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^{n}BuLi-promoted *anti*-Markovnikov selective hydroboration of unactivated alkenes and internal alkynes†

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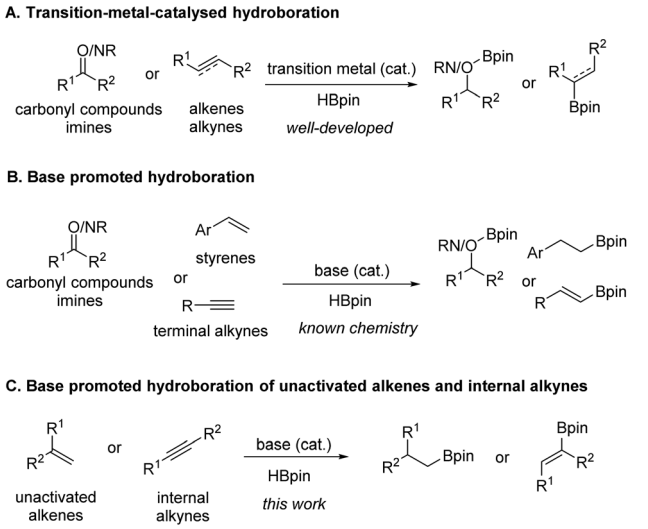
An efficient and general ^{n}BuLi-promoted *anti*-Markovnikov selective hydroboration of various α-alkenes, 1,1-disubstituted alkenes and internal alkynes with pinacolborane for the synthesis of alkylboronic esters is described. This protocol features easy accessibility of catalysts and substrates, a broad substrate scope, and simple operation as well as scale-up ability.

Introduction

Alkylboronic esters have been recognized as highly important and versatile synthetic intermediates in organic synthesis and well known due to their unique transformation of C–B bonds and participation in various transition-metal catalysed C–C coupling reactions to access molecules of high value.[1] Besides, such compounds also exist in pharmaceutically active molecules or act as bioisosteres in drug design.[2] Therefore, a wide array of methods has been developed for the synthesis of these crucial compounds, which mainly includes (1) the classic reactions of organometallic reagents (Grignard or lithium reagents) with suitable boron compounds,[3] (2) catalytic hydroboration and borylation of alkenes, (3) catalytic borylation of alkyl halides,[4] and (4) catalytic C–H bond borylation.[5]

Olefins are a class of compounds that can be obtained in large quantities, and are common raw materials and essential intermediates in organic synthesis reactions. Ideally, the catalytic hydroboration of alkenes provides a straightforward, useful, and atom-efficient method to access alkylboronic esters from readily available starting materials. As a result, various transition-metal-catalysed[6] and main-group-catalysed[7] reactions were advanced to enable highly chemo-, regio- and stereoselective hydroboration of alkenes (Scheme 1A). Along the same line, there is also a research focus on the development of protocols following the principles of green chemistry. For example, it is highly desirable to develop simple base catalysed hydroboration methods[8–12] of alkenes with comparable efficiency from a practical point of view due to the economic and environmental benefits of base catalysts. However, the scopes of known chemistries on base-promoted hydroboration are limited mainly to carbonyl compounds,[9] pyridine[10] or terminal alkyne[11] (Scheme 1B). In 2017, Zhao and co-workers[12] reported that NaOH powder could efficiently promote the hydroboration of carbonyl groups and styrene type substrates in deuterated benzene. However, the scope of styrene substrates was somewhat limited. Very recently, we disclosed ^{n}BuLi-initiated reductive relay hydroboration of allylic alcohol and derivatives to prepare alkylboronic esters in a single operation. Mechanistically, we proposed a



Scheme 1 Transition-metal or base-catalysed hydroboration of unsaturated compounds.

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one-pot three-step process involving *anti*-Markovnikov hydroboration of a transiently formed terminal alkene.[13] However, to our knowledge, a general base-catalysed direct hydroboration method of unactivated alkenes has not been reported. Herein, as our ongoing research on the hydroboration reaction,[13,14] we report a simple base promoted selective hydroboration of unactivated alkenes and 1,1-disubstituted styrenes as well as internal alkynes with HBpin to prepare a wide range of boronic esters.

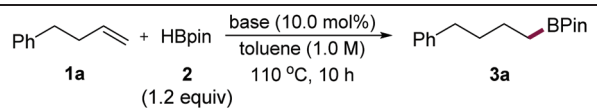
Results and discussion

We started the reaction optimization using 4-phenyl-1-butene (**1a**) as a model substrate in the presence of HBpin (**2**) and various base catalysts. At the outset, the control experiment using **1a** and **2** was conducted at 110 °C without the addition of a base; only trace amounts of the product (**3a**) were formed (<5% yield, Table 1, entry 1). In contrast, the hydroboration reaction in the presence of 10 mol% of KOBu^t gave **3a** in 75% yield (entry 2), suggesting that a base can accelerate the reaction. We reasoned that a base might weaken the B–H bond to enhance the hydride character which would facilitate this process.[15] However, we found that an organic base (entry 3) was not efficient for this transformation. Next, several commercially available and commonly used inorganic bases were extensively evaluated (Table 1, entries 3–9). We were pleased to find that ^{n}BuLi was the best catalyst, the use of which led to a full conversion of alkenes after 10 h of reaction to afford **3a** in 99% yield (entry 9). Besides, reducing the reaction time to 4 h resulted in only 67% yield of the product (entry 10). It needs to be mentioned that all these reactions delivered linear products as a single isomer, highlighting the excellent *anti*-Markovnikov regioselectivity of the hydroboration methods.

Under the optimized reaction conditions, we next surveyed the substrate scope of this novel hydroboration method. As depicted in Table 2, a diverse array of α-alkenes was readily transformed into alkylboronic ester products in high to excellent yields. For example, allylic ether (**3b**), thioether (**3c**), and silane (**3d**) were competent substrates affording products in high yield and regioselectivity. Bulkier terminal alkenes (**3e** and **3f**) were efficiently converted into the corresponding product in excellent yields, suggesting that steric effects have no apparent influence on this reaction. Moreover, alkene substrates bearing free alcohol (**3g**) and a secondary amine (**3h**) successfully participated in this hydroboration after *in situ* protection using an additional amount of HBpin. Importantly, this method tolerated a series of functional groups including ethers (**3b**, **3k–3n**), thioethers (**3c** and **3l**), a silane (**3d**), an alkyl chloride and bromide (**3i**, **3j**), a trifluoromethoxyl group (**3k**) and a methylthio group (**3l**). In addition, various heterocycle substituted alkenes, including a furan (**3m**), a thiophene (**3n**), a pyrrole (**3o**), an indole (**3p**), a carbazole (**3q**), and a pyrazole (**3r**), could be applied to this protocol furnished products in high yields.

Next, we examined the scope of more challenging 1,1-disubstituted alkene substrates, and the results are depicted in Table 3. We first subjected isopropenylbenzene to the standard hydroboration conditions for α-alkenes, but no reaction was observed. However, when the reaction was performed at a higher temperature (130 °C) and concentration (2.5 M), the desired product (**5a**) was obtained in 93% yield. Under these conditions, we found that a diverse variety of α-substituted styrenes (**5a–4l**), and diaryl-substituted (**5m**), and dialkyl-substi-

Table 1 Reaction optimization[a]

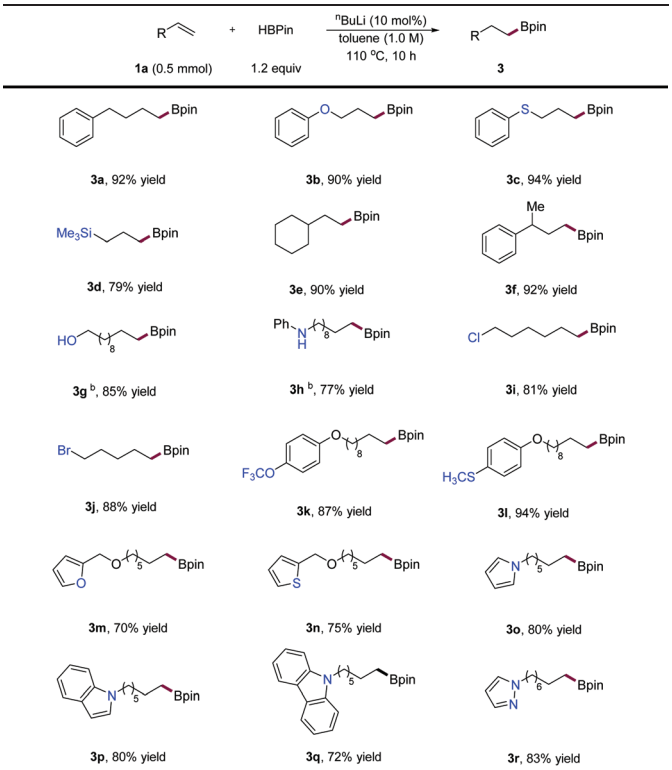


1a **2** (1.2 equiv) **3a**

Entry	Base	Yield (%)	Entry	Base	Yield (%)
1	—	<5	6	Cs_2CO_3	20
2	^{t}BuOK	75	7	CH_3OK	32
3	Et_3N	<5	8	KOH	25
4	K_3PO_4	39	9	^{n}BuLi	99
5	CsF	40	10[b]	^{n}BuLi	67

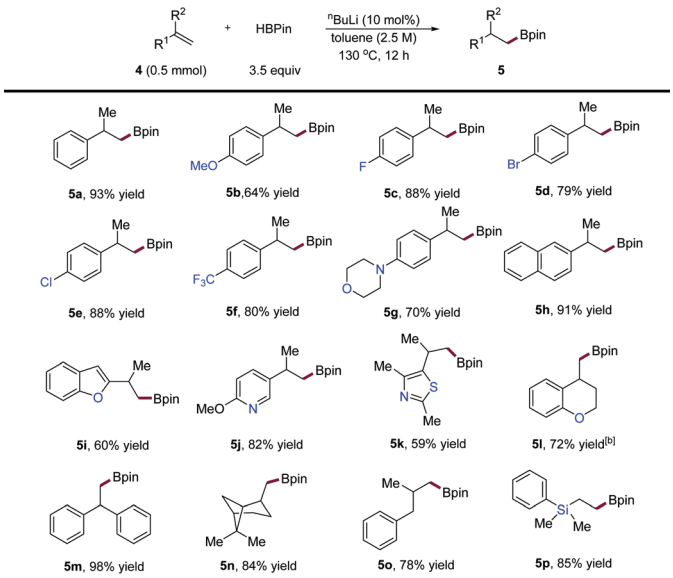
[a] Yields were determined by NMR analysis using 1,3,5-trimethylbenzene as an internal standard; regioselectivities were determined by GC-MS analysis of the crude reaction mixture, single regioisomers (>99/1) of hydroborated products were obtained for all cases. [b] Reaction was run in 4h.

Table 2 Substrate scope of α-alkenes[a]



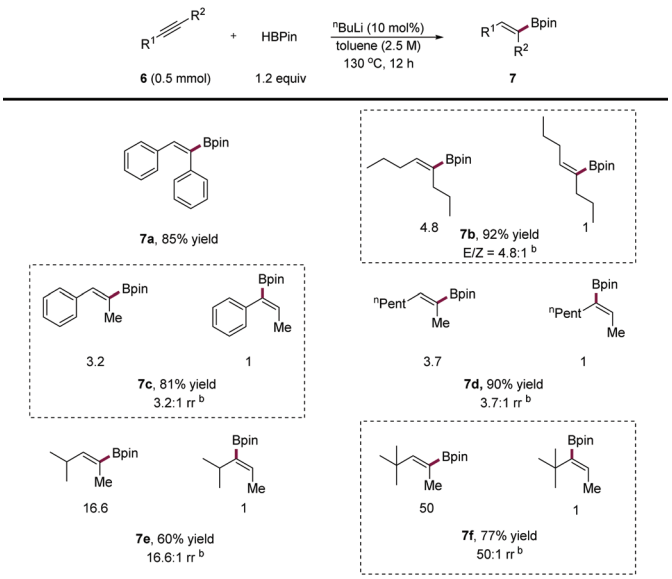
[a] Isolated yields are given; single regioisomers (>99/1) of hydroborated products were obtained as determined by GC-MS analysis. [b] 2.2 equiv. HBpin was used.

Table 3 Substrate scope of 1,1-disubstituted alkenes[a]



[a] Isolated yields are given; single regioisomers (>99/1) of hydroborated products were obtained as determined by GC-MS analysis.

Table 4 Substrate scope of internal alkynes[a]

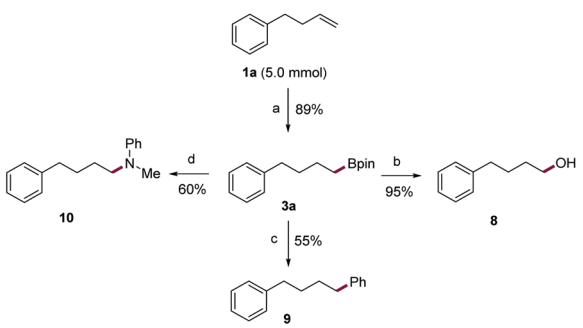


[a] Isolated yields are given. [b] Determined by ^{1}H NMR analysis of the reaction mixture.

tuted (**5n** and **5o**) alkenes were compatible, affording various alkylboronic esters in good to excellent yields. Substrates with functional groups such as aryl halides (**5d** and **5e**), and heterocycles including a morpholine (**5g**), a benzofuran (**5i**), a pyridine (**5j**), a thiazole (**5k**), and a chromane (**5l**) were all hydroborated without accidents giving products in high yields. A limitation of this method is its inapplicability to internal alkene substrates, likely due to their inert properties and steric effects.

Vinyl boronic esters are versatile coupling partners in organic synthesis and have gained attention increasingly. Over the past few years, the catalytic hydroboration of alkynes has mainly relied on the use of transition metal,[16] main group[7b,17] or acid[18] catalysts. In 2019, Xue and co-workers[11] reported that a base efficiently promoted the hydroboration of terminal alkynes to form vinyl boronic esters. However, as indicated by the authors, internal alkynes failed to participate in their reaction conditions and remain an unmet challenge,[17e] presumably due to the lower reactivity of substrates as well as the difficulty in the control of regioselectivity and stereoselectivity. As an extension of our study, we subjected internal alkynes to our conditions. The results are shown in Table 4. We found that symmetrical diaryl or dialkyl alkynes were readily converted into corresponding vinyl boronic esters (**7a**, **7b**) in high yields, although the E/Z selectivity of **7b** is moderate due to easy isomerisation. As for unsymmetrical internal alkynes, both 1,2-alkyl, aryl alkynes (**7c**) and 1,2-dialkyl alkynes (**7d**) efficiently participated in the transformation affording products in high yields, albeit in moderate selectivity. Increasing the steric difference of alkyne substituents (**7e**, **7f**) and hydroborated products could result in excellent anti-Markovnikov selectivity (up to 50 : 1).

Next, a gram-scale reaction using **1a** was smoothly performed with a lower loading of the ^{n}BuLi catalyst (5 mol%) to afford alkylboronic ester **3a** in high yield (89%) (Scheme 2). Then, the C–B bonds in **3a**, a bench-stable alkylboronic ester, were converted into various carbon–carbon and carbon–heteroatom bonds. For example, **3a** can be smoothly oxidized to alcohol **8** in 95% yield. Also, the subjection of **3a** to typical Suzuki conditions readily afforded **9** in good yield. Finally, the C–B bond was transformed into a C–N bond (**10**) in 60% yield through an oxidative amination reaction.[19] Given its simple operation, the ready availability of base catalysts, and the rich chemistry of organic boron compounds, the current



Scheme 2 Gram-scale reaction and transformation of **3a**. [a] **1a** (5.0 mmol, 0.66 g), ^{n}BuLi (5.0 mol%), HBpin (1.2 equiv.), toluene (5.0 mL), 110 °C, 18 h. [b] **3a** (0.2 mmol), $NaBO_3{\cdot}H_2O$ (3.0 equiv.), THF/H_2O (1/1, 2.0 mL), r.t., 6 h. [c] **3a** (0.2 mmol), bromobenzene (1.5 equiv.), Pd$(OAc)_2$ (10.0 mol%), rac-BINAP (12.0 mol%), NaOH (15.0 equiv.), THF/H_2O (5/1 1.2 ml), 100 °C, 16 h. [d] **3a** (0.2 mmol), *N*-methylaniline (1.5 equiv.), ^{t}BuOO^{t}Bu (2.0 equiv.), Cu$(OAc)_2$ (5.0 mol%), toluene (2.0 mL), 80 °C, 24 h.

protocol would constitute a practical means for the transformation of alkenes.

Conclusion

In conclusion, a practical and general base-promoted *anti*-Markovnikov selective hydroboration of α-alkenes, 1,1-disubstituted alkenes, and internal alkynes with HBpin has been developed. Commercially available ^{n}BuLi was employed as a transition-metal-free initiator for this protocol,[20] affording a broad array of alkyl or vinyl boronic esters bearing various functional groups and heterocycles in good to excellent yield and selectivity.

Experimental

General procedure for the hydroboration of α-alkenes

In a nitrogen-purged Schlenk tube containing a magnetic stirring bar, toluene (0.5 mL, 1.0 M), HBpin (87.0 μL, 0.6 mmol, 1.2 equiv.) and ^{n}BuLi (2.5 M in hexane, 20.0 μL, 0.05 mmol, 10 mol%) were added sequentially. Then the mixture was stirred for 5 min at room temperature. The α-alkene substrate (0.5 mmol) was then added dropwise, and the reaction mixture was stirred at 110 °C for 10 h. After completion of the reaction, the reaction mixture was allowed to cool to r.t. and quenched by using HCl (1.0 M in EtOAc). Then the reaction mixture was directly filtered through a short pad of silica gel, and eluted with EtOAc. The solvent was removed *in vacuo*. The linear/branched ratios of crude product mixtures were determined at this stage by GC-MS analysis. The product was purified by chromatography on silica gel.

General procedure for the hydroboration of 1,1-disubstituted alkenes and internal alkynes

In a nitrogen-purged Schlenk tube containing a magnetic stirring bar, toluene (0.2 mL, 2.5 M), HBpin (87 μL, 0.6 mmol, 1.2 equiv.) and ^{n}BuLi (2.5 M in hexane, 20 μL, 0.05 mmol, 10 mol%) were added sequentially. Then the mixture was stirred for 5 min at room temperature. The alkene or alkyne substrate (0.5 mmol) was then added dropwise, and the reaction mixture was stirred at 130 °C for 12 h. After completion of the reaction, the reaction mixture was allowed to cool to r.t. and quenched by using HCl (1.0 M in EtOAc). Then the reaction mixture was directly filtered through a short pad of silica gel and eluted with EtOAc. The solvent was removed *in vacuo*. The linear/branched ratios of crude product mixtures were determined at this stage by GC-MS analysis. The product was purified by chromatography on silica gel.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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