

Catalytic B–H Bond Insertion Reactions Using Alkynes as Carbene Precursors

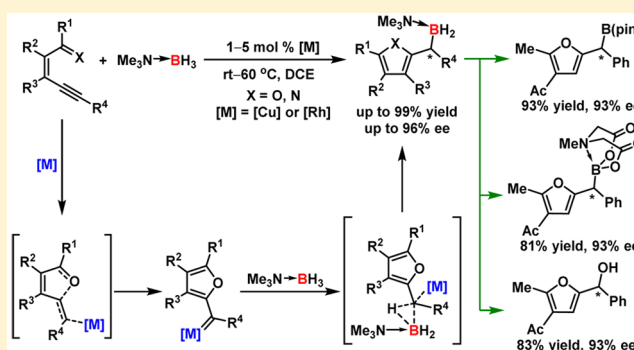
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S Supporting Information

ABSTRACT: Herein, we report transition-metal-catalyzed B–H bond insertion reactions between borane adducts and alkynes to afford organoboron compounds in excellent yields under mild reaction conditions. This successful use of alkynes as carbene precursors in these reactions constitutes a new route to organoboron compounds. The starting materials are safe and readily available, and the reaction exhibits 100% atom-economy. Moreover, an asymmetric version catalyzed by chiral dirhodium complexes produced chiral boranes with excellent enantioselectivity (up to 96% ee). This is the first report of highly enantioselective heteroatom–hydrogen bond insertion reactions of metal carbenes generated in situ from alkynes. The chiral products of the reaction could be easily transformed to widely used borates and diaryl methanol compounds without loss of optical purity, which demonstrates its potential utility in organic synthesis. A kinetics study indicated that the Cu-catalyzed B–H bond insertion reaction is first order with respect to the catalyst and the alkyne and zero order with respect to the borane adduct, and no kinetic isotopic effect was observed in the reaction of the adduct. These results, along with density functional theory calculations, suggest that the formation of the Cu carbene is the rate-limiting step and that the B–H bond insertion is a fast, concerted process.

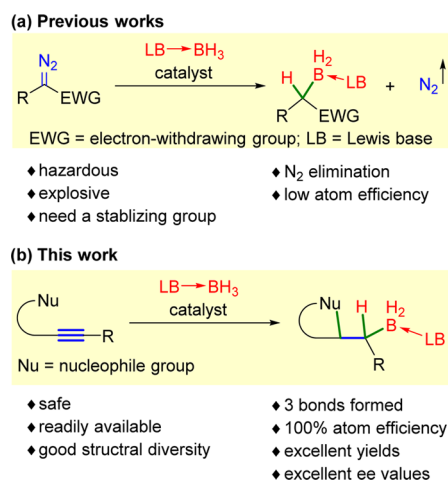


INTRODUCTION

Organoboron compounds have a broad range of applications,¹ and the development of efficient methods for their synthesis is attracting intense interest. Although several powerful methods, such as Brown's hydroboration of olefins,² transition-metal-catalyzed hydroboration of olefins,³ Miyaura's borylation reaction,⁴

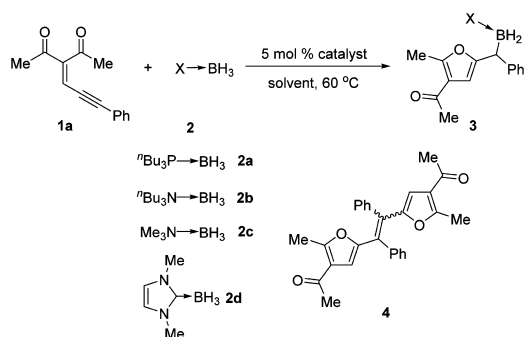
and direct borylation of C–H bonds,⁵ have been established, new efficient reactions for C–B bond formation remain highly desirable to meet the requirements of the diverse syntheses being attempted today. We recently developed a Cu-catalyzed carbene insertion into the B–H bond of amine- and phosphine-borane adducts, which constitutes a straightforward method for the synthesis of diverse α -boryl carbonyl compounds (Scheme 1a).⁶ This method uses highly stable and readily available amine- and phosphine-borane adducts⁷ as boron reagents. Independently, Curran and co-workers reported a Rh-catalyzed B–H bond insertion reaction that uses N-heterocyclic carbene-boranes.⁸ Additional progress has been made in the field of B–H bond insertion reactions through the development of new catalysts, as well as new diazo compounds to serve as carbene precursors.⁹ Although transition-metal-catalyzed B–H bond insertion is a powerful method for the construction of C–B bonds, all of the B–H bond insertion reactions reported to date use metal carbenes generated from diazo compounds. The use of these explosive and toxic compounds restricts the applications of B–H bond insertion reactions, and the paucity of available diazo compounds limits the structural diversity of the organoborane products (Scheme 1a). Thus, the development of

Scheme 1. Transition-Metal-Catalyzed B–H Bond Insertion Reactions



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Table 1. Transition-Metal-Catalyzed B–H Bond Insertion of Alkyne 1a with Borane Adducts 2: Optimization of the Reaction Conditions^a

entry	catalyst	adduct	solvent	time (min)	product	yield (%) ^b
1	IPrAuCl/AgSbF ₆	2a	DCE	10 h	3aa	63
2	AuCl ₃	2a	DCE	10 h	3aa	<5
3	RuCl ₃	2a	DCE	20 h	3aa	37
4	PtCl ₂	2a	DCE	30	3aa	76
5	ZnCl ₂	2a	DCE	12 h	3aa	70
6	[Rh(TFA) ₂] ₂	2a	DCE	30	3aa	89
7	CuCl	2a	DCE	10	3aa	89
8	CuCl ₂	2a	DCE	10	3aa	76
9	CuCl	2a	CH ₂ Cl ₂	10	3aa	79
10	CuCl	2a	CHCl ₃	10	3aa	83
11	CuCl	2a	toluene	10	3aa	84
12	CuCl	2a	THF	10	3aa	79
13	CuCl	2b	DCE	10	3ab	88
14	CuCl	2c	DCE	10	3ac	98
15	CuCl	2d	DCE	10	3ad	60
16	CuCl	HBpin	DCE	2 h	4	93
17 ^c	CuCl	2c	DCE	10	3ac	97
18 ^d	CuCl	2c	DCE	10	3ac	98

^aReaction conditions: catalyst/1a/2 = 0.01:0.2:0.4 (mmol), in 2 mL of solvent at 60 °C. TFA = trifluoroacetate. ^bIsolated yield. ^cReaction was conducted with 40 mmol 1a, and 1.1 g of 3ac was obtained. ^dUsed 1 mol % catalyst.

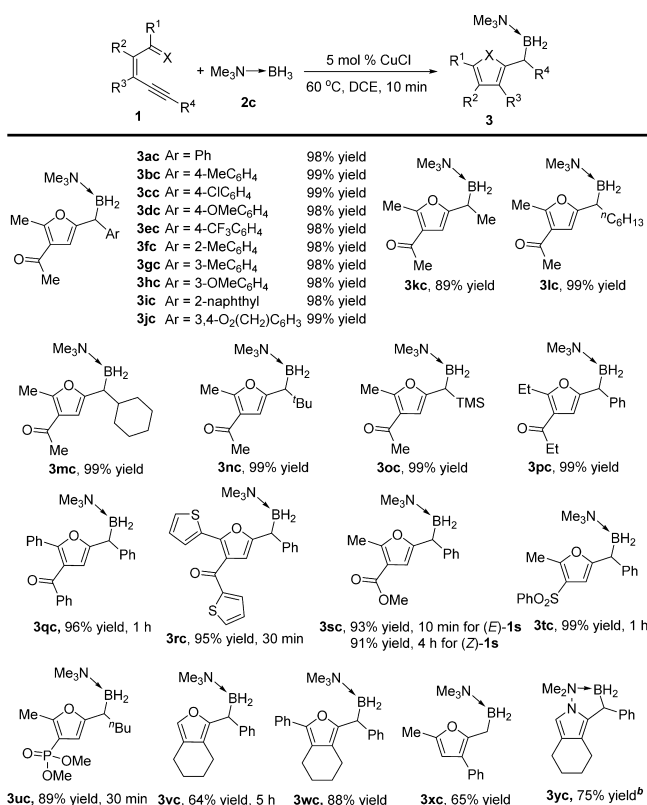
new metal carbene sources is necessary to improve the utility of this method.

Transition-metal-catalyzed carbophilic activation of alkynes is an efficient tool for the construction of complex structures from simple alkynes and has been widely used in organic synthesis during the past decade.¹⁰ Electrophilic metal carbene intermediates are thought to be formed in many reactions of alkynes with transition-metal catalysts. Compared with traditional transition-metal-catalyzed decomposition of diazo compounds, the generation of metal carbenes from alkynes would be more environmentally friendly and atom economical. We envisioned that if metal carbenes generated from alkynes could be trapped by boron adducts, the diversity of products available via B–H bond insertion reactions would be greatly enhanced (Scheme 1b).

Herein, we report the first transition-metal-catalyzed B–H bond insertion reactions between borane adducts and conjugated alkynes. The B–H bond insertion reactions of enyne-carbonyls¹¹ and enyne-imino compounds¹² with borane adducts proceeded smoothly in the presence of a simple copper salt (CuCl) as a catalyst under mild conditions, providing various furan- and pyrrole-2-ylmethylboranes in good to excellent yields (>95% in most cases). By using chiral dirhodium catalysts, we also realized an asymmetric version of the reaction with excellent enantioselectivity (up to 96% ee).

RESULTS AND DISCUSSION

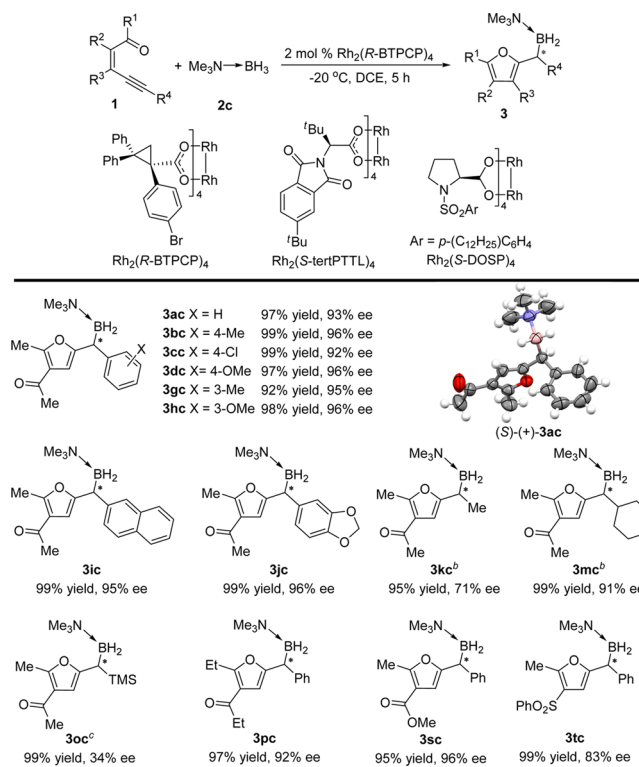
We began by carrying out the reaction of enyne-ketone 1a with phosphine-borane adduct 2a in the presence of 5 mol % IPrAuCl/AgSbF₆ (IPr = 1,3-bis(2',6'-diisopropylphenyl)imidazol-2-ylidene) in 1,2-dichloroethane (DCE) at 60 °C (Table 1). To our delight, desired furan-2-ylmethylborane 3aa was obtained in 63% yield (entry 1). In addition to IPrAuCl, other catalysts, such as RuCl₃, PtCl₂, ZnCl₂, [Rh(TFA)₂]₂, CuCl, and CuCl₂, also promoted the B–H bond insertion reaction (entries 2–8). Of these, CuCl gave the highest yield and the fastest reaction rate. Reactions performed in CH₂Cl₂, CHCl₃, toluene, and THF gave essentially the same outcome as reaction in DCE (entries 9–12). In addition to phosphine-borane adduct 2a, amine-borane adducts 2b and 2c and N-heterocyclic carbene-borane adduct 2d were also suitable borane reagents (entries 13–15). Borane adduct 2c, with less sterically hindered trimethylamine, afforded the highest yield (98%, entry 14). In contrast, pinacolborane (HBpin) did not give the desired B–H bond insertion product; instead, only a 2:3 Z/E mixture of furyl dimer 4 was isolated (93% yield, entry 16). The reaction could be performed on a gram scale with no decrease in the yield, which demonstrates the potential utility of this protocol (entry 17). Moreover, the catalyst loading could

Scheme 2. CuCl-Catalyzed B–H Bond Insertion of Ene-yne-Carbonyls or Iminos 1 with Amine-Borane Adduct 2c^{a,b}

^aReaction conditions: $\text{CuCl}/1/2c = 0.01:0.2:0.4$ (mmol), in 2 mL of DCE at 60 °C. The reaction completed within 10 min unless otherwise noted. ^bX = N-NMe₂. Reaction conditions: $\text{CuCl}/1y/2c = 0.04:0.2:0.4$ (mmol), 80 °C, 1.5 h

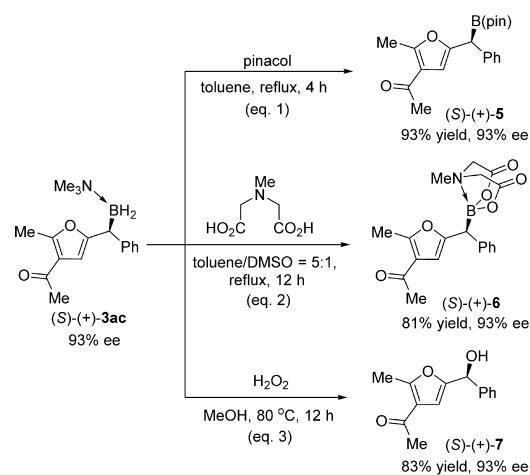
be reduced to 1 mol % without compromising either the reaction rate or the yield (entry 18).

Various ene-yne-carbonyls 1 were then evaluated in the B–H bond insertion reaction with amine-borane adduct 2c under the optimized reaction conditions (Scheme 2). Generally speaking, the reaction had a broad substrate scope and good functional group tolerance. Most of the reactions were complete within 10 min and afforded the desired B–H bond insertion products in almost quantitative yields. The electronic and steric properties of R⁴ had only a slight effect on the reaction rate and yield (3ac–3oc). Notably, silaboronate 3oc, which is a useful synthon but is difficult to prepare,¹³ was obtained from this reaction in excellent yield (99%). In addition to acetyl (3ac–3oc), R² could also be propionyl (3pc), benzoyl (3qc), thienoyl (3rc), ester (3sc), sulfonyl (3tc), phosphonate (3uc), alkyl (3vc, 3wc), or even H (3xc). With less-electron-deficient R² substituents, such as H and alkyl groups, the yields were slightly lower. The carbonyl moiety of substrate 1 could be an alkyl ketone (R¹ = alkyl), an aryl ketone (R¹ = aryl), or even an aldehyde (R¹ = H). It is worth mentioning that both (E)- and (Z)-1s gave desired product 3sc in essentially the same yield, although (Z)-1s required a longer reaction time for full conversion. In addition to ene-yne-carbonyls, an ene-yne-imino compound underwent a B–H bond insertion reaction with amine-borane adduct 2c to produce 2-boryl-substituted pyrrole 3yc in good yield. Interestingly, in product 3yc, the trimethylamine moiety of borane adduct 2c has been replaced by the pyrrole-dimethylamine to form a stable B-hetero five-membered ring.

Scheme 3. Rh-Catalyzed Asymmetric B–H Bond Insertion Reaction of Ene-yne-carbonyls 1 and Trimethylamine-Borane Adduct 2c^{a,b,c}

^aReaction conditions: $[\text{Rh}]/1/2c = 0.004:0.2:0.4$ (mmol), in 2 mL of DCE at –20 °C. ^bUsed Rh₂(S-tertP TTL)₄ as catalyst, in CHCl₃, at –30 °C. ^cUsed Rh₂(S-DOSP)₄ as catalyst, 24 h.

Scheme 4. Transformations of B–H Bond Insertion Product 3ac



We next investigated the asymmetric version of this B–H bond insertion reaction. Copper complexes with chiral ligands exhibited very low enantioselectivity, whereas the chiral dirhodium complexes,¹⁴ Rh₂(R-BTPCP)₄ and Rh₂(S-tertP TTL)₄, afforded excellent yields (92–99%) and high enantioselectivities (>90% ee with few exceptions) in reactions between various ene-yne-carbonyls and amine-borane adduct 2c (Scheme 3). When the R⁴ substituent was a hindered trimethylsilyl group, the product 3oc was also obtained in high yield but with modest ee value. The structure and absolute configuration of (S)-(+)-3ac were

determined by X-ray diffraction of a single crystal.¹⁵ This asymmetric reaction constitutes a new strategy for the construction of a C–B bond with high enantioselectivity. To our knowledge, this is the first report of a highly enantioselective heteroatom–hydrogen bond insertion reaction of metal carbenes generated in situ from alkynes.^{10,11,16}

Borane (+)-**3ac** could be easily converted into borates **5** and **6** by means of simple condensation reactions with pinacol and *N*-methyl imidodiacetic acid (MIDA), respectively (Scheme 4, eqs 1 and 2), and to diaryl methanol **7** by oxidation with H₂O₂ (eq 3). All of these transformations proceeded in high yield with retained optical purity. Because chiral alkylpinacolborates and alkyl-MIDA-borates,^{1,17} as well as diaryl methanol compounds,¹⁸ are useful reagents in organic synthesis, the present B–H bond insertion reaction has high potential for broad applicability.

MECHANISTIC CONSIDERATIONS

To determine the reaction mechanism, we studied the kinetics of the Cu-catalyzed B–H bond insertion reaction between alkyne **1a** and amine-borane adduct **2c** by using in situ IR

spectroscopy at various concentrations of the reaction components to observe the initial rate of the reaction (Figure 1). First-order kinetics were observed for the CuCl catalyst and for alkyne **1a** (Figure 1A,B, respectively). In contrast, zero-order kinetics were observed for **2c** (Figure 1C). The kinetics profiles suggest that CuCl and **1a** are involved in the rate-limiting step ($r = k[\mathbf{1a}][\text{CuCl}]$). We also performed kinetic isotope effect experiments by using in situ IR (Figure 2). The nearly identical profiles of amine-borane adducts **2c** and **2c-d₃** indicate that there was no isotope effect ($k_{\text{H}}/k_{\text{D}} = 1$) in the B–H bond insertion reaction. The results of these kinetics experiments suggest that neither B–H bond cleavage nor C–H bond formation is involved in the rate-limiting step.

COMPUTATIONAL STUDIES

To elucidate the details of the reaction mechanism, we conducted density functional theory calculations (Gaussian 09) on the CuCl-catalyzed reaction of alkyne **1a** and amine-borane adduct **2c** (Figure 3). The calculations indicated that the initial step is coordination of CuCl with **1a** to form chelation complex **8** spontaneously. Then, another molecule of **1a** coordinates to

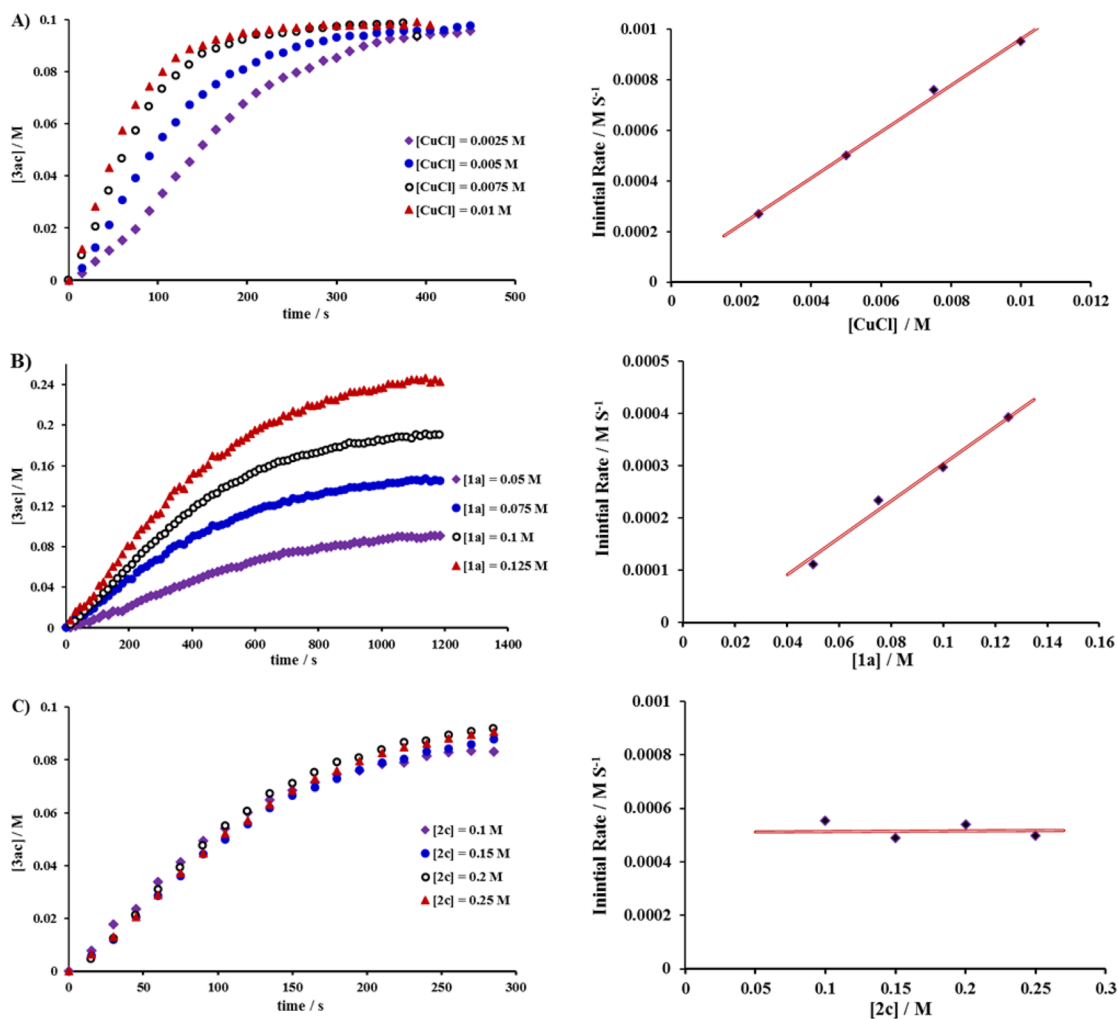


Figure 1. Kinetic profiles of Cu-catalyzed B–H bond insertion reaction of **1a** and **2c**. (A) Kinetic profiles of different initial concentrations of CuCl (from 0.0025 to 0.01 M). Reaction conditions: **1a** (0.1 M), **2c** (0.2 M), carried out in DCE (4 mL) at 30 °C. (B) Kinetic profiles of different initial concentrations of **1a** (from 0.05 to 0.125 M). Reaction conditions: **2c** (0.2 M), CuCl (0.005 M), carried out in DCE (4 mL) at 5 °C. (C) Kinetic profiles of different initial concentrations of **2c** (from 0.1 M to 0.25 M). Reaction conditions: **1a** (0.1 M), CuCl (0.005 M), carried out in DCE (4 mL) at 30 °C.

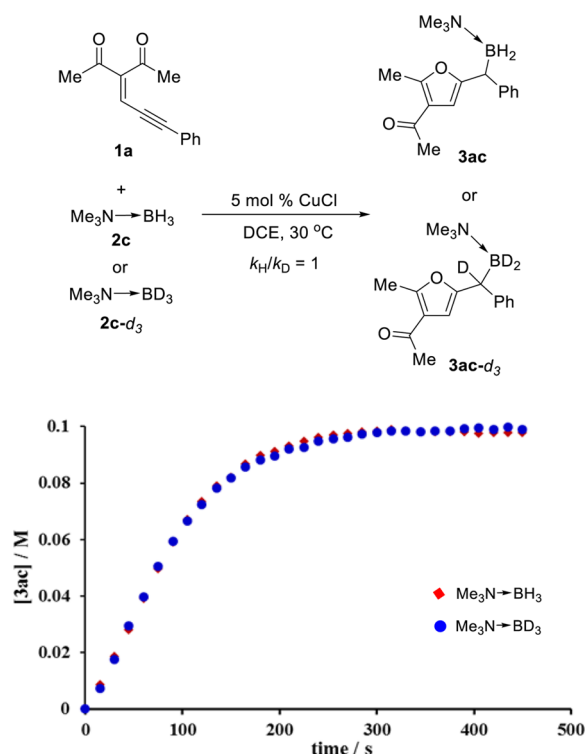


Figure 2. Investigation of kinetic isotope effect. Reaction conditions: **1a** (0.1 M), **2c** or **2c-d₃** (0.2 M), CuCl (0.005 M), carried out in DCE (4 mL) at 30 °C.

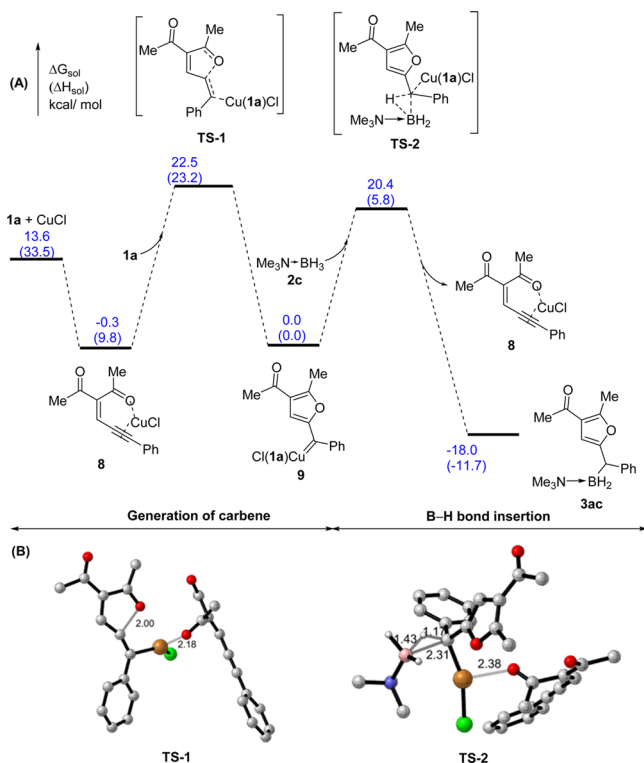


Figure 3. (A) Free energy profile for CuCl-catalyzed B–H bond insertion of **1a** and **2c**. (B) Optimized structures of key stationary points with key bond length (in Å). Trivial H atoms have been omitted for clarity.

the Cu atom of **8** to release the carbonyl group of the pre-coordinated **1a** molecule. The released carbonyl group attacks

the Cu-activated alkyne via **TS-1** to generate electrophilic Cu-carbene intermediate **9**. Intermediate **9** reacts with amine-borane adduct **2c** via a concerted process, in which B–H bond cleavage and formation of the C–H and C–B bonds take place synchronously via a three-membered-ring transition state (**TS-2**), generating the desired product and releasing the catalyst associated with a molecule of **1a**, which can start another catalytic cycle. The calculations showed that the free energy of activation for the generation of carbene species (**8-TS-1-9**) is 2.1 kcal/mol higher than that of the B–H bond insertion step (**9-TS-2-3ac**). This result clearly indicates that Cu-carbene formation rather than B–H bond insertion is the rate-limiting step, which is supported by the results of the kinetics experiments (Figures 1 and 2).

CONCLUSION

In summary, a transition-metal-catalyzed B–H insertion reaction of borane adducts and alkynes was realized. Using this reaction, we efficiently synthesized various furan-2-ylmethylboranes in high yield and excellent enantioselectivity starting from safe and readily accessible ene-yne-carbonyl carbene precursors and borane adducts under mild reaction conditions. The B–H bond insertion products could be easily converted to widely used pinacolborates, MIDA borates, and diaryl methanol compounds. Kinetics experiments showed that the reaction is first order with respect to the concentrations of the Cu catalyst and the alkyne substrate and zero order with respect to the concentrations of the borane adduct. Both the kinetics experiments and density functional theory calculations suggest that formation of a metal carbene is involved in the rate-limiting step and that B–H bond insertion is a fast, concerted process. This successful use of alkynes as carbene precursors in B–H bond insertion reactions opens up a new route to organoboron compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13168.

Experimental procedures and spectral data (PDF)

Metrical parameters for the structure (S)-(+)-**3ac** (CIF)

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Notes

The authors declare no competing financial interest.

Metrical parameters for the structure (S)-(+)-**3ac** are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-1531867.

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