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Regioselective radical hydroboration of electron-deficient alkenes: synthesis of α-boryl functionalized molecules†

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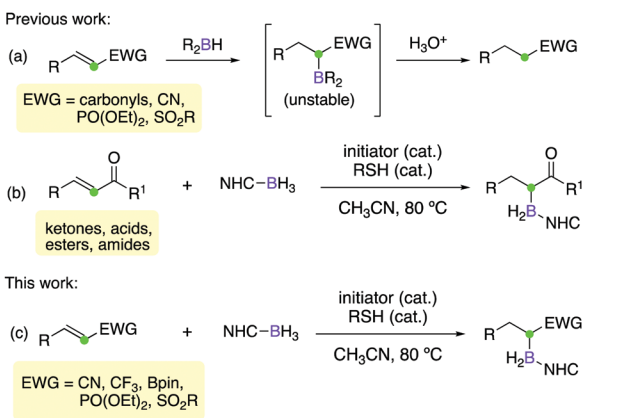
A regioselective radical hydroboration of various electron-deficient alkenes is achieved by the employment of an NHC–boryl radical. A range of α-borylated nitriles, trifluoromethyl molecules, phosphonates, sulfones, and *gem*-diboron compounds have been prepared from readily available starting materials. Further synthetic applications of these products are also demonstrated.

Hydroboration of alkenes is among the most powerful methods to access organoboron compounds,[1] which have shown significant applications in modern chemical synthesis.[2] In this context, electron-deficient alkenes have been widely used in nucleophilic β-borylation to prepare β-borylated products.[3] On the other hand, the synthesis of α-boryl functionalized products is problematic, as in most cases the resulting α-borylated compounds undergo a quick 1,3-boron shift to give thermodynamically more stable boron-enolate analogues.[4] These compounds then undergo facile hydrolysis to give hydrodeboration products instead (Scheme 1(a)). Recently, Chiu reported an elegant copper-catalyzed hydroboration of α,β-unsaturated carbonyl compounds to synthesise C-boron enolates, whereas rigorous reaction conditions were still required to prevent the conversion to O-bound isomers.[5] More recently, the Ingleson group disclosed an iodine-promoted concerted hydroborylation of α,β-unsaturated esters with NHC–BH_3.[6] Although notable, the reactions with other electron-deficient alkenes to afford varied α-boryl functionalized molecules have remained less explored.[7] Therefore, developing conceptually new hydroboration protocols, which are generally applicable for a wide variety of electron-deficient alkenes, is highly desirable.

N-Heterocyclic carbene (NHC)–boryl radicals have recently emerged as a class of powerful species to enable various organic transformations.[8] Our group has been interested in developing radical borylation reactions of alkenes and alkynes to synthesise organoboron compounds.[9] More recently, we have disclosed a unique radical α-borylation of α,β-unsaturated carbonyl compounds[10] (Scheme 1(b)). In this reaction, an NHC–boryl radical undergoes a specific α-addition reaction, leading to a variety of α-boryl carbonyl molecules. These products are air stable and can be isolated by silica gel chromatography.[11] Furthermore, we have performed detailed DFT and kinetic studies to rationalize the α-regioselectivity. The results showed that both the nature of substrates and the thiol catalysts play important roles in determining the regioselectivity. Despite this, the reactivity and selectivity of the reactions with other electron-poor alkenes still remains elusive. Such a study would be of great importance, since it would not only provide more information to elucidate the α-regioselectivity, but also offer a new strategy to synthesise structurally diverse α-borylated molecules which are not easily prepared by other means. Herein, we report our new findings on the radical hydroboration of a diverse array of electron-deficient alkenes (Scheme 1(c)). Significantly, the reactions proceed with exclusive α-regioselectivity, affording a broad range of α-borylated nitriles,



Scheme 1 Hydroboration of electron-deficient alkenes.

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trifluoromethyl molecules, phosphonates, sulfones, and *gem*-diboron compounds.

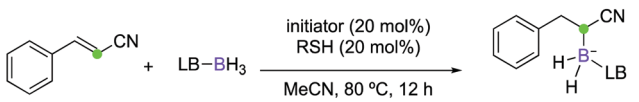
We commenced our study by examining the radical hydroboration of cinnamonitrile (**1a**) with 1,3-dimethylimidazol-2-ylidene borane (**2a**) as the boryl radical precursor. As expected, the reaction proceeded smoothly in the presence of AIBN as the radical initiator and *tert*-dodecanethiol as the polarity reversal catalyst,[12] giving the desired product **3a** in 53% yield (Table 1, entry 1). Using PhSH as the catalyst afforded **3a** in 75% isolated yield. The reactions with other thiol catalysts, such as benzenethiols (4-$MeOC_6H_4SH$, 2-$CO_2MeC_6H_4SH$) and $PhCH_2SH$, also functioned well, producing **3a** in comparable yields (entries 3–5). Switching the radical initiator to ABVN and ACCN led to moderate yields (entries 6 and 7). Further screening of Lewis base-boryl radical precursors revealed that the reaction took place nicely when NHC–BH_3 complexes (**2b** and **2c**) were employed (entries 8 and 9), while no reaction occurred for pyridine-BH_3 (**2d**) and Me_3N–BH_3 (**2e**) with the recovery of **1a** (entries 10 and 11). In addition, only a trace amount of **3a** was detected in the absence of a thiol catalyst (entry 12), suggesting that hydrogen atom transfer (HAT) from a thiol plays an important role in determining the reactivity. Moreover, the reaction did not occur without a radical initiator, supporting a radical reaction mechanism (entry 13).

With the optimized reaction conditions in hand, the scope and generality of this radical hydroboration protocol was investigated (Table 2). A wide range of α,β-unsaturated nitriles were converted to α-boryl nitriles in moderate to good yields. A variety of functional groups on the β-aryl ring were compatible, regardless of their electronic nature and substitution patterns (for **3b–3e**). An additional simple alkene motif was tolerated (for **3f**). A range of β-heteroaryl rings, including quinolone (for **3g**) and indole (for **3h**), could be installed. The reaction of β-dialkyl substituted substrates also afforded α-addition products solely (for **3i** and **3j**). Notably, the reaction of **1k** bearing a cyclopropane moiety led to a ring-opening product **3k** in 39% yield, which further supported a radical borylation mechanism. Moreover, the present method allowed for the facile synthesis of a wide range of borylated nature product derivatives, including nerol (for **3l**), estrone (for **3m**), menthol (for **3n**), and vitamin E (for **3o**).

The scope of this radical hydroboration protocol was further examined using other electron-deficient alkenes. As shown in Table 3, a wide range of alkenes bearing various electron-withdrawing groups, such as CF_3, $PO(OEt)_2$, SO_2Ar, and Bpin, underwent exclusive α-regioselective borylation, furnishing a series of structurally useful α-boryl functionalized products **5** in good yields. It is worth noting that the hydroboration of trifluoromethyl-substituted alkenes often suffered from regioselectivity[13] and B–F elimination issues.[13a,14] Advantageously, the present protocol only led to the sole formation of stable α-borylated products, thus highlighting its significant applications in the synthesis of versatile α-trifluoromethylated organoboron compounds.

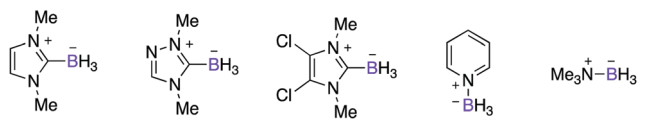
Based on our previous mechanistic studies and the control experimental results in this work, a radical hydroboration

Table 1 Optimization studies[a]



1a **2** **3a**

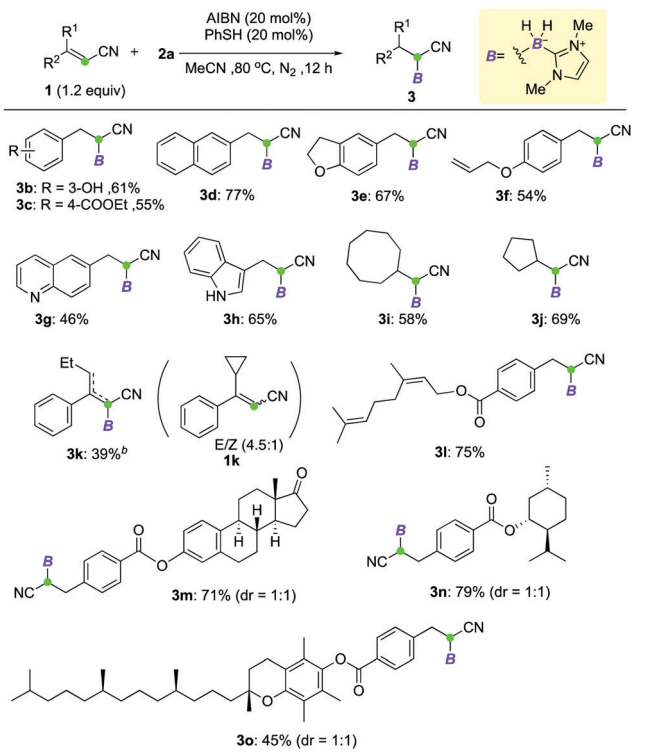
Entry	2	Initiator	RSH	3a Yield[b] (%)
1[c]	**2a**	AIBN	*tert*-Dodecanethiol	53 (15)[d]
2	**2a**	AIBN	PhSH	75[e]
3	**2a**	AIBN	4-$MeOC_6H_4SH$	70
4	**2a**	AIBN	2-$CO_2MeC_6H_4SH$	75
5	**2a**	AIBN	$PhCH_2SH$	73
6[f]	**2a**	ABVN	PhSH	61
7[g]	**2a**	ACCN	PhSH	68
8	**2b**	AIBN	PhSH	63[e]
9	**2c**	AIBN	PhSH	76[e]
10	**2d**	AIBN	PhSH	ND (98)[h]
11	**2e**	AIBN	PhSH	ND (84)[h]
12	**2a**	AIBN	—	trace (60)[d]
13	**2a**	—	PhSH	ND (79)[d]



2a **2b** **2c** **2d** **2e**

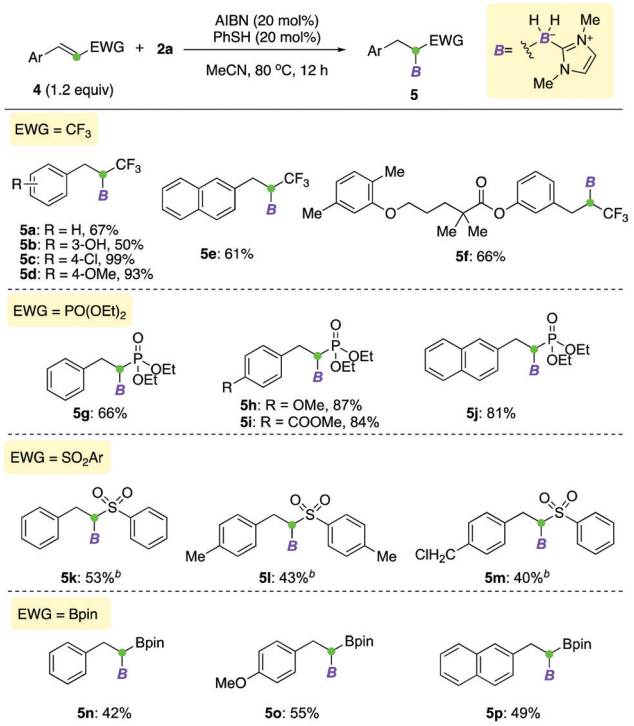
[a] Reaction conditions: **2** (0.2–0.5 mmol), **1a** (1.2 equiv.), initiator (20 mol%), RSH (20 mol%), CH_3CN (0.1 M), 80 °C, 12 h. [b] NMR yield using tetrachloroethane as an internal standard. [c] *tert*-Dodecanethiol (50 mol%) was used. [d] Recovery yield of **2a** is shown in parentheses. [e] Isolated yield. [f] The reaction was carried out at 65 °C. [g] The reaction was carried out at 95 °C. [h] Recovery yield of **1a** is shown in parentheses.

Table 2 Scope of radical hydroboration of α,β-unsaturated nitriles[a]



[a] Reaction conditions: **2a** (0.2–0.5 mmol), **1** (1.2 equiv.), AIBN (20 mol%), PhSH (20 mol%), CH_3CN (0.1 M), 80 °C, 12 h. [b] The yield was determined by NMR.

Table 3 Scope of radical hydroboration of varied electron-deficient alkenes[a]



[a] Reaction conditions: **2a** (0.2–0.5 mmol), **4** (1.2 equiv.), AIBN (20 mol%), PhSH (20 mol%), CH_3CN (0.1 M), 80 °C, 12 h. [b] The reaction was run at 40 °C using TBHN (40 mol%) as the initiator for 24 h.

pathway should account for the present transformation (the detailed mechanism is shown in the ESI†). To gain more insight into the reaction process, the rate constants for the addition of the NHC–boryl radical to varied electron-deficient alkenes were measured by laser flash photolysis (LFP) experiments.[15] As shown in Table 4, the observed rate constants for **1a**, **4a**, **4k**, and **4n** are 5.13×10^7, 1.72×10^6, 2.23×10^7, and 1.23×10^7 M^{-1} s^{-1}, respectively. As reported, the rate constant of HAT from PhSH to the resulting benzyl radical is 3.0×10^5 M^{-1} s^{-1}.[16] These results indicate that the NHC–boryl radical addition is much faster than the following HAT, therefore the α-regioselectivity is determined by the thermodynamically more favorable α-addition step. Namely, the resulting α-addition intermediates (benzyl radicals) exhibit more stabilization than the corresponding β-addition intermediates,[17] thus making α-addition predominant. This finding is consistent with the one we observed for the radical α-borylation of α,β-unsaturated carbonyl compounds. In addition, the α-regioselectivity for β-alkyl α,β-unsaturated nitriles is most likely driven by the energetically more favorable HAT from PhSH to a tertiary alkyl radical ($k_H = 1.4 \times 10^8$ M^{-1} s^{-1}).[16]

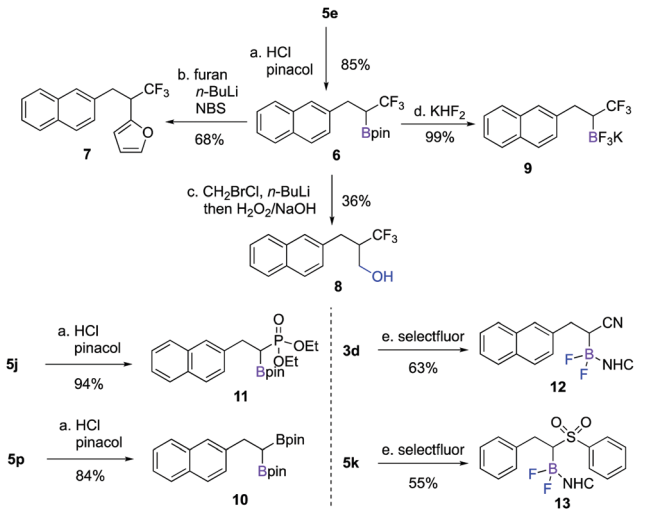
Table 4 Rate constants for NHC–boryl radical addition to varied electron-deficient alkenes

Substrates	1a	4a	4k	4n
k_{add} (M^{-1} s^{-1})	5.13×10^7	1.72×10^6	2.23×10^7	1.23×10^7

It should be noted that no reaction occurred when the β-aryl group in **4** was replaced by an alkyl one. This implies that the electronic properties of substrates play an important role in determining the reactivity. Detailed mechanistic studies for a better elucidation are currently under investigation in our laboratory.

The synthetic utility of the hydroboration products was demonstrated (Scheme 2). Treatment of **5e** with 2 M HCl in the presence of pinacol afforded alkyl pinacol boronic ester **6** in 85% yield. Using Aggarwal's arylation protocol,[18] a furan moiety was incorporated to form product **7** in 68% yield. Homologation of **6** followed by oxidation provided **8** in an overall 36% yield. Furthermore, synthetically useful potassium trifluoroborate **9** was obtained in a quantitative yield after treatment with KHF_2. The NHC–borane handled phosphate **5j** was converted to the corresponding pinacol boronic ester **11** in 94% yield. A *gem*-diboron compound **10** was also isolated in 84% yield. Eventually, NHC–difluoroboranes **12** and **13**, which could be utilized as organoboronic acid derivatives, were accessed following Curran's protocol.[19]

In summary, we have developed a regioselective radical hydroboration of electron-deficient alkenes. This method offers a straightforward and practical route to synthesise a wide range of α-borylated nitriles, trifluoromethyl compounds, phosphonates, sulfones, and *gem*-diboron molecules. The specific α-regioselectivity for β-aryl substituted alkenes is determined by a thermodynamically more favorable α-addition. An energetically more favored HAT from PhSH is responsible for the formation of α-products from β-alkyl substituted α,β-unsaturated nitriles. The resulting borylated products were converted to versatile building blocks. Exploration of their applications in natural product synthesis and medicinal chemistry is currently undergoing in our lab.



Scheme 2 Transformations of hydroboration products. Reaction conditions: (a) aq. HCl (2 M, 3.0 equiv.), pinacol (1.4 equiv.), CH_3CN, 40 °C, 17 h; (b) (1) furan (1.2 equiv.), *n*-BuLi (1.2 equiv.), THF, −78 °C −r.t. 1 h, (2) NBS (1.2 equiv.), THF, −78 °C, 1 h; (c) (1) CH_2BrCl (2.5 equiv.), *n*-BuLi (2.0 equiv.), THF, 18 h, (2) H_2O_2 (30%, 8.0 equiv.), MeOH/MeCN, 40 °C, 20 h; (d) KHF_2 (2.5 equiv.), MeOH, r.t. 3 h; and (e) selectfluor (2.7 equiv.), MeCN, r.t. 4 h.

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Conflicts of interest

There are no conflicts to declare.

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