Boron-Catalyzed Hydroamination/Hydroallylation and Hydroamination/Hydrocyanation of Unactivated Alkynes

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Abstract: $B(C_6F_5)_3$-catalyzed tandem double hydrofunctionalization reactions initiated by intramolecular hydroamination of unactivated alkynes are described herein. In the hydroamination/hydroallylation reaction, in situ preparation of anhydrous $B(C_6F_5)_3$ from $B(C_6F_5)_3{\cdot}nH_2O$ and the use of 2,6-di-*tert*-butylphenol as a proton source were effective. In the hydroamination/hydrocyanation reaction, a combination of $B(C_6F_5)_3{\cdot}nH_2O$ and H_2O as the proton source provided good results.

Nitrogen-containing heterocycles (N-heterocycles) are important substructures in naturally occurring and biologically active compounds.[1] Polysubstituted pyrrolidines are often present in these compounds (Figure 1).[2] Intramolecular hydroamination of unsaturated C–C bonds is an atom economical strategy to construct N-heterocycles.[3] In particular, the double hydrofunctionalization involving intramolecular hydroamination of an alkyne, the formation of iminium species by protonation of the resultant enamine, and addition of a nucleophile, provides a promising methodology for the synthesis of polysubstituted N-heterocycles (Scheme 1a). Che and co-workers reported the Au(I)-catalyzed tandem synthesis of pyrrolo[1,2-*a*]quinolines involving hydroamination/hydroalkynylation.[4] Hammond and co-workers reported Cu(I)-catalyzed hydroamination/hydroalkynylation to synthesize alkynyl-substituted N-heterocycles.[5] They also successfully developed hydroamination/hydrocyanation, hydroamination/hydrotrifluoromethylation, and hydroamination/hydrophosphorylation.[6] An alkynophilic metal catalyst such as Au and Cu enables double hydrofunctionalization reactions.[7] Although several double hydrofunctionalization reactions have been developed, nucleophiles that are applicable to the second hydrofunctionalization are limited.

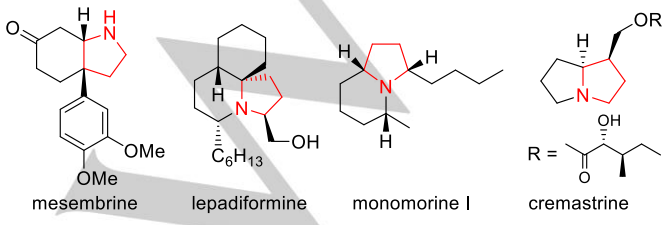
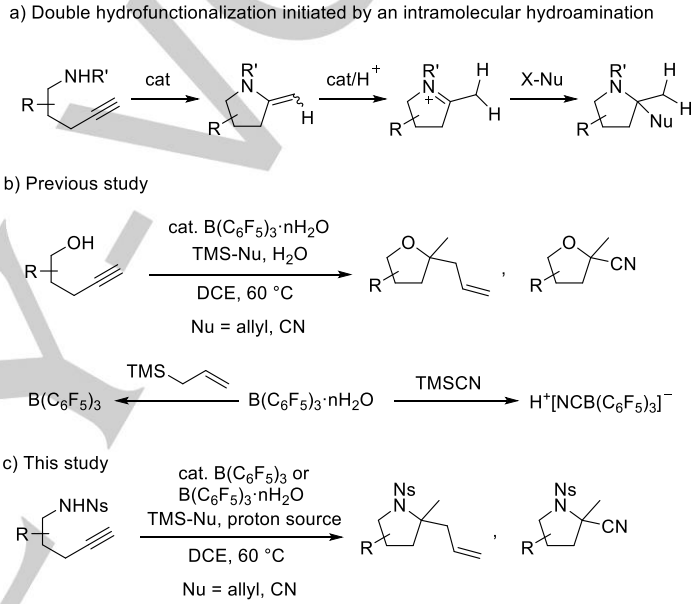


Figure 1. Biologically active compounds that contain polysubstituted pyrrolidines.



Scheme 1. (a) Double hydrofunctionalization initiated by an intramolecular hydroamination. (b) Previous study. (c) This study.

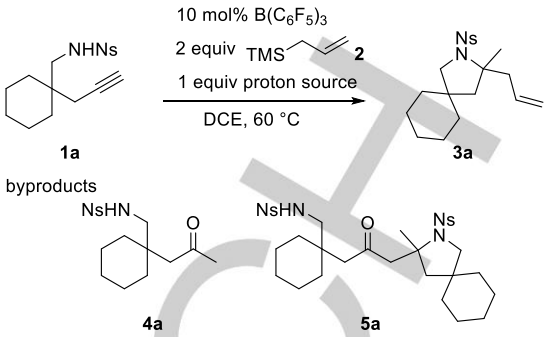
In addition, relatively simple alkynyl amines with no substituents on the linker between the nitrogen atom and alkyne were used in the investigation of these reactions.[5,6] Recently, we reported the intramolecular hydroalkoxylation/hydroallylation and hydroalkoxylation/hydrocyanation by the main group metal catalyst, tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] (Scheme 1b).[8,9] Synthetically versatile allyl and cyano groups can be introduced in a second hydrofunctionalization. In addition, we found unique reactivities: $B(C_6F_5)_3{\cdot}nH_2O$ is dehydrated by allyltrimethylsilane to generate anhydrous $B(C_6F_5)_3$, whereas $B(C_6F_5)_3{\cdot}nH_2O$ reacts with trimethylsilyl cyanide (TMSCN) to generate $H^+[NCB(C_6F_5)_3]^-$.[8,10,11] These catalytic species enable the activation of unactivated alkynes in the presence of the silyl nucleophiles, promoting intramolecular hydroalkoxylation. In this study, we were interested in the applicability of a catalytic system that uses $B(C_6F_5)_3{\cdot}nH_2O$ for intramolecular hydroamination-initiated double hydrofunctionalization reactions (Scheme 1c).

First, we applied the optimal conditions of the hydroalkoxylation/hydroallylation reaction to nosylamide **1a**. As a result, the conversion was low, although a small amount of the desired product **3a** was obtained (Table 1, entry 1). This was

presumably because allylsilane **2** and H_2O (the proton source) were consumed prior to the desired reaction as follows. As we previously reported, $B(C_6F_5)_3{\cdot}nH_2O$ can be dehydrated by allylsilane **2** to produce propylene and TMSOH/TMS_2O with the formation of anhydrous $B(C_6F_5)_3$.[8b] Because the hydration of anhydrous $B(C_6F_5)_3$ immediately occurs in the presence of H_2O, these reactions lead to a shortage of allylsilane **2** and/or H_2O in the reaction mixture. To prevent the reaction of H_2O with allylsilane **2**, several different proton sources instead of H_2O were examined. In the following study, anhydrous $B(C_6F_5)_3$ generated in situ from $B(C_6F_5)_3{\cdot}nH_2O$ and allylsilane **2** was used as the catalyst. This was prepared in the presence of alkyne **1** before the slow addition of a solution of the proton source and allylsilane **2**. When 2,6-dimethylphenol (**6**) was used as the proton source, the reaction efficiency obviously improved, affording **3a** in 60% yield in addition to **4a** and **5a** (entry 2). The uses of phenol (**7**) and 4-nitrophenol (**8**) resulted in a decrease in the yield of **3a** (entries 3 and 4).[12] In these reactions, moderate yields of ketone **4a** and dimeric ketone **5a** were obtained as the byproducts. Specifically, **4a** was produced by the hydrolysis of the corresponding iminium intermediate during the workup process (also see Scheme 2a). Dimer **5a** was formed by the condensation of the corresponding enamine and iminium intermediates followed by hydrolysis. These results suggested that the hydroamination proceeded whereas the following allylation did not occur. This occurred presumably because the direct silylation of the proton source by allylsilane **2** with the production of propylene occurred, resulting in a shortage of allylsilane **2** and/or the proton source. To suppress the undesired reaction, a bulky proton source, 2,6-di-*tert*-butylphenol (**9**), was used. Although 10 mol% $B(C_6F_5)_3$ and 2 equiv of allylsilane **2** still afforded a small amount of **4a** with a 70% yield of **3a,** 20 mol% $B(C_6F_5)_3$ and 5 equiv of allylsilane **2** afforded **3a** in 90% yield without producing detectable amounts of **4a** or **5a** (entries 5 and 6). Reducing the amount of $B(C_6F_5)_3$ or **2** from the reaction conditions of entry 6 had a detrimental effect on the yield of the desired product (entries 7 and 8). Finally, the reaction was examined without the dehydration of $B(C_6F_5)_3{\cdot}nH_2O$ before the reaction (entry 9). This result suggests that in situ preparation of anhydrous $B(C_6F_5)_3$ is necessary before the reaction, even though anhydrous $B(C_6F_5)_3$ can be formed during the reaction without the dehydration operation. Interestingly, while differences in the protocol have a crucial effect on the reaction efficiency of the hydroamination/hydroallylation, this effect was not observed for the hydroalkoxylation/hydroallylation.[8b] Although we also examined the reaction in the presence of allyltributyltin instead of allylsilane **2**, **3a** was produced in low yield.

We explored the substrate scope under the conditions for entry 6 in Table 1 (Table 2). Tosylamide **1b** efficiently underwent the desired reaction to afford **3b** in 69% yield, whereas the reaction of aniline **1c** did not afford the desired product (entries 1 and 2). 4-Alkyl-substituted pyrrolidines **3d** and **3e** were efficiently formed in high yields (i.e., 85% and 74%) with good diastereoselectivities (entries 3 and 4). The reaction of **1f** afforded a moderate yield of 4-phenyl-substituted pyrrolidine **3f**, although the reason of the moderate reaction efficiency was unclear (entry 5). Additionally, 30 mol% $B(C_6F_5)_3$ and 7.5 equiv of allylsilane **2** improved the yield of **3f** to 69%.

Table 1. Optimization of reaction conditions of hydroamination/hydroallylation[a]

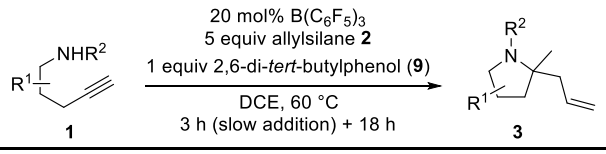


entry	proton source	**3a** (%)	**4a** (%)	**5a** (%)
1	H_2O	16	ND	ND
2[b]	2,6-dimethylphenol (**6**)	60	11	13
3	phenol (**7**)	9	50	5
4[c]	4-nitrophenol (**8**)	17	51	15
5	2,6-di-*tert*-butylphenol (**9**)	70	18	trace
6[c,d,e]	2,6-di-*tert*-butylphenol (**9**)	90	ND	ND
7[d]	2,6-di-*tert*-butylphenol (**9**)	68	6	4
8[e]	2,6-di-*tert*-butylphenol (**9**)	81	<4	<5
9[d,e,f]	2,6-di-*tert*-butylphenol (**9**)	62	12	3

[a] 0.6 equiv allylsilane **2** was added to a solution of 10 mol% $B(C_6F_5)_3{\cdot}nH_2O$ and **2**. After anhydrous $B(C_6F_3)_3$ was prepared, a solution of allylsilane **2** (2 equiv) and the proton source (1 equiv) was slowly added over 3 h at 60 °C. Then, the reaction mixture was stirred for 18 h. [b] The reaction mixture was stirred for 30 min after the slow addition. [c] The reaction mixture was stirred for 18 h. [d] 20 mol% $B(C_6F_3)_3$. [e] 5.0 equiv of allylsilane **2** and 2.0 equiv **9** were used. [f] A solution of 6.2 equiv of allylsilane **2** and 2.0 equiv **9** in DCE was slowly added to a solution of $B(C_6F_5)_3{\cdot}nH_2O$ over 3 h at 60 °C.

The reactions of **1g** and **1h** smoothly proceeded to afford 5-alkyl substituted pyrrolidines **3g** and **3h** in good yields, respectively, although the diastereoselectivities were low (entries 6 and 7). Straight-chain alkyne **1i** also underwent cyclization to afford **3i** in a good yield (entry 8). We observed that the starting materials disappeared right after the complete addition of a solution of **9** and **2** in these reactions, which suggests that intramolecular hydroamination is sufficiently fast compared with the following allylation. However, the hydroaminations of **1j** and **1k** were slow. The reactions of **1j** and **1k** afforded small amounts of **3j** and **3k** with the recovery of **1j** and **1k**, respectively (entries 9 and 10).

Table 2. Substrate scope of the hydroamination/hydroallylation reaction



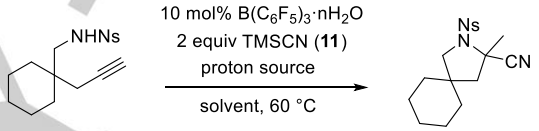
1 3

entry	alkyne	product	Yield (%)[a]	note
1	R = Ts **1b**	**3b**	69	
2	R = Ph **1c**	**3c**	0	**4c** 47%[b]
3	**1d**	**3d**	85 *trans*:*cis* = 93:7	
4	**1e**	**3e**	74 *trans*:*cis* = 89:11	
5	**1f**	**3f**	46 *trans*:*cis* = 93:7 (69 *trans*:*cis* = 93:7)[c]	**4f** 13% (**4f** 2%)
6	**1g**	**3g**	62 *dr* = 55:45	
7	**1h**	**3h**	61 *dr* = 75:25	
8	**1i**	**3i**	75	
9	**1j**	**3j**	12[b] *dr* = 62:38	**1j** 21% **4j** 36%[b] **10j**14%[b]
		10j		
10	**1k**	**3k**	10	**1k** 65% **4k** 14%

[a] Isolated yield. [b] NMR yield. [c] 30 mol% $B(C_6F_5)_3$ and 7.5 equiv of allylsilane were used.

Next, we examined the hydroamination/hydrocyanation using **1a** as a substrate (Table 3). Our previous study suggested that $H^+[NCB(C_6F_5)_3]^-$ formed from $B(C_6F_5)_3$ and TMSCN (**11**) is a catalytic species of the hydroalkoxylation/hydrocyanation.[8b] Therefore, our studies commenced with an investigation of the catalytic reactivity of $H^+[NCB(C_6F_5)_3]^-$ for the hydroamination/hydrocyanation. After the preparation of $H^+[NCB(C_6F_5)_3]^-$ from $B(C_6F_5)_3{\cdot}nH_2O$ and TMSCN (**11**) in the presence of H_2O as the proton source in DCE, alkyne **1a** was added to the solution. Unfortunately, the desired reaction was slow, and **12a** was obtained in 25% yield after 24 h (entry 1). When 3 equiv of TMSCN (**11**) was added to the solution of 10 mol% $B(C_6F_5)_3{\cdot}nH_2O$ with 2.0 equiv of H_2O in DCE, $H^+[(C_6F_5)_3B(\mu\text{-}CN)B(C_6F_5)_3]^-$ was formed as the major species.[13] Thus, after the preparation of $H^+[(C_6F_5)_3B(\mu\text{-}CN)B(C_6F_5)_3]^-$, **1a** was added. As the result, a trace amount of **12a** was formed (entry 2). These Brønsted acids did not show sufficient catalytic activities, whereas **12a** was obtained in a better yield by the protocol used to suppress the formation of the Brønsted acids. More specifically, **1a** was added to the solution of $B(C_6F_5)_3{\cdot}nH_2O$ in DCE before the addition of TMSCN (**11**).

Table 3. Optimization of reaction conditions of hydroamination/hydrocyanation.[a]

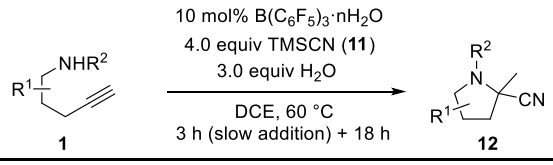


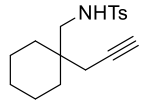
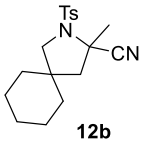
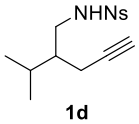
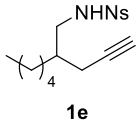
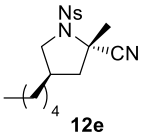
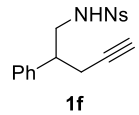
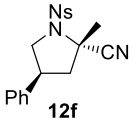
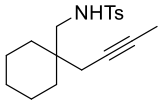
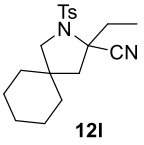
1a 12a

entry	**11** (equiv)	proton source (equiv)[b]	solvent	**12a** (%)[c]	**4a** (%)
1[d]	2.0	H_2O (2.0)	DCE	25 (46)	11
2[e]	3.0	H_2O (2.0)	DCE	trace (89)	trace
3	2.0	H_2O (2.0)	DCE	45 (31)	8
4	4.0	H_2O (2.0)	DCE	74 (8)	1
5	4.0	H_2O (3.0)	DCE	78 (5)	2
6	5.0	H_2O (3.0)	DCE	54 (24)	1
7	4.0	TMSOH (6.0)	DCE	70 (17)	1
8	4.0	**9** (6.0)	DCE	62 (27)	1
9	4.0	H_2O (3.0)	CF_3Ph[f]	72 (10)	5
10	4.0	H_2O (3.0)	1,4-dioxane[f]	30 (30)	2
11[g,h]	5.0	H_2O (3.0)	DCE	93	trace

[a] After **1a** was added to the solution $B(C_6F_5)_3{\cdot}nH_2O$ in DCE, a solution of TMSCN (**11**) and the proton source in DCE was slowly added to the solution over 3 h at 60 °C. Then, the reaction mixture was stirred for 21 h. [b] Numbers in parentheses represent amounts of the proton source. [c] Numbers in parentheses are yields of recovered **1a**. [d] After $H^+[NCB(C_6F_5)_3]^-$ was prepared from 10 mol% $B(C_6F_5)_3{\cdot}nH_2O$ and 2 equiv of TMSCN (**11**) in the presence of 2.0 equiv of H_2O in DCE, a solution of **1a** in DCE was slowly added over 3 h at 60 °C. The reaction mixture was stirred for 21 h. [e] After 3 equiv TMSCN (**11**) was added to the solution of 10 mol% $B(C_6F_5)_3{\cdot}nH_2O$ and 2.0 equiv H_2O in DCE, a solution of **1a** in DCE was added at 60 °C. The reaction mixture was stirred for 21 h. [f] The reaction temperature was 100 °C. [g] 1.0 equiv of $B(C_6F_5)_3{\cdot}nH_2O$ was used. [h] The reaction mixture was stirred for 4 h after the slow addition.

Table 4. The hydroamination/hydrocyanation reaction of different several substrates.



entry	alkyne	product	Yield(%)[a]
1	 **1b**	 **12b**	75 (15)[b]
2	 **1d**	 **12d**	87 (2) *trans*:*cis* = 66:34
3	 **1e**	 **12e**	59 (16)[b] *trans*:*cis* = 59:41
4	 **1f**	 **12f**	56 (8)[b,c] *trans*:*cis* = 62:38
5	 **1l**	 **12l**	46 (26)

[a] Numbers in parentheses are yields of recovered substrates. [b] The desired products were obtained as a mixture with starting materials. The yields were determined by H NMR analysis of the mixture. [c] The reaction time was 3 days.

Although the yield of the desired product **12a** was 45% with the addition of 2 equiv of TMSCN (**11**), the addition of 4 equiv of TMSCN (**11**) improved the yield to 74% (entries 3 and 4). The yield of **12a** slightly improved to 78% in the presence of 3.0 equiv of H_2O (entry 5). Because a small amount of **1a** was still recovered in this case, 5 equiv of TMSCN (**11**) was added (entry 6). However, this led to a decrease in the reaction efficiency. Although other proton sources were screened to improve the reaction efficiency, no better result than that for the reaction using H_2O was obtained (entries 7 and 8). We also conducted the reaction at higher temperature using α,α,α-trifluorotoluene or 1,4-dioxane as the solvent to achieve full conversion (entries 9 and 10). However, **1a** was recovered in both reactions. To probe the cause of the recovery of **1a**, the reaction mixture was analyzed by ^{19}F NMR under the conditions of entry 5. It was observed that $H^+[(C_6F_5)_3B(\mu\text{-}CN)B(C_6F_5)_3]^-$ and the adduct **12a**·$B(C_6F_5)_3$ were formed at the end of the reaction. The formation of adduct **12a**·$B(C_6F_5)_3$ in addition to $H^+[(C_6F_5)_3B(\mu\text{-}CN)B(C_6F_5)_3]^-$ may be one reason that the reaction efficiency decreased. The reaction using 1.0 equiv $B(C_6F_5)_3\cdot nH_2O$ afforded **12a** in 93% yield with full conversion (entry 11).

We examined the hydroamination/hydrocyanation of several substrates under the conditions of entry 5 in Table 3 (Table 4). Although **1b** and **1d** afforded the desired products in high yields, the reactions of **1e**, **1f**, and **1l** were slow to afford the desired products in moderate yields. Simultaneous formations of $H^+[NCB(C_6F_5)_3]^-$ and $H^+[(C_6F_5)_3B(\mu\text{-}CN)B(C_6F_5)_3]^-$ with low catalytic activities may decrease the efficiency of the reaction.

In conclusion, although there is room for improvement, we developed the catalytic hydroamination/hydroallylation reaction and the hydroamination/hydrocyanation reaction of unactivated alkynes to synthesize polysubstituted pyrrolidines. In situ prepared anhydrous $B(C_6F_5)_3$ exhibited a higher catalytic efficiency than $B(C_6F_5)_3\cdot nH_2O$ in the hydroamination/hydroallylation reaction. Low nucleophilic 2,6-di-*tert*-butylphenol was effective as the proton source for hydroamination/hydroallylation. $B(C_6F_5)_3\cdot nH_2O$ worked as the effective catalyst for hydroamination/hydrocyanation. Further efforts to expand the scope of boron-catalyzed double hydrofunctionalization reactions are underway.

Acknowledgements

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Keywords: boron • hydroamination • tandem reaction • allylation • cyanation

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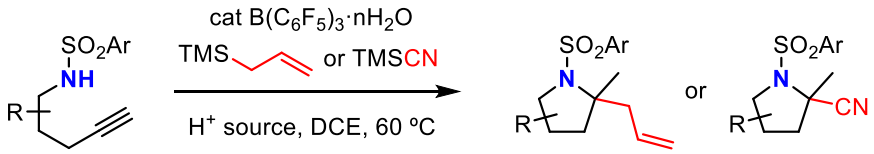

Polysubstituted pyrrolidines can be constructed by intramolecular hydroamination-initiated double hydrofunctionalization reactions. The main group metal catalyst, tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] works as the efficient catalyst. In situ preparation of anhydrous $B(C_6F_5)_3$ from $B(C_6F_5)_3 \cdot nH_2O$ was effective for hydroamination/hydroallylation.