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Communication

Insertion of Alkylidene Carbenes into B−H Bonds

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Cite This: https://dx.doi.org/10.1021/jacs.0c09596
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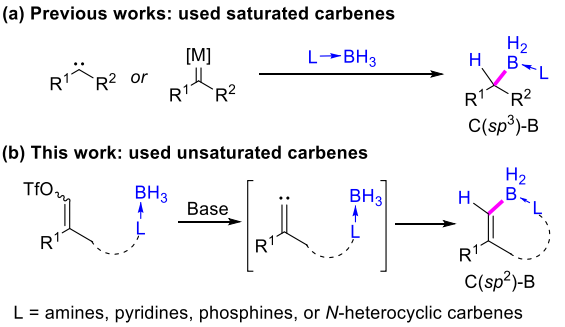
ABSTRACT: We have developed a protocol for insertion of alkylidene carbenes into the B−H bonds of amine−borane adducts, enabling, for the first time, the construction of C(sp^2)−B bonds by means of carbene-insertion reactions. Various acyclic and cyclic alkenyl borane−amine adducts were prepared from readily accessible starting materials in good to high yields and were subsequently subjected to a diverse array of functional group transformations. The unprecedented spiro B−N heterocycles prepared in this study have potential utility as building blocks for the synthesis of pharmaceuticals. Preliminary mechanistic studies suggest that insertion of the alkylidene carbenes into the B−H bonds of the amine−borane adducts proceeds via a concerted process involving a three-membered-ring transition state.

Organoboron compounds are widely used in organic synthesis, the pharmaceutical and agrochemical industries, materials science, and many other fields.[1] Therefore, the development of new C−B-bond-forming reactions that permit efficient synthesis of organoboron compounds has long been of interest to synthetic chemists. Recently, the insertion of carbenes into the B−H bonds of stable borane adducts—such as amine boranes, phosphine boranes, and N-heterocyclic carbene boranes—has emerged as a promising method for constructing C−B bonds (Scheme 1a).[2] This method has many advantages for the synthesis of functionalized organoboranes because boron adducts are readily accessible and highly stable[3] and carbenes can be generated from a variety of precursors.[4] However, to date, only saturated carbenes (that is, disubstituted carbenes) have been successfully used in B−H bond insertion reactions, which form alkyl boranes.[2]

Scheme 1. B−H Bond Insertion Reactions



We envisioned that alkenyl boron compounds could be accessed by B−H bond insertion reactions if borane adducts could trap alkylidene carbenes, which are typical unsaturated carbenes and which have been utilized in the synthesis of functionalized and unfunctionalized olefins[5] (Scheme 1b). Herein, we report a protocol for B−H bond insertion reactions involving alkylidene carbenes and borane adducts. Specifically, in the presence of ^{t}BuOK, alkylidene carbenes generated in situ from readily available alkenyl triflates smoothly inserted into the B−H bonds of borane adducts to produce alkenyl boranes in good to high yields. An intramolecular version of this reaction allowed us to synthesize various BN heterocycles, which have not previously been reported and hard to prepare through the well-established C−B-bond-forming reactions.[1,6] The alkenyl borane adducts produced by this method could undergo many types of C−C- and C−X- (X = heteroatom) bond-forming reactions to afford trisubstituted olefins.

Inspired by the work of Stang et al.,[7] who reported that alkylidene carbenes can be generated by base-induced α-elimination reactions of alkenyl triflates, we began our study with the reaction of alkenyl triflate **1a** and trimethylamine−borane (**2a**, 2 equiv) in the presence of ^{t}BuOK in 1,2-dimethoxyethane at 0 °C (Table 1). To our delight, these conditions afforded desired alkenyl borane **3aa** in 47% yield (entry 1). The O−H bond insertion product (4-(*tert*-butoxymethylene)cyclohexyl)benzene was the main byproduct. Tetrahydrofuran, *tert*-butyl methyl ether, dichloromethane, PhCl, toluene, and hexane were also suitable solvents (entries 2−7), with dichloromethane giving the highest yield (entry 4). The strength of the base was critical to the reaction outcome: the use of the weaker base ^{t}BuONa markedly reduced the yield (entry 8), and no reaction occurred when ^{t}BuOLi or MeONa was used (entries 9 and 10). This reaction is temperature dependent and the one performed at 0 °C exhibiting best outcomes (Table S1). Higher yields were achieved by increasing the amount of adduct **2a** (entries 11 and 12). The electronic and steric nature of the donor in the borane adduct

Received: September 7, 2020

https://dx.doi.org/10.1021/jacs.0c09596
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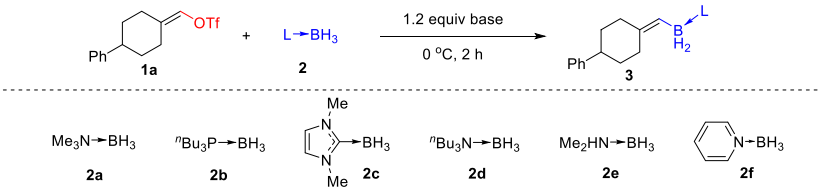
Table 1. B−H Bond Insertion of Alkylidene Carbene: Optimization of the Reaction Conditions[a]



entry	adducts	base	equiv of **2**	solvents	products	yield (%)[b]
1	**2a**	^{t}BuOK	2	DME	**3aa**	47
2	**2a**	^{t}BuOK	2	THF	**3aa**	50
3	**2a**	^{t}BuOK	2	MTBE	**3aa**	60
4	**2a**	^{t}BuOK	2	DCM	**3aa**	70
5	**2a**	^{t}BuOK	2	PhCl	**3aa**	50
6	**2a**	^{t}BuOK	2	toluene	**3aa**	39
7	**2a**	^{t}BuOK	2	hexane	**3aa**	39
8	**2a**	^{t}BuONa	2	DCM	**3aa**	30[c]
9[d]	**2a**	^{t}BuOLi	2	DCM	**3aa**	N.D.[e]
10[d]	**2a**	MeONa	2	DCM	**3aa**	N.D.
11	**2a**	^{t}BuOK	3	DCM	**3aa**	72
12	**2a**	^{t}BuOK	4	DCM	**3aa**	77
13[f]	**2b**	^{t}BuOK	4	DCM	**3ab**	70
14	**2c**	^{t}BuOK	4	DCM	**3ac**	75
15	**2d**	^{t}BuOK	4	DCM	**3ad**	<5
16[d]	**2e**	^{t}BuOK	4	DCM	**3ae**	N.D.
17	**2f**	^{t}BuOK	4	DCM	**3af**	N.D.

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6−1.2 mmol), ^{t}BuOK (0.36 mmol), 3 mL of CH_2Cl_2, 0 °C. Full conversion of **1a** was observed unless otherwise noted. [b]Isolated yield. [c]Reaction time: 12 h. [d]<10% conversion of **1a**. [e]N.D. = not detected. [f]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

also affected the reaction outcome. Specifically, tributylphosphine−borane adduct **2b** and N-heterocyclic carbene−borane adduct **2c** gave yields similar to that obtained with **2a**, whereas tributylamine−borane adduct **2d** afforded a poorer yield (entries 13−15). Dimethylamine−borane adduct **2e** and pyridine−borane adduct **2f** did not undergo the desired reaction under the tested conditions (entries 16 and 17 and Table S2).

Using the optimized conditions (Table 1, entry 12), we evaluated various alkenyl triflates **1** in B−H bond insertion reactions with amine−borane adduct **2a** (Table 2). Cyclic and acyclic 2,2-dialkylsubstiuted alkenyl triflates were suitable carbene precursors and gave satisfactory yields of the corresponding products (**3ba**−**3ha**, entries 2−8). The reaction of acyclic alkenyl triflates with long alkyl chain (**1g**) accompanied by the intramolecular C−H bond insertion, which generated a cyclopentene derivative as a major byproduct. The reaction of a mixture of (*Z*)- and (*E*)-2,2-dialkylsubstituted alkenyl triflates **1h**, which have two different alkyl groups, gave a mixture of *E*- and *Z*-**3ha** (entry 8). Under the standard conditions, a phenyl-substituted alkenyl triflate did not undergo the bond-insertion reaction, instead affording 1-phenylpropyne (entry 9).

Next, we turned our attention to the synthesis of boron-containing heterocycles, which are attracting increasing attention because of their great promise for a variety of applications.[8] We expected that intramolecular B−H bond insertion reactions of alkylidene carbenes would allow us to prepare BN heterocycles. We began by attempting an intramolecular B−H bond insertion reaction of adduct **4a** (R = Bn, $R^1 = R^2$ = Me) with ^{t}BuOK as a base, which afforded 1,2-BN-cyclopentene **5a** in 61% yield (Scheme 2). Then we systematically explored the substrate scope of the reaction. First, the effect of the amine moiety of the amine−borane adduct was evaluated. Borane adducts derived from aliphatic tertiary amines generally afforded the desired insertion products (**5a**−**5h**) in moderate to good yields. The reaction could be scaled up with no reduction in the yield (a 76% yield of **5c** was obtained from a gram-scale reaction). Substrates derived from secondary amines also gave the desired products (**5i** and **5j**), albeit in lower yields. To our delight, borane adducts derived from cyclic amines produced the corresponding BN spirocycles (**5d**−**5h**) in good yields under the standard conditions; to the best of our knowledge, BN spirocycles have not previously been reported. We also demonstrated that our protocol could be used for modification of drug molecules. As examples, borane derivatives of the drugs paroxetine, nortriptyline, and fluoxetine were prepared (**5k**−**5m**). In the intramolecular B−H bond insertion reactions, controlling the stereochemistry of the trisubstituted alkene products was not a problem, because the insertion reaction could take place only on the same face of the double bond as the amino group. For instance, both (*E*)- and (*Z*)-**4e** gave the cyclic product **5e** in essentially the same yield.

The electronic properties of the substituent on the benzyl group of the alkenyl triflate slightly affected the yields of products **5n**−**5q**. In addition to a benzyl group, R could be a linear or branched alkyl group; desired products **5r**−**5u** were obtained in acceptable yields. Some alkylidene carbene intermediates behaved differently in inter- and intramolecular reactions. For instance, intermolecular reactions of 2-phenyl-substituted alkenyl triflates yielded not the expected B−H

https://dx.doi.org/10.1021/jacs.0c09596
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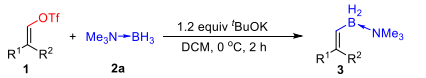
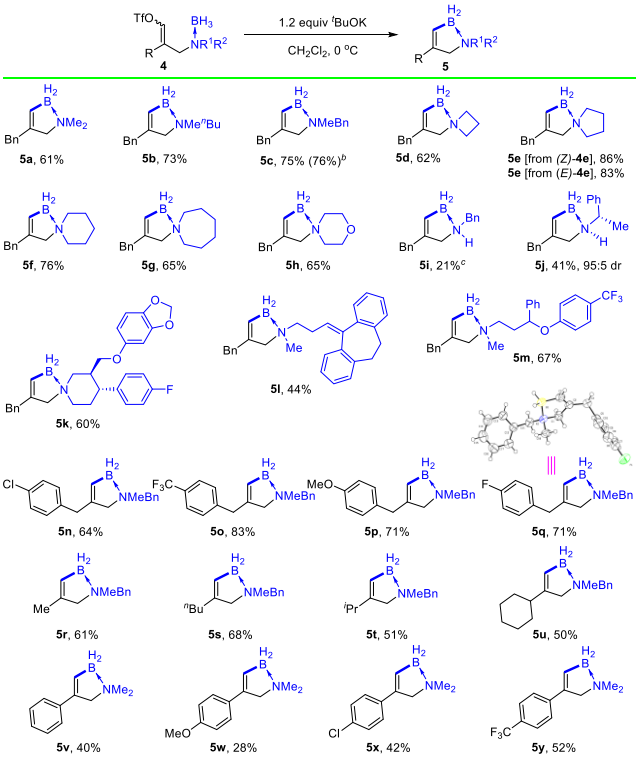
Table 2. Intermolecular B−H Bond Insertion of Alkylidene Carbenes[a]



entry	1	3	yield (%)[b]
1	**1a**	**3aa**	77
2	**1b**	**3ba**	80
3	**1c**	**3ca**	81
4	**1d**	**3da**	73
5	**1e**	**3ea**	63
6	**1f**	**3fa**	79
7	**1g**	**3ga**	47
8	**1h**, *Z*/*E* = 45/55	**3ha**, *Z*/*E* = 63/37	73
9	**1i**, *Z*/*E* = 45/55		72

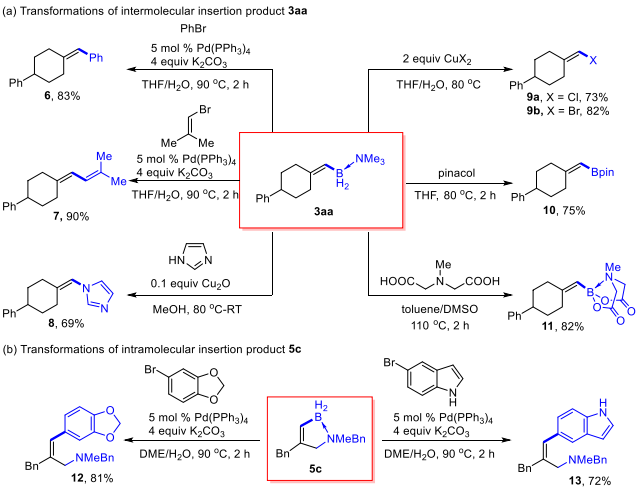
[a]Reaction conditions: **1a**/**2**/^{t}BuOK = 0.3:1.2:0.36 (mmol), in 3 mL CH_2Cl_2 at 0 °C. [b]Isolated yield.

Scheme 2. Intramolecular B−H Bond Insertion of Alkylidene Carbenes[a]



[a]Reaction conditions: **4a**/^{t}BuOK = 0.3:0.36 (mmol), in 3 mL CH_2Cl_2 at 0 °C. [b]Reaction was conducted with 5.5 mmol **4c**, and 1.1 g of **5c** was obtained. [c]Reaction was conducted with 0.5 mmol **4i.**

Scheme 3. Transformations of B−H Bond Insertion Products



bond insertion products but rather phenyl migration by-products. However, an intramolecular reaction of 2-phenyl-substituted alkenyl triflate **4v** afforded phenyl-substituted 1,2-BN-cyclopentene **5v** in 40% yield. To our knowledge, this is the first example of the trapping of a phenyl-substituted alkylidene carbene generated from an alkenyl triflate.[5a,c,7b] Further experiments revealed that a substrate with a strongly electron-withdrawing CF_3 group on the phenyl ring (**4y**) gave a higher yield than one with an electron-donating OMe group (**4w**). The structure of **5q** was confirmed by X-ray diffraction analysis of a single crystal.[9]

The alkenyl borane compounds prepared in this study were stable to common purification procedures (e.g., chromatography and recrystallization) and were stable during long-term storage. More importantly, they could undergo a diverse array of transformations (Scheme 3a). For example, **3aa** underwent Pd-catalyzed Suzuki coupling with both an aryl bromide and an alkenyl bromide to form C−C bonds (**6** and **7**), as well as Cu-catalyzed Ullman coupling with imidazole to form a C−N bond (**8**), and the yields were good in all cases. Reaction of **3aa** with CuX_2 (X = Cl or Br) afforded halide **9a** or **9b** in high yield. In addition, **3aa** could be converted to alkenyl borate **10** or **11** by means of a condensation reaction with pinacol or *N*-methylimidodiacetic acid, respectively.

Intramolecular insertion product **5c** could also undergo Suzuki coupling reactions, affording *Z*-allyl amines **12** and **13** in good yields (Scheme 3b). Allylamines are commonly found in natural products and pharmaceuticals[10] and can serve as multipurpose intermediates in organic synthesis.[11] Moreover, the BN heterocycles obtained by means of this reaction are isosteres of cyclopentene, which is a ubiquitous moiety in natural products and pharmaceuticals.[12] Therefore, our protocol has high potential utility for applications in drug discovery.

To elucidate the reaction mechanism, we carried out a labeling experiment using BH_3 and BD_3 adducts, which showed no kinetic isotope effect (k_H/k_D = 1.01, Scheme 4a), indicating that B−H bond insertion was not involved in the rate-limiting step. However, the result of a labeling experiment using alkenyl triflate **1a** and alkenyl triflate **1a**-*d* with one

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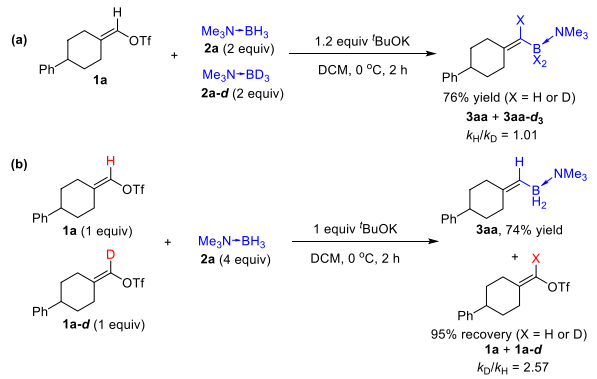
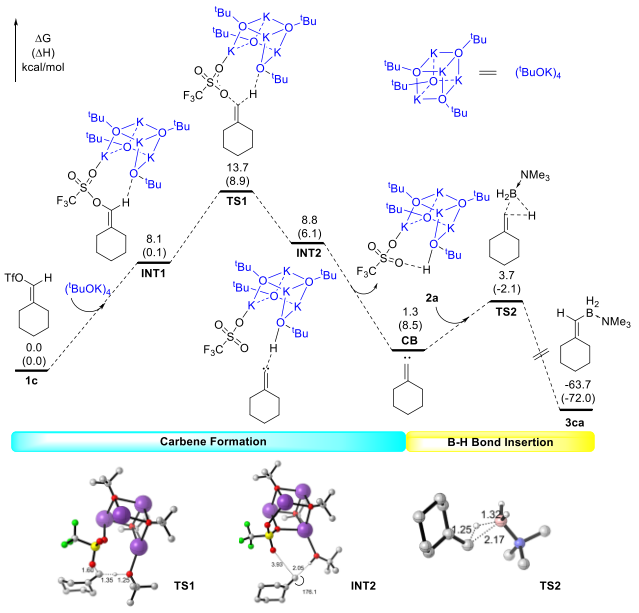
Scheme 4. Kinetic Isotopic Effect Experiments



terminal D (k_D/k_H = 2.57, Scheme 4b) indicated that deprotonation may be involved in the rate-limiting step. Then, we performed the calculations of the B−H bond insertion reaction between alkenyl triflate **1c** and amine−borane adduct **2a** by means of the M06-2X-D3/6-311++G(2df, 2p)//B3LYP/6-31+G(d) method in dichloromethane solution (using the SMD model) with the Gaussian 09 program package (Scheme 5; see the Supporting Information for details). The calculations suggested that the ^{t}BuOK tetramer[13] in DCM facilitates α-elimination of **1c** to generate **INT2** via **TS1**. The activated energy for this step is 13.7 kcal/mol. Once formed, the **INT2** (ΔG = 8.8 kcal/mol) can release the electrophilic alkylidene carbene intermediates **CB** (ΔG = 1.3 kcal/mol), which is a thermodynamically favorable process. This carbene can be captured quickly by trimethylamine−borane **2a** via a concerted process in which cleavage of the B−H bond and formation of the C−H and C−B bonds occur synchronously via a three-membered-ring transition state (**TS-2**), yielding the desired product **3ca**. This B−H bond insertion step has an activated energy of 2.4 kcal/mol, which is much lower than 13.7 kcal/mol for α-elimination step. This calculation indicates that α-elimination rather than B−H bond insertion is the rate-limiting step, a conclusion that is supported by the results of the kinetic isotope effect experiment (Scheme 4). Even both the B−H bond insertion of alkylidene carbenes and hydroboration of alkynes can afford alkenyl boron compounds, the mechanisms of these two reactions are quite different according to calculations.[14]

Scheme 5. Density Functional Theory Calculations: (A) Free Energy Profile for B−H Bond Insertion of 1c and 2a; (B) Optimized Structures of Key Transition States and Intermediate with Key Bond Length (Å)[a]



[a]Trivial H atoms have been omitted for clarity.

In summary, we have developed what is, to our knowledge, the first protocol for B−H bond insertion reactions of unsaturated carbenes. This protocol serves as an efficient method for the construction of C(sp^2)−B bonds, and when used for intramolecular B−H bond insertion reactions of alkylidene carbenes, it constitutes a new strategy for the preparation of BN heterocycles. The acyclic and cyclic alkenyl borane adducts prepared by this method can undergo efficient C−C- and C−X-bond-forming reactions, making these adducts promising synthetic building blocks. Mechanistic studies showed that the B−H bond insertion reaction occurs via a concerted insertion process. Our findings provide a bridge between unsaturated carbene chemistry and organoboron chemistry and can be expected to advance both fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09596.

Experimental procedures and characterization data, computational study results, Cartesian coordinates, and spectral data (PDF)

Crystal data for **5q** (CIF)

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https://dx.doi.org/10.1021/jacs.0c09596
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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Author Contributions

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Notes

The authors declare no competing financial interest.

Metrical parameters for the structures **5q** are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-1908176.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21625204, 21790332, 21532003, 21971119), the "111" project (B06005) of the Ministry of Education of China, and Key-Area Research and Development Program of Guangdong Province (2020B010188001) for financial support. Dedicated to the 100th Anniversary of Chemistry at Nankai University.

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https://dx.doi.org/10.1021/jacs.0c09596
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX