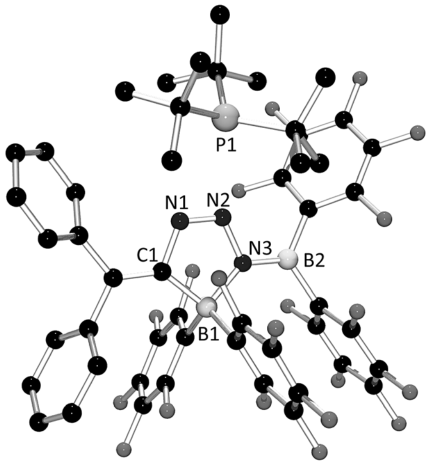


Figure 2. POV-ray depiction of **7**. Hydrogen atoms are omitted for clarity.

Performing the reaction of **1** and **2** in non-aromatic solvents (e.g. *n*-hexane, dichloromethane) led only to unidentified mixtures of products. It is also noteworthy that these reactions are not expected to tolerate functional-group substituents as donor groups may coordinate to B and inhibit these distorted click reactions.

In conclusion, we have demonstrated the uncatalyzed reaction of $B(C_6F_5)_2$-substituted alkynes and azides does not proceed by the classical click reaction to give a triazole derivative. Instead, exceptional N_3BC heterocycles are formed by cyclization and C–H activation of the corresponding aromatic solvent. These heterocycles react with less sterically demanding Lewis bases like PMe_3 to yield classical P/B adducts at the exocyclic boron. In contrast, the more sterically encumbered Lewis base P*t*Bu$_3$ effects deprotonation, thus providing access to BCN_3-heterocyclic salts. Current efforts are aimed at targeting the synthesis of related systems, which are capable of such C–H activations, and exploring further reactivities of these remarkable heterocycles.

CCDC 987434, 987435, and 987436 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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