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Title: Metal-Free Intermolecular C–H Borylation of N-Heterocycles at B–B Multiple Bonds

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Metal-Free Intermolecular C–H Borylation of N-Heterocycles at B–B Multiple Bonds


Dedicated to Prof. Guy Bertrand on the occasion of his 70th birthday

Abstract: Carbene-stabilized diboranes of the form BB(L) (L = N-heterocyclic carbene (NHC) or cyclic alkyl(amine)carbene (CAAC)) induce rapid, high yielding, intermolecular ortho-C–H borylation at N-heterocycles at room temperature. A simple pyridylidiborane is formed when an NHC-stabilized diborane is combined with pyridine, while a CAAC-stabilized diborane leads to activation of two pyridine molecules to give a tricyclic alkylideneborane, which can be forced to undergo further H-shift resulting in a zwitterionic, doubly benzofused 1,3,2,5-diazadiborinone by heating. Use of the extended N-heteroaromatic quinoline leads to a borylmethylideneborane under mild conditions via an unprecedented boron-carbon exchange process.

The now ubiquitous Suzuki-Miyaura cross-coupling reaction,[1,2] and the growing realization that C–B bonds can act as near-universal placeholders for the functionalization of organic molecules,[3,4] has spurred enormous interest in the efficient synthesis of boronylidynes. Transition-metal catalyzed C–H borylation has emerged as a promising, direct, and often selective route to borylated precursors for Suzuki-Miyaura cross-coupling reactions.[5,6] However, the toxicity and environmental impact of the transition metals used in catalysis, and the expense related to their removal from the products, has caused concern in the chemical industry. Consequently, the search for metal-free C–H borylation protocols has become a hotly-contested area of research.[7,11] However, this chemistry is hampered by the relative inertness of most C–H bonds and chemoselectivity issues arising from the multiple C–H sites present in most target molecules. In particular, protocols for selective C–H borylation of heterocyclic compounds with relatively reactive auxiliary sites, such as the N atoms of pyridines, present further synthetic challenges, and are exceedingly rare even with the assistance of transition-metal catalysts.[14,15]

The recent development of highly reactive molecules containing B–B multiple bonding[6,16] provides interesting opportunities for novel bond activation reactions. Indeed, doubly Lewis-base-stabilized diboranes, of the form [LB=BL] (L = Lewis base such as N-heterocyclic carbene or cyclic alkyl(amine)carbene), have already been shown to undertake a number of interesting intermolecular bond activation reactions, leading to 1,2-additions across their B–B triple bonds. These include the H–H bond of dihydrogen,[19] the C–O bonds of CO and CO2,[20,21] B–H,[22] and B–B[23] bonds, S–S and Se–Se bonds,[24] and even the activated C–H bonds of acetonitrile and alkyne.[25,26] The demonstrably high reactivity of diboranes makes them good candidates for the highly challenging task of activating the C–H bonds of (hetero)arenes, prompting us to combine these two classes of reagents in this work.

Herein we report three different modes of regioselective, intermolecular C–H borylation of N-heterocycles with carbene-stabilized diboranes, compounds with varying degrees of boron-boron multiple bonding.[16,17] All of these reactions occur at ambient temperature and in the absence of catalysts or additives. Depending on the diborane precursor, either one or two molecules of pyridine can be activated, leading either to a simple pyridylidiborane or a tricyclic alkylideneborane, respectively. Use of the larger heteroaromatic quinoline leads initially to the simple C–H borylation product, which spontaneously undergoes a highly unusual B/C exchange, leading to a borylmethylideneborane.

The doubly carbene-stabilized diboranes [[SiDes][Des]=B(Sides)][1, Sides = 1,3-bis-(2,6-diethylphenyl)-imidazol-2-ylidene] and [(CAAC)B=CAAC][2, Scheme 1; CAAC = 1-(2,6-disopropylphenyl)-3,3,5,5-tetramethylpyrrolidin-2-ylidene] have thus far shown the most facile reactivity of all of the known species of the form BB=BL.[16,17] Consequently, we chose these two species in initial reactivity tests with N-heteroaromatics. Previous results have indicated that strongly-binding ligands such as NHCs and CO can form adducts with diboranes such as 2,[27,28] suggesting that pyridines and their derivatives could potentially form similar adducts of the form [LBB[pyr]] (pyr = N-bound pyridine derivative) with 1 or 2.

Thereby, treatment of 1 with an equimolar amount or an excess of pyridine led to an immediate color change from red to blue and a new set of 11B NMR signals at 35 and 25 ppm (1: 8:18 = 56 ppm). After evaporation of all volatiles under high vacuum and washing with hexane, the blue solid 3 was isolated in 82% yield (Scheme 1). A single-crystal X-ray diffraction (SCXRD) study unequivocally revealed 3 to be not a simple pyridine adduct of 1 but a doubly base-stabilized 1-hydro-2-pyrlylidiborane, suggesting ortho-C–H borylation of pyridine...
A signal corresponding to the boron-bound hydrogen was detected in the $^1$B-decoupled $^1$H NMR spectrum of $3$ at 3.35 ppm as a broad singlet. Apart from those corresponding to the carbene carbon nuclei, the most low-field $^1$C NMR resonance can be assigned to the boron-bound carbon atom of the pyridyl substituent (180.3 ppm), identified by a 2D $^{13}$C- $^1$H HMBC NMR experiment. The solid-state structure of diborene $3$ (Figure 1) shows a B1–B2 distance of 1.591(5) Å, lying in the expected range for doubly NHC stabilized diborenes. The nearly identical B1–C1 (1.546(5) Å) and B2–C2 (1.563(5) Å) distances, the distinct B2–C3 single bond (1.589(5) Å), as well as the ca. 50° twist of the pyridyl ring from the central diborene plane, suggest negligible π-delocalization between the B=B and pyridyl groups. This is supported by DFT-calculated molecular orbitals (MOs) of 3, with both the HOMO and LUMO resembling those of conventional doubly NHC-stabilized diborenes (Figure 2). The HOMO displays delocalization of π electron density over the $\text{C}^{\text{NHC}}$=B=B–$\text{C}^{\text{NHC}}$ axis, while the LUMO shows π* antibonding character at the B=B bond and π bonding character at the B–C bonds.

While combining CAAC-stabilized diboryne $2$ with one equivalent of pyridine led to roughly half of the precursor remaining unreacted, adding two equivalents of pyridine to a benzene solution of $2$ (Scheme 1) at room temperature led to a color change from purple to pink within one hour. The $^1$B NMR spectrum of the reaction mixture displayed new resonances at 32 and 22 ppm, upfield of those of the starting material (1: δ($^1$B) = 80 ppm) after workup. A purple solid was obtained in 82% yield. An SCXRD study revealed the compound to be the tricyclic diazadiborinine derivative $4$, resulting from activation of two pyridine molecules. The $^1$H NMR spectrum of $4$ shows, in addition to expected aromatic signals of the CAAC ligands, only four additional protons in this region, with an additional set of signals found in the alkene region (5.89–5.54 ppm), confirming the loss of aromaticity of one pyridyl group and subsequent formation of a butadiene-like structural motif. A signal at 4.26 ppm can be assigned to the hydrogen atom now bound to a former carbene carbon atom (H2 in Figure 1, middle), in line with previous observations of H-shifts onto CAAC ligands. A broad $^1$H NMR spectroscopic signal at 3.33 ppm (H1 in Figure 1, middle) shows a cross-signal to a resonance in the $^1$C–$^1$H HSQC NMR spectrum at 65.2 ppm, corresponding to the hydropropyridyl carbon atom bound to boron (C2 in Figure 1, middle). The solid-state structure of $4$ (Figure 1, left) shows a distinct butadiene-like structure of the...
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Figure 2. Canonical Kohn-Sham MOs of 3. Level of theory: wB97X-D/6-311+G(d,p)/wB97X-D/6-31G(d,p). Selected hydrogen atoms are omitted for clarity. Isovalence: 0.03.

hydro.pyridyl unit, with alternating C=C bond distances (C5–C6: 1.342(4); C6–C7: 1.450(4); C7–C8: 1.328(4) Å), while the aromatic pyridyl unit shows typical bond equilibration (1.425(4)–1.346(4) Å), comparable to those of a recently published CAAC-stabilized diboraanthracene diradical.[32] These differences are confirmed by the calculated zz components of the shielding tensor nucleus-independent chemical shift (NICS$_{zz}$(1)) elements (Figure 3). Also notable are the B–C distances: while the B1–C2 distance (1.611(4) Å) suggests a single bond, the B1–C3 distance (1.507(4) Å) indicates double bond character and the presence of an alkylideneborane unit.[33] The B1–C1 distance (1.521(4) Å) is in the expected range for a diazine CAAC–B interaction with significant n-bonding character, whereas the B2–C4 (1.615(4) Å) distance suggests a single covalent bond.

Heating a C$_5$Ns solution of 4 at 80 °C for 14 h led to an additional color change of the reaction mixture from light to dark pink, the 11B NMR spectrum of which showed only a single resonance at 28 ppm (δ(11B) = 32, 22 ppm). The purple solid 5 was obtained after workup in nearly quantitative yield, the 1H NMR spectrum of which showed the absence of signals in the alkene region and no hydro.pyridyl signal comparable to that of 3 (δ(1H) = 3.33 ppm). Instead, two signals corresponding to protonated CAAC substituents were observed (4.96 and 4.87 ppm). These data suggested rearrangement of the hydro.pyridyl unit and a concomitant H-shift to the remaining CAAC unit (Scheme 1).

A SCXRD study of 5 using crystals obtained from a saturated pentane solution indicated the presence of an essentially planar tricyclic central unit, with the aryl substituents of both CAAC substituents oriented on opposite sides of the tricyclic core. Alternatively, a solid-state structure derived from crystals prepared using benzene as crystallization medium shows both aryl substituents to be oriented on the same side of the tricyclic core, leading to a butterfly-like structure with an angle of 21° (Figure 1, right).

Together, these spectroscopic and structural data indicate that 5 is a very rare example of a 1,3,2,5-diazadiborinine. The high symmetry of 5 results in disorder in the molecular structure shown in Figure 1, whereby a molecule with swapped C and N atoms is superimposed on the first. This disorder led to reduced precision in the structure, prompting us to turn to DFT calculations to gain a better idea of the structure and energetics of 5. All distances of the central core, both experimental and calculated (1.422–1.532 Å), lie in the range of elongated double bonds, suggesting extended delocalization; similar to results reported by Kinjo et al. for their 1,3,2,5-diazadiborinines.[26,27] The calculated NICS$_{zz}$(1) values (Figure 3) of the outer rings of 5 suggest greater aromaticity than those of 4, with the zwiterionic inner B=N=C core being relatively aromatic. These NICS values underscore the similarity of 5 to its purely hydrocarbon analogue anthracene, which is known to exhibit a higher NICS(0) for its central ring relative to the outer rings.[30] Accordingly, the transformation of 4 to 5 is exergonic by −25.9 kcal mol$^{-1}$ based on DFT calculations at the SMD(benzene):wB97X-D/6-311+G(d,p)/wB97X-D/6-31G(d,p) level of theory. For reference, the NICS$_{zz}$(1) value of benzene at the same level is −29.75 ppm, while those of anthracene are −25.37 ppm (outer rings) and −35.09 ppm (central ring).

In order to test if diborene 3 also undergoes thermally-induced reactivity, benzene solutions of 3 were heated independently to 60 °C and 80 °C. However, in both cases this led only to decomposition.

Given the intriguing reactivity of diborines with monocyclic N-heterocycle pyridine, we sought to expand our scope to bicyclic N-heterocycle quinoline. The reaction of 2 with quinoline gave an inseparable mixture of products, however, treatment of 1 with quinoline resulted in an immediate color change from red to blue, similar to the above reaction of 2 with pyridine. 11B NMR spectroscopic resonances at 25 and 30 ppm were observed after a few minutes, suggesting the presence of diborene 6, analogous to 3. However, the resonance at 25 ppm had disappeared after 10 minutes, while the signal at ca. 30 ppm had broadened significantly. An additional color change to green occurred within one hour, and a near-complete decoloration took place overnight, the remaining light yellow solution suggesting the absence of diborene in the mixture. After workup by washing the dried reaction mixture with hexane and crystallization from a saturated hexane solution, the product was identified by SCXRD as the borylalkylideneborane 7 (Scheme 2), a constitutional isomer of the presumed intermediate 6 in which one of the carbene carbon atoms has exchanged with one boron atom. The unexpected and highly unusual structure of 7 is confirmed by its NMR spectra. A singlet resonance corresponding to the alkylideneborane C–H proton was found in the $^1$H NMR spectrum at 3.79 ppm, presenting a cross-signal to a $^{13}$C NMR resonance at 104.3 ppm in the $^{13}$C/$^1$H HSQC NMR spectrum. This resonance is downfield of typical alkenic resonances, but is in the same range as that of a cyclic borylalkylideneborane reported by Berndt et al. (115.2 ppm).[31] The broad resonance observed in the $^1$B NMR spectrum of 7 (30 ppm) can be rationalized by the superposition of two signals.

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for which was determined by quantum chemical c

quinoline instead of pyridine gives a borylmethyleneborane, heating of the tricyclic alkylideneborane intermediate. Using pyridine leads to a

thermodynamically relatively stable. Similar ring reaction mechanism shows this transformation goes through

B1 (via \( = \)) relatively easily and one of the nitrogens of the bridging SIDep ligand

renders more acidic in

shorter than 15.7 kcal/mol (higher than the reverse reaction via

quinoline to pyridine increases the energy barrier in

TS

6

®

2

39.7 kcal/mol (higher than the reverse reaction via

quinoline to pyridine increases the energy barrier in

TS

A7

®

2

4.4 kcal/mol) which stabilizes B7 by \( \Delta G = -4.9 \)

kcal/mol; ii) a second sigmatropic rearrangement (TS

A6

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2

10.6 kcal/mol) to obtain the spirocyclic boryl species A8 (\( \Delta G = -14.0 \)

kcal/mol); and finally, iii) decoordination of quinoline from

A8

®

2


2015,

349, 513–516.


Crystallographic data for this manuscript have been deposited with the Cambridge Crystallographic Data Center (CCDC numbers: 2204262 (3), 2204261 (4), 2204260 (5), 2204259 (7)).


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Carbene-stabilized diborynes of the form LBB(L (L = N-heterocyclic carbene or cyclic alkyl(amino)carbene) induce rapid, high yielding, intermolecular ortho-C-H borylation at N-heterocycles at room temperature. The reaction initially provides the simple hydroarylated diborene, but in some cases proceeds further, providing unusual 1,3,2,5-diazadiborinine and base-stabilized alkylidene products.