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Chemoselective addition of in situ prepared lithium alkynyl borates to aldehydes: a practical and transition metal free approach toward the synthesis of propargylic alcohols

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ABSTRACT

A convenient synthesis of functionalized propargylic alcohols arising from the 1,2-addition of lithium alkynyl-trimethyl borate onto aldehydes under transition metal free mild conditions is reported. The reaction tolerates a wide range of functional groups, is highly chemoselective and the propargylic alcohols are isolated in good to excellent yields.

1. Introduction

Propargylic alcohols are versatile building blocks in the synthesis of many natural products and pharmaceuticals.[1,2] Over the past few decades many methods to obtain propargylic alcohols have been presented. Most of them involved alkynylmetals in nucleophilic addition to carbonyl compounds. The alkynyl lithium or magnesium reagents generally employed in such processes are typically prepared from acetylene derivatives and organolithium[3] or organomagnesium[4] bases. However such strong basic and nucleophile reagents are often incompatible with a large range of functional groups. Recent efforts on this subject have led to the use of less reactive but highly efficient alkynylmetals involving metal species such as Cs,[5] Zn,[6] In,[7] Rh,[8] Ag,[9] Cu,[10] Ga,[11] Ce,[12] V,[13] B,[14] and Ti,[15] to a large extent in catalytic enantioselective procedures with aldehydes and ketones.

Although many significant results have been achieved in this field, the development of new procedures, allowing for a better compatibility between the reactivity of nucleophilic species and the substitution pattern of carbonyl compounds and alkynes, have still a considerable interest.

Because of their mildness, large availability, and ready preparation,[16] alkynyl borates have been extensively used in organic synthesis. We recently described their use in Pd-catalyzed Suzuki coupling with aromatic halides.[17–19] They also have been successfully used in the addition to aldehydes and ketones as isolated B-alkynyl-9-BBN derivatives.[14]

In this Letter, we describe the use of in situ prepared lithium alkynyltrimethyl borate in the metal-free 1,2-addition to aldehydes as an efficient and selective straightforward way to synthesize propargylic alcohols. This reaction is in agreement of functional-group tolerance, environmental sustainability, and economy, factors that are in constant demand nowadays. Processes that do not require any transition metal catalyst are of great interest because it avoids the elimination of traces of metal in the final compound.

2. Results and discussion

In an initial approach we chose to study the reaction of 1-octyne with benzaldehyde. Hence, the metallation of 1-octyne with 1 equiv of BuLi in THF at −78 °C during 1 h afforded the lithium 1-octynyl intermediate which was treated with 1.35 equiv of trimethylborate in THF at −78 °C. Two hours are normally sufficient to convert the alkynyl lithium in alkynyl borate derivative as confirmed by ^{11}B NMR[20] spectra. Addition by cannula of the in situ prepared lithium octynyl trimethyl borate to the aldehyde in THF at room temperature afforded after 1 h at reflux the desired coupling product in 98% yield. In the same reaction conditions methyl benzoate is completely unreactive in evidence of absence of lithium 1-octynyl intermediate (Scheme 1).

Further investigations showed that oxygenated, polar solvents such as THF and DME, which are equally effective in terms of

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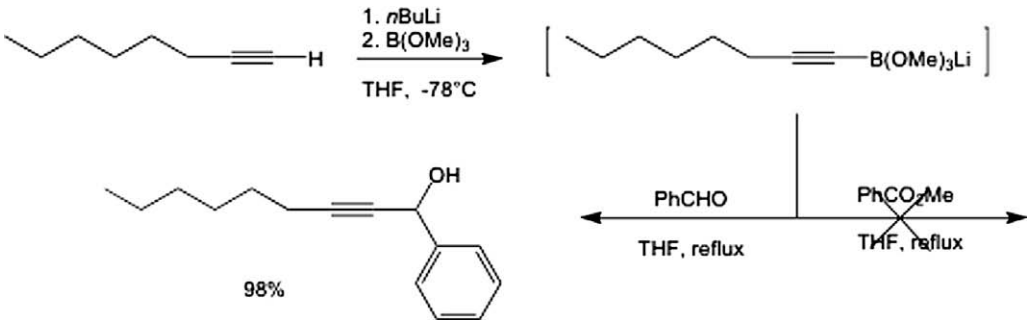


Scheme 1. Differences in the chemical behavior of lithium alkynyl borate with respect to benzaldehyde and benzoic ester.

conversion rates and reaction times, are the most suitable to our purposes. In a typical experiment a solution of lithium alkynyl-trimethyl borate, formed in situ after the addition of $B(OMe)_3$ on the corresponding alkynyl lithium at −78 °C in THF, is added to a solution of the desired aldehyde at room temperature. The temperature is increased to reflux and the aldehyde consumption is monitored by TLC (1–4 h are normally sufficient). This protocol was also demonstrated to work among different alkyne species and a wide series of aldehyde partners. Results obtained with 1-octyne are listed in Table 1.[21]

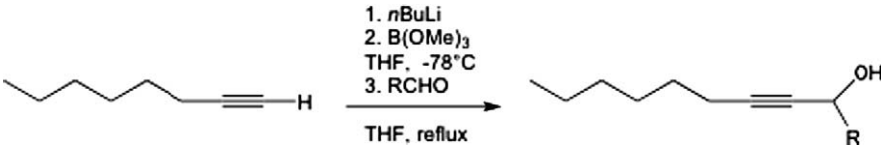
Good to excellent results were obtained in the coupling reaction between lithium octynyl trimethyl borate and aliphatic or aromatic aldehydes. Coupling with activated aromatic aldehydes in the presence of electron-withdrawing substituents on the aromatic moiety led in high yields to the corresponding propargylic alcohols (Table 1, entries 5–8). In cases of entries 6 and 8, 3 equiv of alkynyl borate salt has been used because no reaction occurred under normal conditions. One explanation could be the coordination of the oxygens of the nitro- or ester groups to the boron species. Very interesting are the cases in entries 7 and 8 showing that when the 4-acetyl- and 4-methylcarboxylate-benzaldehyde are used, the coupling reaction occurred exclusively on the aldehyde giving in good yield the corresponding products as a proof of the complete chemoselectivity of this method. We also performed the addition with aromatic aldehydes substituted in *ortho* or *para* position with halide atom (Table 1, entries 9 and 10) giving in satisfactory yields the related propargylic alcohols. In accordance with literature observations, with an electron-donating substituent on the aromatic ring (Table 1, entry 11), only 47% yield of the isolated adduct was obtained as expected in reason of a lower reactivity of the aldehyde toward the carbonyl addition. It has to be noticed that aromatic aldehydes bearing electron-donating substituent are rarely used in those kind of organic processes.

In order to evaluate the scope of the reaction also in regard to the electronic properties of the starting alkyne further tests have been performed. The results with phenylacetylene in association with several aldehydes are presented in Table 2.

In a general extent we observed that phenylacetylene gave good to excellent results with various aldehydes suggesting that electronic properties of the borate intermediate also play a key role. The *i*-butyraldehyde gave the best result (Table 2, entry 2) among the aliphatic aldehydes that have been used (Table 2, entries 1–4). With aromatic aldehydes excellent results were obtained and, to our delight, with electron-donating groups such as a methoxy on the phenyl ring (Table 2, entries 10 and 11) 75% and 98% yields were achieved for *ortho* and *para* position, respectively, despite to their inactivating function. On the contrary the 4-cyano benzaldehyde (Table 2, entry 6) gave only 65% yield. Aromatic aldehydes with halogenated substituent also showed a great reactivity, allowing high yields (Table 3, entries 7–9) especially in the case of a fluorine which gave the addition product in nearly quantitative yield.

The case of TMS substituent, that turns to be useful for further functionalization, was also explored (Table 3) but we observed the

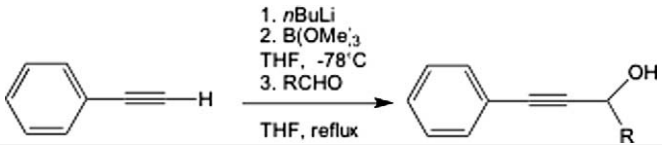
Table 1
1,2-Addition of in situ formed lithium 1-octynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%)
1	C_6H_5	98
2	*n*-C_5H_{11}	65
3	*i*-Pr	65
4	*t*-Bu	99
5	*p*-(CN)C_6H_4	97
6	*p*-(NO_2)C_6H_4[c]	62
7	*p*-(COMe)C_6H_4	68
8	*p*-(CO_2Me)C_6H_4[c]	75
9	*p*-(Br)C_6H_4	61
10	*o*-(F)C_6H_4	68
11	*p*-(OMe)C_6H_4	47

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: 1-octyne/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.
[c] 3 equiv of lithium octynyl trimethyl borate.

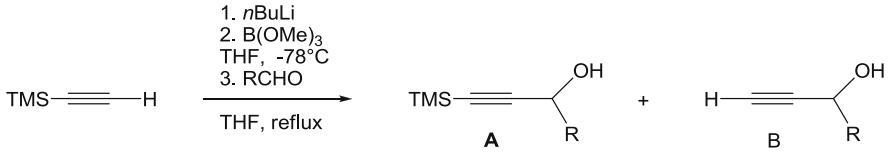
Table 2
1,2-Addition of in situ formed lithium phenylethynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%)
1	*n*-C_5H_{11}	77
2	*i*-Pr	91
3	*t*-Bu	87
4	Cyclohexyl	71
5	C_6H_5	88
6	*p*-(CN)C_6H_4	65
7	*o*-(F)C_6H_4	95
8	*o*-(Cl)C_6H_4	65
9	*p*-(Br)C_6H_4	71
10	*o*-(OMe)C_6H_4	75
11	*p*-(OMe)C_6H_4	98

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: phenyl acetylene/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.

Table 3
1,2-Addition of in situ formed lithium trimethylsilylethynyl-trimethyl borate to aliphatic and aromatic aldehydes[a]



Entry	R	Yield[b] (%) **A** (**A** + **B**)[c]
1	*t*-Bu	89 (95)[c]
2	1-Pentenyl	87
3	C_6H_5	54
4	*p*-(OMe)C_6H_4	56
5	*mm'p*-$(OMe)_3C_6H_2$	(81)[c]
6	*p*-(CO_2Me)C_6H_4	43 (83)[c,d]
7	*p*-(COMe)C_6H_4	48 (99)[c]

[a] Unless otherwise stated, reactions were run under argon by using a commercially available 1.6 M *n*BuLi solution in hexane with the following molar ratios: TMS-acetylene/*n*BuLi/$B(OMe)_3$/aldehyde = 1.3:1.3:1.35:1.
[b] Isolated yields after chromatography.
[c] Yield of compound **A** + **B**.
[d] 3 equiv of lithium octynyl trimethyl borate.

formation of a product which corresponds to the deprotected propargylic alcohol. Excellent yields were reached with aliphatic aldehydes as pivalaldehyde and *n*-hexanal with only 6% of the deprotected triple bond in the case of pivalaldehyde (Table 3, entries 1 and 2). Benzaldehyde and *p*-anisaldehyde are quite equally effective giving 54% and 56%, respectively, of the propargylic alcohol (Table 3, entries 3 and 4). Surprisingly with 3,4,5-trimethoxybenzaldehyde, 81% of the byproduct without TMS was obtained and when the 4-acetyl and the 4-methylcarboxylate benzaldehyde are used, an equal mixture of coupling products with and without TMS is obtained in excellent yields (Table 3, entries 6 and 7). The deprotection of the triple bond is probably caused by two different factors. The excess of the lithiated ate complex, as well as the hydrolysis during the work up, could affect the amount of the deprotected alcohol as confirmed by TLC. Such process seems to be independent from the electronic properties of starting materials.

In summary a new, practical, and efficient reaction involving lithium alkynyltrimethyl borate in the 1,2-addition to aldehydes is presented. This novel process constitutes a straightforward and chemoselective protocol to functionalized propargylic alcohols from simple and cheap precursors. Further studies on an asymmetric version are currently under investigation.

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20. $[B(OMe)_3]$: ^{11}B NMR ($CDCl_3$, 400 MHz, 25 °C) δ 19.7 ppm [lithiated 1-octynyl-trimethyl borate]: ^{11}B NMR ($CDCl_3$, 400 MHz, 25 °C) δ 4.3 ppm.
21. Preparation of lithiated 1-octynyl-trimethyl borate and 1,2-addition to pivalaldehyde (Table 1, entry 4): A solution of *n*-butyllithium (1.6 M in hexane, 1.3 mmol, 800 μL) was slowly added to a solution of 1-octyne (1.3 mmol, 192 μL) in THF (7 mL). After 1 h at −78 °C, trimethyl borate (1.35 mmol, 150 μL) was slowly added and the mixture was stirred for further 2 h. The temperature was raised up to 20 °C during 20 min and the solution was added by cannula to a solution of pivalaldehyde (1 mmol, 110 μL) in THF (1 mL). The reaction was heated under reflux until complete disappearance of the starting aldehyde (TLC) and allowed to cool to room temperature. After the addition of water (15 mL) and extraction with ethyl acetate (3 × 15 mL), the combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent = cyclohexane/ethyl acetate 98:2). Yield 99%.