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Triethoxysilane-Catalyzed Single and Sequential Regioselective Hydroboration of Terminal Alkynes: Sustainable Access to *E*-Alkenylboronate and Alkyl *Gem*-Diboronate Esters by Non-Covalent Interactions

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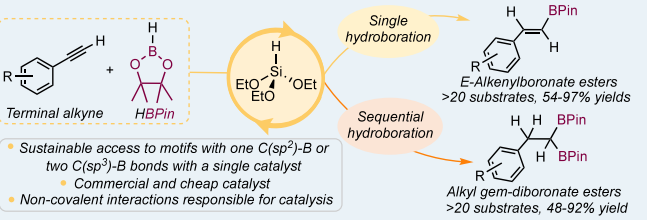
ABSTRACT: Triethoxysilane was found to be an efficient catalyst for the synthesis of *E*-alkenyl- and alkyl-di-boronate esters by the single and sequential hydroboration of terminal alkynes, respectively, with pinacolborane. Mechanistic studies support that the formation of diboronate esters proceeds by a double hydroboration pathway with the steric and electronic profile at Si being key to enabling the second hydroboration step. Weak non-covalent interactions involving the Si and the C≡C or C═C bonds in the alkynes or alkenylboronate esters have been identified as responsible for substrate activation toward the addition of HBPin.



KEYWORDS: *silicon catalysis, sequential hydroboration, non-covalent interactions, terminal alkynes, C(sp³)-B bonds*

INTRODUCTION

Boronate esters with C(sp³)−B bonds[1] are attractive precursors for the synthesis of drugs[2] containing 3D non-flat motifs.[3] One of the most convenient transformations to access molecular scaffolds with two C(sp³)−B bonds is the sequential hydroboration of terminal alkynes with pinacolborane (HBPin). Enabling the second hydroboration step remains challenging for main-group[4] and transition-metal catalysts,[5] with only three transition-metal complexes[6] and $(9\text{-BBN})_2$ (9-borabicyclo[3.3.1]nonane dimer, Scheme 1a)[7a] reported efficient for the transformation. The key behind 9-BBN efficiency relies on its ability to add across the multiple C−C bonds of the substrates and promote subsequent transborylation steps with HBPin. While neutral silicon catalysis is still in its infancy,[8] covalent bonding between the perfluorinated strong Lewis acid $Si(^{F}Cat)_2$ (^{F}Cat = perfluorocatecholate)[9] and aldehydes has been reported key for the hydrosilylation of aldehydes (Scheme 1b).[9a] However, weaker non-covalent interactions promoted by weak Lewis acidic Si compounds, such as siloxanes, are unknown to promote additions across multiple bonds. While promising in catalysis,[10] non-covalent interactions are still restricted to the presence of Lewis basic functional groups in the substrates, such as ketones or esters.[11]

In this work, we report that the neutral, weak Lewis acidic Si compound, $HSi(OEt)_3$, is an efficient regio- and stereoselective catalyst for the single and sequential hydroboration of terminal alkynes affording synthetically valuable *β*-*E*-alkenylboronate and alkyl *gem*-diboronate esters respectively (Scheme 1c). This work constitutes the first example of sustainable,[12] neutral Si catalysis to construct C−B bonds in hydrocarbons relying on non-covalent interactions to activate multiple C−C bonds.

METHODS

Our research commenced with the assessment of the catalytic efficiency of 30 mol % of $HSi(OEt)_3$ for the hydroboration of 4-fluorophenylacetylene (**1**) with 3 equiv of HBPin in a 1.0 M solution of 1,4-dioxane at 80 °C for 2 h. Under these conditions, the *E*-alkenylboronate ester **1a** was formed as the exclusive product in an 80% yield (92% conversion of **1**). In contrast, when the reaction was conducted for 24 h under the same conditions, the diboronate ester **1b** was formed as the exclusive product in 84% yield (>99% conversion of **1**). These results support $HSi(OEt)_3$ as an efficient catalyst for the hydroboration of **1** with HBPin, the time being the determining factor for a single or sequential hydroboration yielding **1a** or **1b**, respectively. Control experiments supported the need of $HSi(OEt)_3$ to access **1a** and **1b** in a synthetically useful yield (pp S10−S12 in the SI). For both processes, reactions on the gram-scale were conducted under the optimized conditions shown in Scheme 2a and b (see Tables

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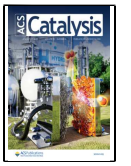

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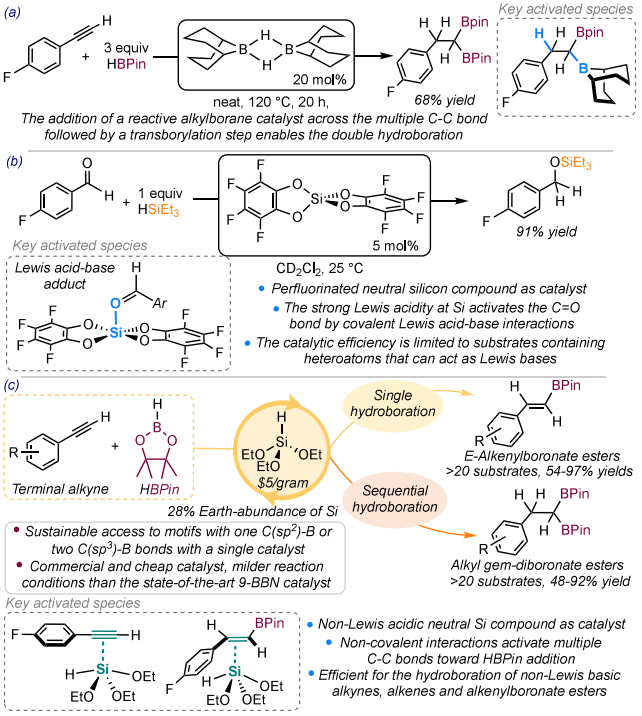
Scheme 1. Main-Group Catalysis for the Hydrofunctionalization of Multiple Bonds and Key Activated Species[a]



[a](a) Sequential hydroboration of 4-fluorophenylacetylene with HBPin catalyzed by 9-BBN;[7a] (b) hydrosilylation of aldehydes catalyzed by a neutral Si compound;[9a] and (c) this work: $HSi(OEt)_3$-catalyzed single and sequential hydroboration of terminal alkynes enabled by non-covalent interactions.

S3 and S4 in the SI for the full optimization of conditions) and the substrate scope was explored (Scheme 2c and d). Aromatic alkynes with electron-withdrawing groups afforded products in lower yields than those with electron-donating alkyl groups (*e. g.*, 54% for **6a and** 92% for **9a**) suggesting that increased electronic density at the aryl ring resulted in more efficient catalysis. However, substituents at the *ortho* position of the aryl ring led to decreased product yields (*e. g.*, 60% for **11a and** 92% for **9a**), hinting that increased steric hindrance at the C≡C bond resulted in decreased catalyst efficiency. Polyfluorinated aromatic alkynes **4**, **5**, and **7**[13] as well as **13** and the dialkyne **18** were efficiently hydroborated for the first time, affording novel diboronate esters (**4b**, **5b**, **7b**, **13b**, and **18b** respectively, boxed in gray in Scheme 2d). $HSi(OEt)_3$ was also efficient for the aliphatic alkynes **21**−**23** and for the single hydroboration of 4-fluorostyrene (**24**, Scheme 2f), the sequential hydroboration of the alkynylboronate **25** (Scheme 2g),[14] and the single hydroboration of **1** with HBCat (Cat = catecholate, product **1c** in p S6 in the SI), and was found inefficient for the hydroboration of the alkynes depicted in Scheme 3e (p S45 in the SI). Control experiments employing BH_3-THF as the precatalyst and trapping BH_3 experiments (pp S12−S17 in the SI) ruled out hidden-boron catalysis[15] as responsible for observed yields of **1a** and **1b**; however, BH_3 formed at late stages of the reaction could contribute to a minor extent (<11%) to the yield of **1b**. The synthetic approach described here presents significant advantages over the reported $Sc(OTf)_3$[16] and 9-BBN[7a] catalysts for the single and sequential hydroboration of terminal alkynes respectively, mainly the milder temperature and lower catalyst loadings in the absence of a strong hydride source as *in situ* activator.[16] Furthermore, unlike $Sc(OTf)_3$[16] and 9-BBN,[7a] $HSi(OEt)_3$ is capable of accessing both, alkenyl- and alkyldiboronate esters, under the appropriate conditions.

To elucidate the keys behind catalyst efficiency, the hydroboration of **1** with 3 equiv of HBPin in the presence of 50 mol % of $HSi(OEt)_3$ in THF-d_8 at 80 °C was monitored by ^{1}H, ^{19}F, ^{11}B, ^{13}C, and ^{29}Si NMR spectroscopy. The ^{19}F and ^{1}H NMR spectra showed the conversion of **1** (at −110.7 ppm in the ^{19}F NMR spectrum) into **1a** (at −112.8 ppm in the ^{19}F NMR spectrum) and of **1a** into **1b** (at −118.9 ppm in the ^{19}F NMR spectrum; p S47 in the SI), supporting two operative sequential hydroboration cycles (Schemes 3a and b). Independent monitoring of the hydroboration of **1a** further supported the formation of **1b** from **1a** (pp S64−S69 in the SI). The fluorinated analog $HSi(OCH_2CF_3)_3$[17] was found more efficient for the transformation (pp S57−S58 in the SI), as evidenced by the times required to reach 92% conversion of **1** (2 h and 5 min) and 51% conversion of **1a** (10 h and 30 min), shorter than those when $HSi(OEt)_3$ was employed (4 h 30 min and 14 h 30 min, respectively, Scheme 3b). Furthermore, the times required for the formation of **1b** are longer than those for **1a**, suggesting slower turnover for the second cycle and/or loss of catalyst efficiency over time. In both cases, signals attributable to H_2 (4.50 ppm) in the ^{1}H NMR spectra and to a mixture of products containing B (broad signals at 22.14 (major) and 35.00 ppm (minor) in the ^{11}B NMR spectra) and Si (−68.55, −40.01, −42.49 ppm in the ^{29}Si NMR spectra) were observed, the intensity of which grew over time. The signal at 22.14 ppm in the ^{11}B NMR spectra was attributed to $O(BPin)_2$ based on the ^{11}B and ^{13}C NMR spectra. The NMR monitoring of the reaction of $HSi(OEt)_3$ with 1 equiv of HBPin showed the same signals (pp S76−S79 in the SI) supporting reactions involving these species taking place during catalysis. The addition of an equimolar mixture of **1** and HBPin to the isolated mixture of species and heating at 80 °C for 24 h resulted in recovery of the starting materials, supporting the side reactions involving HBPin and $HSi(OEt)_3$ as deactivation pathways that could result in decreased catalyst efficiency over time.

The ^{1}H NMR spectra of the catalytic reaction did not show any changes in the multiplicity of the signals attributed to **1**, **1a**, and $HSi(OEt)_3$, suggesting that covalent bonding between the substrates and $HSi(OEt)_3$, including the addition of the Si−H bond across the multiple bonds of **1** or **1a**,[7a] did not take place during catalysis. However, the signals attributed to **1**, **1a**, and $HSi(OEt)_3$ shifted from those of samples of the individual reagents in the ^{1}H, ^{13}C, and ^{29}Si NMR spectra throughout catalysis (*e.g.*, ^{1}H $\Delta\delta$[18] (HSi(OEt)$_3$) = +0.013 ppm; ^{13}C $\Delta\delta$(*C2* in **1**) = +0.066 ppm upon mixing the reagents and $\Delta\delta$(*C2* in **1a**) = +0.012 ppm at 21% conversion of **1a**, see Scheme 3a for labeling scheme; and ^{29}Si $\Delta\delta$(H*Si*(OEt)$_3$) = −0.062 ppm upon mixing the reagents and −0.244 ppm at 21% conversion of **1a**, see Table S8 in the SI). The shift of the signals suggests that non-covalent interactions between $HSi(OEt)_3$ and **1** or **1a** are present during the catalytic reaction. The direction of the shifts, downfield for the C2 in **1** and **1a** and upfield for the Si in $HSi(OEt)_3$, suggest that the non-covalent interactions increase the electronic density on the Si and deplete that of the C≡C and C=C bonds in **1** and **1a**, respectively, facilitating the addition of HBPin.

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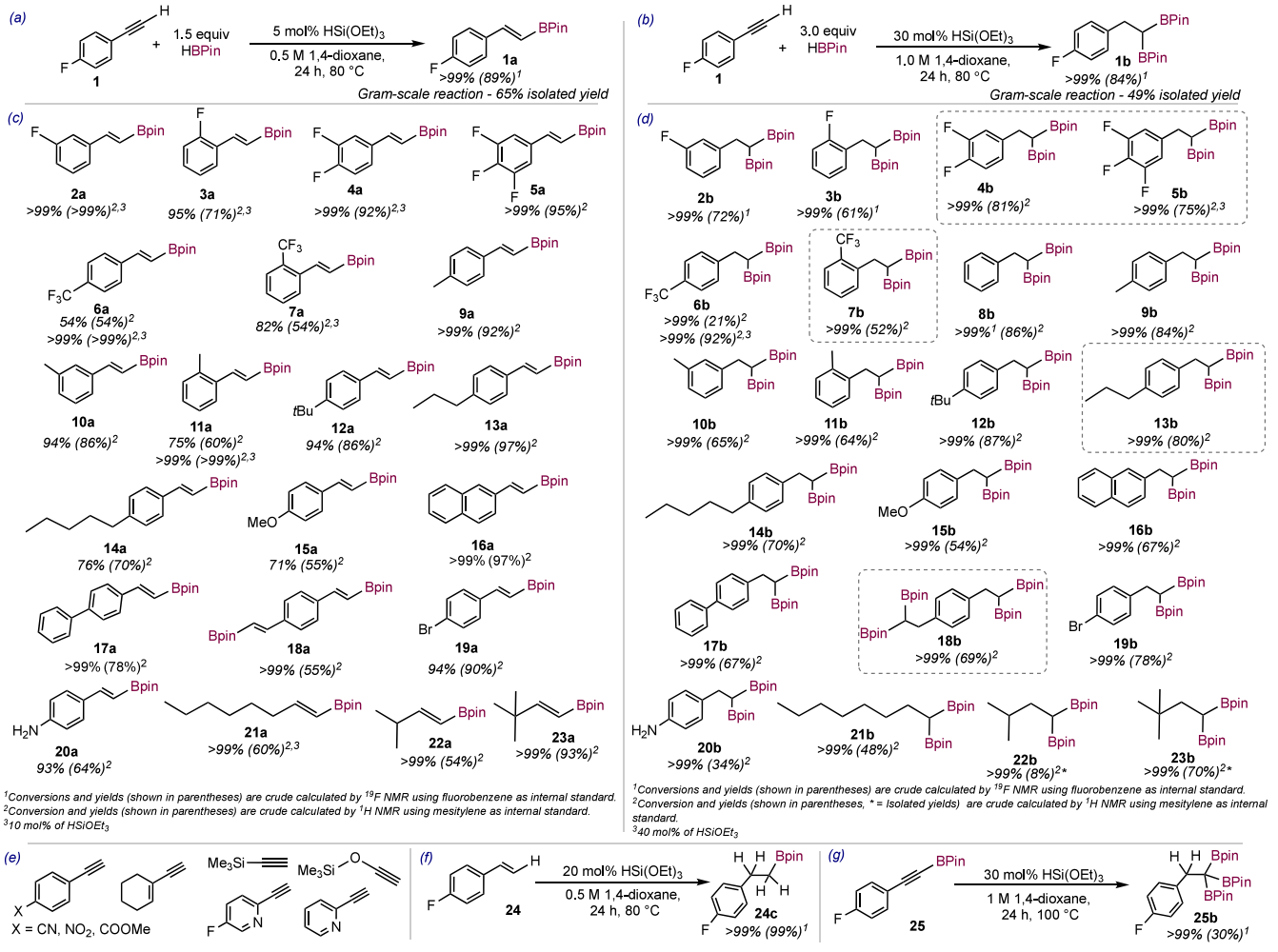
Scheme 2. (a) Single and (b) Sequential Hydroboration of 4-Fluorophenylacetylene with HBPin Catalyzed by $HSi(OEt)_3$ under Optimized Conditions to Access (a) *E*-Alkenylboronate and (b) Alkyldiboronate Esters, Including the Syntheses of 1a and 1b on the Gram Scale; Substrate Scope for the (c) Single Hydroboration and (d) Sequential Hydroboration (New Molecules Are Boxed in Grey); (e) Substrates for Which $HSi(OEt)_3$ Was Inefficient (see p S45 in the SI); (f) Single Hydroboration of 4-Fluorostyrene under Optimized Conditions and (g) Sequential Hydroboration of 4-Fluorophenylalkynylboronate Ester under Nonoptimized Conditions



To gain some insights into plausible intermediates in the catalytic cycle, stoichiometric reactions between the components of the catalytic system were conducted (Scheme 3c). The addition of 1 equiv of $HSi(OEt)_3$ to dioxane/CD_2Cl_2 (12:1) solutions of **1** or **1a** at room temperature resulted in an immediate upfield shift of the signal attributable to $HSi(OEt)_3$ in the ^{29}Si NMR spectra ($\Delta\delta^{19}$ ($HSi(OEt)_3$) = −0.026 and −0.053 ppm for the mixtures with **1** and **1a**, respectively) concomitant with downfield shifts of the signals attributed to **1** (*e.g.*, $\Delta\delta$ (*C2* in **1**) = +0.213 ppm) or **1a** ($\Delta\delta$ (*C2* in **1a**) = +0.276 ppm), respectively, in the ^{13}C NMR spectra (Tables S13 and S14 in the SI), in the same direction as those observed during the catalytic reaction. For both **1** and **1a**, the ^{13}C NMR $\Delta\delta$ for the aryl C atoms (*e.g.*, $\Delta\delta$ (*C5* in **1**) = +0.053 ppm and $\Delta\delta$ (*C5* in **1a**) = +0.067 ppm) were smaller than those of C1 (+0.741 ppm for **1**) and C2 (+0.213 ppm for **1** and +0.276 ppm for **1a**) engaged in the C≡C and C═C bonds of **1** and **1a**, respectively. This observation points toward the interactions of **1** and **1a** with $HSi(OEt)_3$ taking place mostly through the multiple C−C bonds. Titration experiments involving the addition of increasing amounts of $HSi(OEt)_3$ to CD_2Cl_2 solutions of **1** or **1a** showed analogous shifts of the signals, further supporting non-covalent interactions between the catalyst and the substrates (pp S69−S75 in the SI). Based on these observations, plausible adducts present in solutions of $HSi(OEt)_3$ and **1** (**1**-SiH$(OEt)_3$) or **1a** (**1a**-SiH$(OEt)_3$) are depicted in Scheme 3c (see p S92 in the SI for other plausible adducts in equilibrium). The addition of 1 equiv of HBPin to the **1a**-SiH$(OEt)_3$ solution resulted in additional shifts of the signals attributed to **1a**-SiH$(OEt)_3$ and HBPin in the ^{13}C NMR spectrum, as well as of that of the Si in the ^{29}Si NMR spectrum (pp S84−S87 in the SI), suggesting that HBPin interacted with the **1a**-SiH$(OEt)_3$ adduct. Heating the solutions of **1a**-SiH$(OEt)_3$ and of **1**-SiH$(OEt)_3$ after the addition of HBPin at 80 °C for 1.5 h resulted in the formation of products **1a** and **1b** respectively (Scheme 3c), supporting the adducts as catalytically competent. The adduct obtained by the addition of 1 equiv of HBPin to a $HSi(OEt)_3$ (1 equiv) solution showed analogous results upon the addition of **1a** (pp S88−S91 in the SI), suggesting that interaction of any of the substrates, HBPin, **1**, or **1a**, with $HSi(OEt)_3$ can lead to catalytically active adducts.

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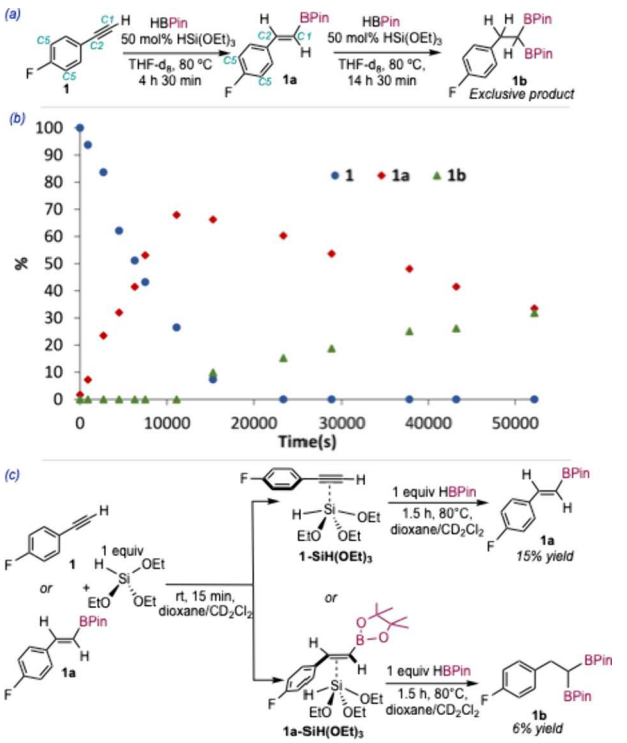
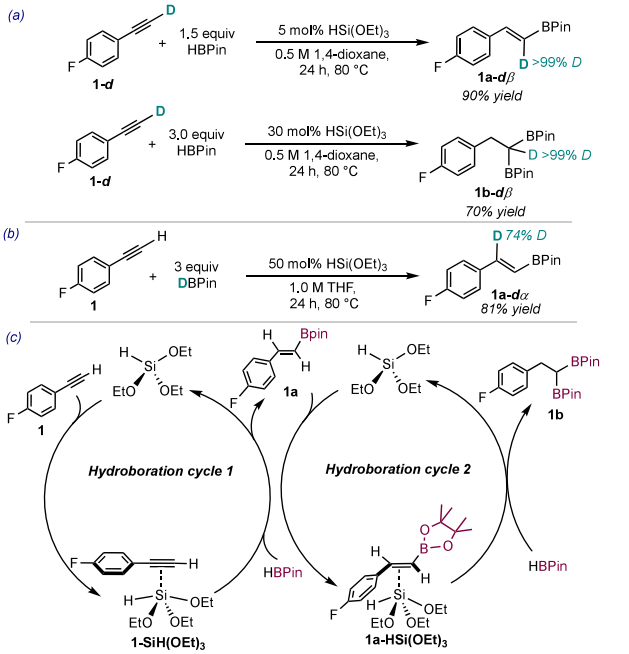
Scheme 3. (a) Reaction Pathway for the $HSi(OEt)_3$-Catalyzed Sequential Hydroboration of Terminal Alkynes; (b) Quantitative Reaction Profile; (c) Stoichiometric Reactions Supporting the Presence of Non-Covalent Interactions in Catalysis



The increased efficiency of $HSi(OEt)_3$ for alkynes with electron-donating substituents at the *para* position as well as the increased efficiency of $HSi(OCH_2CF_3)_3$ suggest that electron-rich substrates with low steric hindrance, or a more electron-deficient catalyst, render adducts with stronger catalyst−substrate interactions, resulting in an increased C−C bond activation toward the addition of HBPin. Additionally, when 1 equiv of $OPEt_3$ or pyridine was added to the catalytic reaction, **1b** was not detected and **1a** was formed in lower yields than under the optimized catalytic conditions (pp S26−S27 in the SI), suggesting that Lewis bases compete with **1** and **1a** to engage in interactions with $HSi(OEt)_3$, leading to decreased catalyst efficiency. Lower product yields were also obtained when the strong Lewis acids $SiCl_4$ or $BF_3{\cdot}OEt_2$ were employed as catalysts (pp S25−S26 in the SI), highlighting that the weak Lewis acidic $HSi(OEt)_3$ and $HSi(OCH_2CF_3)_3$[20] override the efficiency of strong Lewis acids for this transformation. Furthermore, the catalytic efficiency for the sequential hydroboration was unique to $HSi(OEt)_3$, as evidenced by the diminished or lack of efficiency of other commercial silicon compounds such as $HSi(OiPr)_3$ (p S18 in the SI), which was capable of engaging in non-covalent interactions with **1a** (see p S74 in the SI for titration experiments) but did not render product **1b** under catalytic conditions.

Deuterium-labeling experiments employing **1**-*d* as starting material resulted in the formation of products **1a**-*dβ* and **1b**-*dβ* in analogous yields to those of **1a** and **1b** and with >99% D incorporation (Scheme 4a), supporting that C(sp)−H bond activation of **1** does not take place during catalysis.[21] When the catalytic reaction was conducted employing a 1.05 M solution

Scheme 4. Deuterium Labelling Experiments Employing 1-*d* for the Single (a, Top) and Sequential (a, Bottom) Hydroboration and DBPin (b), and (c) Proposed Catalytic Cycle



of DBPin in THF under the conditions optimized for the formation of **1b**, only **1a**-*dα* was formed in 81% yield (Scheme 4b), suggesting that the cleavage of the D−B bond hinders the formation of **1a** and **1b**.[22] NMR monitoring of the reaction of DBPin and $HSi(OEt)_3$ supported that H/D exchange took place under the catalytic reaction conditions after 15 min (p S22 in the SI), accounting for the <99% D incorporation observed in **1a**-*dα* (Scheme 4b).

Based on the results presented, catalytic cycles that account for the formation of **1a** and **1b** by the $HSi(OEt)_3$-catalyzed hydroboration of **1** are depicted in Scheme 4c. In both cycles, $HSi(OEt)_3$ enters the cycles by interaction of **1** or **1a** to afford the **1**-$SiH(OEt)_3$ and **1a**-$SiH(OEt)_3$ adducts, respectively, which promote the H−B bond cleavage of HBPin and its addition across the C≡C and C═C bonds, yielding products **1a** and **1b**, respectively.

CONCLUSION

In conclusion, $HSi(OEt)_3$ was found to be an efficient catalyst for the single and sequential hydroboration of alkynes showing a wide substrate scope. Mechanistic experiments supported non-covalent interactions between the multiple C−C bonds of the alkyne or the alkenylboronate ester and the Si atom in $HSi(OEt)_3$ as responsible for their activation toward the addition of HBPin.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c06845.

Complete experimental details, characterization data, NMR spectroscopic data (PDF)

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Author Contributions

R.A. conceived the project, designed the experiments, supervised the experimental work, and drafted the manuscript. H.K. conducted the optimization of the reaction conditions, the control experiments, the evaluation of the substrate scope for the single hydroboration of alkynes, the single hydroboration of 4-fluorostyrene, the double hydroboration of the alkynylboronate ester, and the mechanistic studies and drafted the SI and the manuscript. H.A. conducted the evaluation of the substrate scope for the double hydroboration of alkynes and the hydroboration experiments employing strong Lewis acids and in the presence of Lewis bases and drafted the SI. H.K. and H.A. conducted the experiments for the manuscript revisions. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to the memory of Prof. Julio Perez.

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(18) For the catalytic reaction, the $\Delta\delta$'s were calculated as follows: $\Delta\delta = \delta$ ([signal attributed to atom] in [reagent] in the catalytic reaction) $- \delta$ ([signal attributed to atom] in [reagent] in an independent sample containing only the reagent). All the spectra were recorded in THF-d_8 at 23 °C.

(19) For the stoichiometric reactions, the $\Delta\delta$'s were calculated as follows: $\Delta\delta = \delta$ ([signal attributed to atom] in [reagent] in the stoichiometric reaction) $- \delta$ ([signal attributed to atom] in [reagent] in an independent sample containing only the reagent). All the spectra were recorded in THF-d_8 at 23 °C.

(20) ^{31}P NMR $\Delta\delta$ ($POEt_3$) was −0.01 ppm for $HSi(OEt)_3$ and + 0.07 ppm for $HSi(OCH_2CF_3)_3$, significantly lower than that reported in reference 9a for $Si(^FCat)_2$ (+35.9). Assessed by the Gutmann−Beckett method (see pp S24−S25 in the SI for a full description).

(21) A C−H borylation/semihydrogenation pathway could lead to the products from hydroboration, and it has been previously reported operative for the hydroboration of terminal alkynes with HBPin catalyzed by manganese complexes, see reference 5f.

(22) When the reaction was conducted for 72 h, a mixture of **1a**-*dα* and **1b**-*dα* along with other unidentified products was obtained (see p S23 in the SI).

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