Site-Fixed Hydroboration of Alkenes under Metal-Free Conditions: Scope and Mechanistic Studies

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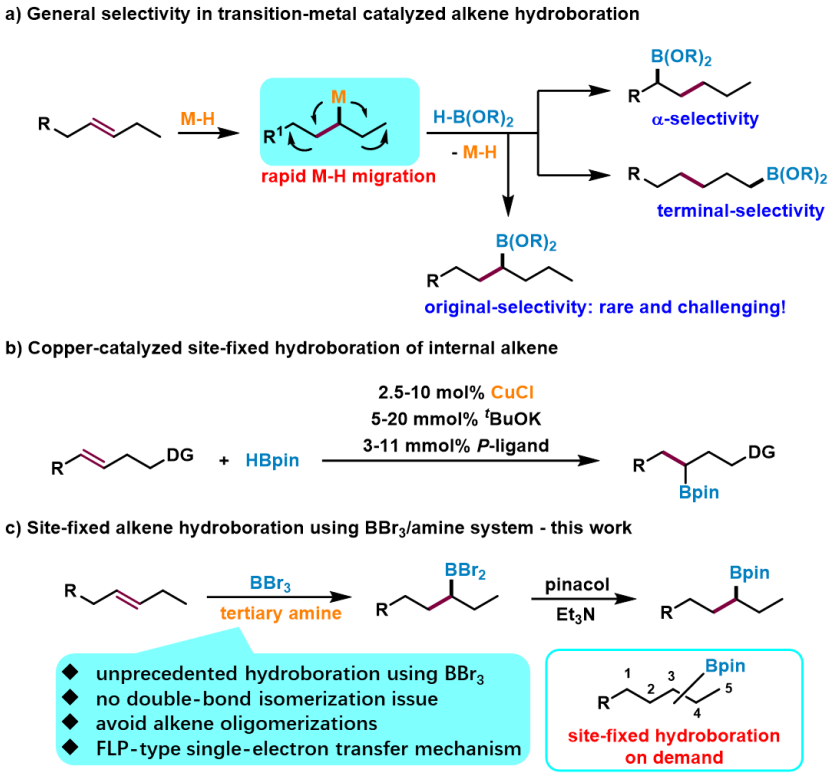
ABSTRACT: An unprecedented and general metal-free hydroboration of alkenes with BBr_3 as the boration reagent in the presence of $^{i}Pr_2NEt$ is reported. The addition of $^{i}Pr_2NEt$ not only suppresses alkene oligomerization and bromoboration side reactions, but also provides a proton source for hydroboration. More importantly, the site-fixed installation of a boryl group at the original position of the internal double-bond is easily achieved using our strategy as compared with traditional transition-metal-catalyzed hydroboration processes. Preliminary studies on the mechanism revealed a distinct reaction pathway that involves radical species and may operate through frustrated-Lewis-pair-type single-electron transfer.

Organoboronates are synthetically valuable compounds used for a wide range of transformations due to their relative stability, high functional group compatibility, and versatile reactivity.[1] Boron-containing molecules also play key roles in medicinal chemistry and material science.[2] Remarkable progress has been made for boronate synthesis through advances in reaction design, catalysis development, and system optimization.[3] These include, for instance, the transition-metal-catalyzed boration of (pseudo)halides,[4] direct C–H boration of (hetero)arenes or alkanes,[5] and carbene insertion into B–H bonds, *etc*.[6] Among them, the catalytic hydroboration of alkenes with borane (H-BR_2), is a common route for the construction of C–B bonds because it offers advantages of both atom economy and wide substrate availability.[7] However, despite the great advances in alkene hydroboration, the site-fixed introduction of a boron moiety at the original position of an internal double-bond remains challenging. Traditional catalyst-free hydroboration of internal alkene with BH_3 produces internal boronate esters, but with no regioselectivity and low functional group tolerace.[8] Although improved regioselectivity could be obtained with HBcat, an elevated reaction temperature (100 °C) was required.[9] It is expected that with transition-metal catalyst, a mild reaction condition could be achieved. However, only a few transition-metals catalyzed site-fixed hydroboration of internal alkenes were known, mainly due to the competitive alkene isomerization which mostly led to the installation of boron moieties at the activated α-carbon of an aryl or boryl unit or at the less-hindered terminal position or mixture of isomers (Scheme 1a). In this respect, copper catalyst, literally occurs without competing alkene isomerization, were shown to be a promising candidate as were demonstrated by Hoveyda,[10] Hartwig,[11] and Yun (Scheme 1b).[12] Hence, a general approach that incorporates a boryl group exclusively at the original double-bond position of terminal and internal alkenes remains elusive and more work are needed.

Apart from rational ligand design, system development and chose of suitable transition metals, we envision that another possible strategy to avoid double-bond isomerization, is to use a boron reagent that does not containing or produce B–H species during the reaction.[13] Noting the emerging application of BX_3 (X = Cl, Br) in the intramolecular borylative cyclization[14] and C–H bond borations,[15] we decided to explore the possibility of using BX_3 as alkene hydroboration reagent. Indeed, the reaction of BBr_3 with alkynes and allenes has been reported, which, however, resulted in *syn* addition of the B–Br bond to the unsaturated bonds (known as the bromoboration reaction).[16] In the presence of stoichiometric amount of silanes, the reaction of BBr_3 with alkene was achieved

via $HBBr_2$, which was formed in-situ.[17] An substrate-limited classic electrophilic boration of terminal alkenes with BBr_3 in the presence of 2,6-disubstituted pyridines to vinyl boronate esters was reported.[18] Thus, there is no general system available yet for the application of BBr_3 in alkene hydroboration given the challenges of chemoselectivity, functional group tolerance, and general substrate scope. Herein, we report our finding of a mechanism distinct utilization of BBr_3 as hydroboration reagent of a wide range of alkene under metal-free conditions. More importantly, using our strategy, the exclusive installation of a boron moiety at the original double-bond position of internal alkenes is achieved (Scheme 1c). Studies on the mechanism indicate a reaction pathway that might operate via frustrated Lewis pair (FLP)-type single-electron transfer.[19]

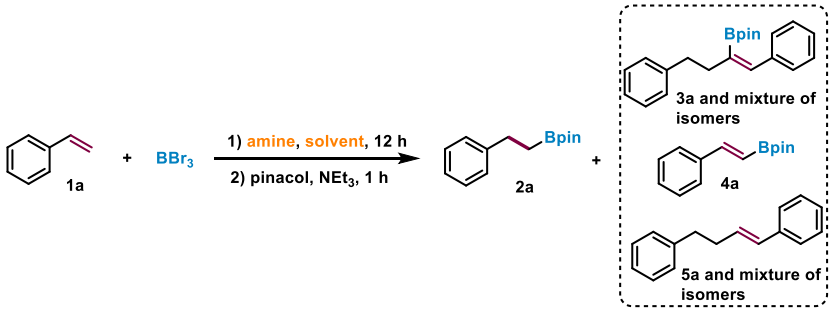


Scheme 1. Site-Fixed Hydroboration of Alkenes: Challenges and Our Strategy.

To apply BBr_3 as an efficient boron source in alkene hydroboration, we first need to prevent the alkene oligomerization and bromoboration side reactions. We considered the addition of an amine source would tune the acidity of BBr_3. In addition, it is known that boron-containing Lewis acids can be used to abstract a hydrogen atom from the α-position of a tertiary alkylamine;[20] hence, it is expected that the addition of a tertiary amine will not only tune the acidity of the system but also provide a proton source for the hydroboration. To test our hypothesis, the reaction of styrene (0.2 mmol) with BBr_3 (1.0 M in dichloromethane (DCM), 1.5 equiv.) and tertiary amine (3 equiv.)

was selected as a model. However, when the reaction was conducted with Et_3N, Bn_3N, or $^nPr_3N$ at room temperature for 12 h, almost no conversion was observed (Table 1, entries 1–3). As expected, without tertiary amine, styrene dimerization product **5a** and its boration product **3a** with their isomers were obtained in around 8% yield with no detection of any styrene left on GC/MS which indicated that the rest styrene might be oligomerized (entry 4) (formation of product **3a**, **5a** or their isomers was unambiguous confirmed by the GC-MS spectra, please see the supporting information GC-MS spectra section); this was also the case when Ph_3N was added (entry 5). Using 2,6-lutidine as the amine source, only 25% of the classic electrophilic boration product **4a** was produced (entry 6). Interestingly, when $^iPr_2NEt$ was added, 80% of the target alkyl boronate ester was observed with no detectable side products **3a**–**5a** (entry 7). Changing the solvent from DCM to toluene, hexane, or dichloroethane (DCE), or replacing BBr_3 (1.0 M in DCM) with $BBr_3{\cdot}SMe_2$ all gave inferior results (entries 8–11). Interestingly, we found that our strategy also worked for BCl_3, in which case 75% of **2a** was obtained (entry 12).

Table 1. Effect of Amine and Solvent in the Hydroboration of Styrene with BBr_3[a]



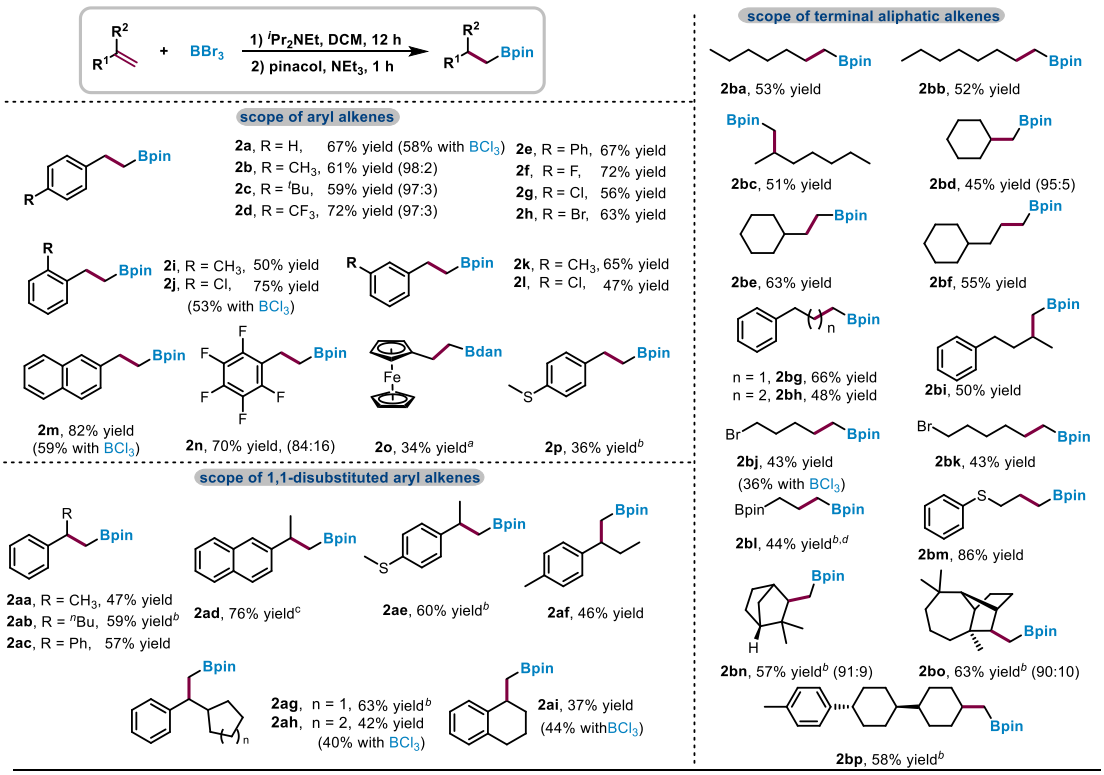
Entry	Amine	Solvent	Yield **2a** [%][b]	Side products
1	Et_3N	DCM	-	trace **3a**
2	Bn_3N	DCM	-	trace **3a**
3	$^nPr_3N$	DCM	-	-
4	-	DCM	-	8% **3a** and **5a** (1:9)
5	Ph_3N	DCM	-	8% **3a**
6	2,6-lutidine	DCM	-	25% **4a**
7	**$^iPr_2NEt$**	**DCM**	**80**	**-**
8	$^iPr_2NEt$	toluene	31	-

9	$^{i}Pr_2NEt$	hexane	26	-
10	$^{i}Pr_2NEt$	DCE	12	-
11[c]	$^{i}Pr_2NEt$	DCM	23	-
12[d]	$^{i}Pr_2NEt$	DCM	75	-

[a]Reaction conditions: 0.2 mmol **1a**, BBr_3 (1.0 M in DCM, 1.5 equiv.), amines (3 equiv.), and 1 mL DCM in a 5 mL glass crimp vial at 0 °C - rt for 12 h and then pinacol and Et_3N were added and stirred for another 1 h; [b]yields of **2a** were determined by GC/MS with dodecane as internal standard; [c]$BBr_3 \cdot SMe_2$ was used; [d]BCl_3 (1.0 M in DCM, 1.5 equiv.) was used.

Under the optimized reaction conditions (Table 1, entry 7), we then studied the substrates generality of our strategy. First, the reaction with terminal aryl alkenes was performed, we were pleased to find that our methodology worked well for a series of electronically and sterically varied aryl alkenes (Scheme 2). Substrates with –Me, –^{t}Bu, –CF_3, or –Ph groups at various positions on the phenyl ring reacted smoothly in our system with moderate to good yields (**2a**–**e**, **2i**, **2k**, 50–72% isolated yields) and >97% regioselectivities. The use of halogen-substituted aryl alkenes selectively produced the corresponding hydroboration product without side reactions arising from C–X bonds (**2f**–**h**, **2j**, **2l**). In addition, vinyl naphthalene and pentafluorostyrene gave boronate esters **2m** and **2n** in yields of up to 82%. Vinyl ferrocene and methyl(4-vinylphenyl)sulfane also reacted, albeit with lower yields (**2o**, **2p**).

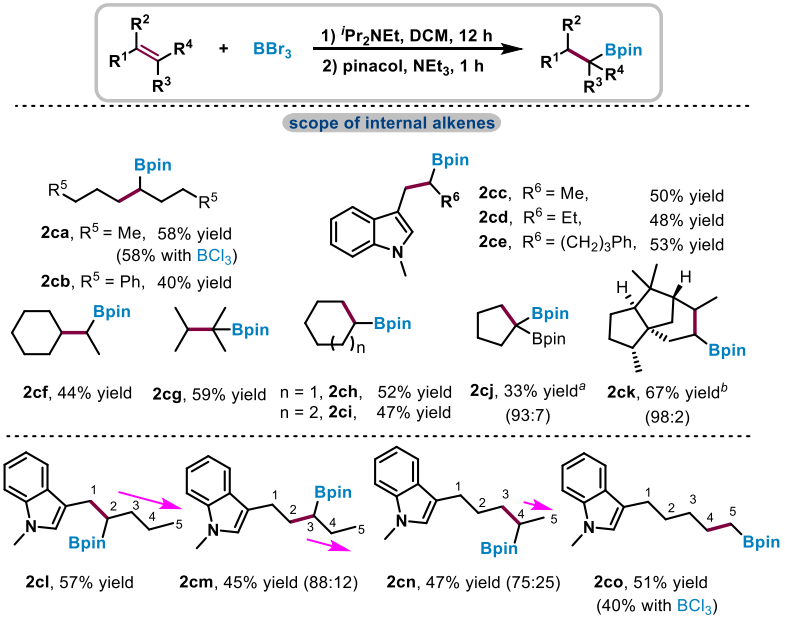
The substrate scope with respect to 1,1-disubstituted aryl alkenes was then studied. In general, α-methyl-substituted alkenes containing electronically varied aryl groups reacted smoothly, and yields up to 76% were obtained (**2aa**, **2ad**–**2af**). Moreover, changing the α-substituent from –Me to –^{n}Bu and –Ph resulted in higher yields (**2ab**, **2ac**). In addition, alkenes with sterically varied cyclic aliphatic substituents reacted without problems (**2ag**–**2ai**). We then applied our protocol to long-chain aliphatic alkenes and found that it worked with a series of bulk aliphatic alkenes with different carbon lengths (**2ba**–**2bc**) and substituents such as cyclohexyl-, and phenyl-substituted aliphatic alkenes (**2bd**–**2bi**). Noticed that, for bromide-substituted aliphatic alkenes, the -Br was kept intact (**2bj**-**2bk**). In addition, allyl boronate ester and alkenes containing *sulfur*-atom gave the corresponding product in up to 86% yields (**2bl**-**2bm**). Furthermore, bio-derived alkenes such as camphene or longifolene, and alkenes from 4′-tolyl-bicyclohexyl-4-one reacted well in our system with > 90% linear selectivity (**2bn**–**2bp**).



Scheme 2. Reaction conditions: 0.2 mmol alkenes, BBr_3 or BCl_3 (1.0 M in DCM, 1.5 equiv.), $^{i}Pr_2NEt$ (3 equiv.), and 1 mL DCM in a 5 mL glass crimp vial at 0 °C - rt for 12-24 h and then pinacol and Et_3N were added and stirred for another 1h, yields of isolated products are given. [a]use 1,8-diaminonaphthalene instead of pinacol; [b]60 °C for 48 h; [c]80 °C for 48 h; [d]NMR yield against anisole.

With the successful installation of the boronate unit at the terminal position of alkenes, we then further explored the possibility of applying our system for the site-fixed installation of a boronate unit at the original double-bond position of internal alkenes (Scheme 3). The reaction with 4-octene regioselectively produced the corresponding alkyl boronate **2ca** in 58% yield. (*E*)-1,6-Diphenylhex-3-ene underwent similar transformations without issue (**2cb**). In addition, for *N*-methyl-indole-substituted internal alkenes with methyl or ethyl group attached to other side of the double-bonds, regioselective hydroboration took place at the β-position to the indole group (**2cc**, **2cd**); this was also the case when a longer carbon chain was attached (**2ce**). Moreover, sterically bulkier tris- and tetra-substituted internal alkenes were hydroborated without problems to give products **2cf** and **2cg**, respectively, in up to 59% yield. The strategy was also applicable to cyclic internal alkenes such as cyclohexene and cycloheptene (**2ch**, **2ci**). Interestingly, for cyclic vinyl boronate ester, selective boration at the α-position of the bulky –Bpin group was observed (**2cj**). In addition, for bio-derived internal alkenes α-cedrene, 67% of the corresponding boronate ester **2ck** was obtained. Finally, to

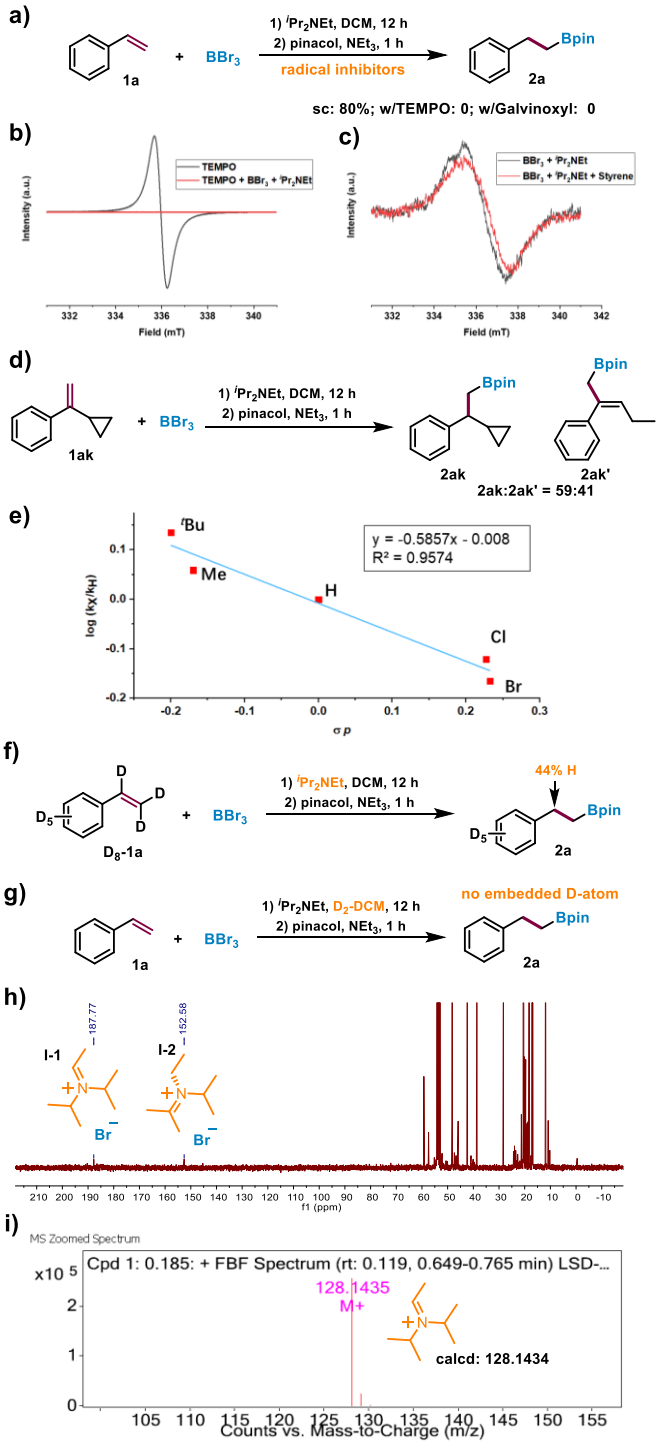
best demonstrate our strategy for site-fixed hydroboration of alkenes, substrates bearing double-bonds at different positions were applied, and the regioselective hydroboration along the carbon chain at 2-, 3-, 4-, and 5-positions was achieved (**2cl**–**2co**) (Scheme 3). It is also noteworthy to mention that several substrates were also tested using BCl_3 as the boration reagent, though slightly lower yields were obtained, those results best demonstrated the application generality of our strategy and indicated a distinct mechanism difference with traditional electrophilic boration reactions.[14a-c]



Scheme 3. Reaction conditions: 0.2 mmol alkenes, BBr_3 or BCl_3 (1.0 M in DCM, 1.5 equiv.), $^{i}Pr_2NEt$ (3 equiv.), and 1 mL DCM in a 5 mL glass crimp vial at 0 °C - rt for 12-48 h and then pinacol and Et_3N were added and stirred for another 1h, yields of isolated products are given. [a]60 °C for 48 h; [b]80 °C for 48 h.

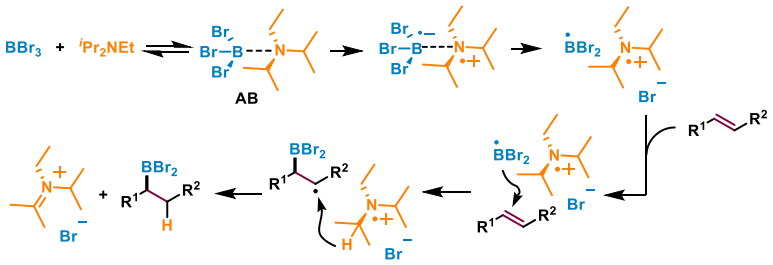
To understand the reaction mechanism, several control experiments were conducted. First, when radical inhibitors such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-[(3,5-di-*tert*-butyl-4-λ1-oxidanylphenyl)methylidene]cyclohexa-2,5-dien-1-one (galvinoxyl) were added, inhibition of the reaction was observed (Scheme 4a). A complete lack of electron paramagnetic resonance (EPR) signal from the reaction mixture was also noted with the addition of TEMPO (Scheme 4b). Furthermore, by adding 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) (0.5 equiv.) into a solution of BBr_3/$^{i}Pr_2NEt$ or BBr_3/$^{i}Pr_2NEt$/styrene, EPR active signals were detected, which implies the formation of radical species (Scheme 4c). The involvement of radical species was also confirmed using **1ak** as a radical clock reaction substrate; in this case, the ring-opening product **2ak′** was detected in addition to the hydroboration product **2ak** (Scheme 4d). To assess the potential

electronic effect of the radical process, the reaction of an electronically different set of *p*-substituted styrene with BBr_3 was carried out. A Hammett plot was constructed, the results revealed a linear correlation between the $\log(k_X/k_H)$ and the Hammett constants (σ_p) of the para-substituents with a negative slope of −0.59. The Hammett plot signifies the electrophilic nature of the radical intermediate (Scheme 4e). When D_8-styrene was reacted with BBr_3 in the presence of $^{i}Pr_2NEt$, 44% H-incorporation into the β-position of **2a** was identified (Scheme 4f). The possible H-atom source should be $^{i}Pr_2NEt$ or dichloromethane. Thus, the reaction of styrene in D_2-dichloromethane was conducted, and we found no D-incorporation in product **2a** (Scheme 4g). Furthermore, analyzing the reaction solution of mixed BBr_3/$^{i}Pr_2NEt$ by ^{13}C NMR spectroscopy, two peaks at 187.8 and 152.6 ppm signaled the possible presence of iminium species **I-1** or **I-2** (Scheme 4h). Altogether, the deuterium-labeling experiments and the formation of iminium species indicated that the H-atom came from $^{i}Pr_2NEt$. Finally, the presence of iminium species was further confirmed by ESI-MS analysis (Scheme 4i).



Scheme 4. Mechanism studies: a) addition of different radical inhibitor into the standard reaction; b) EPR spectra of 0.1 mmol tempo with (—) and without (–) 0.3 mmol of BBr_3 and 0.3 mmol $^{i}Pr_2NEt$ in a mixture of 1 mL of DCM and 1 mL of toluene; c) EPR spectra of 0.1 mmol of DMPO with 0.3 mmol of BBr_3 and 0.6 mmol $^{i}Pr_2NEt$ in a mixture of 1 mL of DCM and 1 mL of toluene with (—) and without (–) 0.2 mmol styrene; d) radical clock reaction with substrates **1ak** at 0.2 mmol scales under standard reaction conditions; e) Hammett plot of different set of *p*-substituted styrene; f) deuterium-labeling experiments with D_8-styrene; g) standard reaction with styrene and use D_2-dichloromethane as solvent; h) ^{13}C NMR spectrum of 0.3 mmol BBr_3 and 0.6 mmol $^{i}Pr_2NEt$ in 1 mL of D_2-dichloromethane; i) ESI-MS spectrum of 0.3 mmol BBr_3 and 0.6 mmol $^{i}Pr_2NEt$ with 0.2 mmol styrene in 1 mL of dichloromethane.

Based on the abovementioned observations and recent reports on single-electron transfer of FLP chemistry[19] and boryl radical formations,[21] a tentative reaction pathway involving the formation of radical species was proposed (Scheme 5). First, complexation of BBr_3 with $^{i}Pr_2NEt$ forms a Lewis acid–base adduct **AB**. The reversible formation of **AB** at room temperature was crucial for the single-electron transfer FLP chemistry to take place, which was confirmed by ^{11}B NMR spectroscopy studies (Figure S7). Then single-electron transfer between $^{i}Pr_2NEt$ and BBr_3 by transferring one electron from $^{i}Pr_2NEt$ to form the amine radical cation and BBr_3 radical anion. Subsequent cleavage of $BBr_3^{\cdot-}$ radical anion forms a $BBr_2^{\cdot}$ radical and Br^-, the presence of Br^- was also confirmed by the ^{11}B NMR signal of BBr_4^- (Figure S8). The $BBr_2^{\cdot}$ radical then adds to the double bond of the alkene to form a new alkyl radical, which abstracts a H-radical from the amine radical cation to give the final hydroboration product.



Scheme 5. Tentatively proposed reaction pathway.

In summary, we have developed a transition-metal-free alkene hydroboration system simply using BBr_3 as the boration reagent in the presence of $^{i}Pr_2NEt$. The addition of $^{i}Pr_2NEt$ not only suppresses the alkene oligomerization and bromoboration side reactions but also plays a key role in the hydroboration reaction by providing a proton source. A series of alkenes, including aryl alkene, 1,1-disubstituted alkenes, aliphatic alkenes, and bio-derived alkenes were readily hydroborated. More importantly, the site-fixed installation of the boryl group at the original position of the internal alkene was also realized, which is otherwise difficult to achieve using traditional transition-metal catalysts. Studies on the mechanism revealed a reaction pathway that might operate through FLP-type single-electron transfer.

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Data availability

All data are available upon request.

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