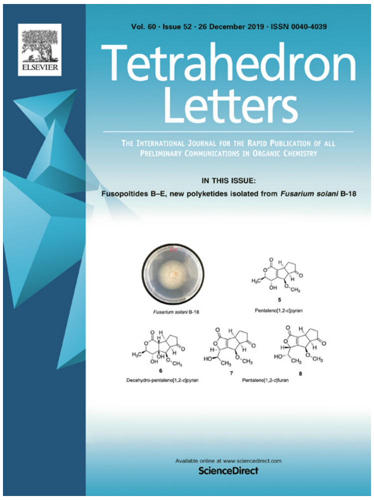

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Solvent- and metal-free hydroboration of alkynes under microwave irradiation

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ABSTRACT

1. Introduction

Boronic ester derivatives are important to create carbon-carbon and carbon-heteroatom bonds[1] as exemplified by the Suzuki-Miyaura cross-coupling reaction,[2] or oxidative boron Heck reaction.[3] The scope of boron-mediated reactions has been expanded in organic chemistry to the design and synthesis of various lead compounds in both the pharmaceutical and agricultural industries.[4,5] Considering the widespread use of organoboron derivatives, it would be of interest to develop a simple and eco-friendlier method to quickly synthesize boronic esters. Alkenylboronic esters have been traditionally obtained by the reactions of Grignard reagents with trialkylboronates but the hydroboration of alkynes has also found to be very efficient.[6,7]

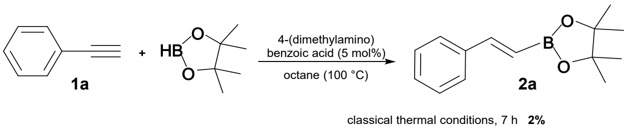
The most often described hydroborations of alkynes were conducted under thermal conditions with prolonged reaction times.[8] Moreover, numerous alkyne borylations have been described including transition metal-catalyzed reactions.[9–12]

In recent years, metal-free approaches have also been investigated: tris(2,4,6-trifluorophenyl)borane could be considered as a good catalyst for the direct hydroboration of terminal alkynes.[13] Another example involved (diacetoxyiodo)benzene (PIDA) catalysis and *t*-BuONa for the highly selective hydroboration of terminal alkynes under air conditions.[14] Recently, Jin and co-workers proposed a hydroboration of alkynes in solution using carboxylic acid-based catalysis.[15] However, the main drawback to these approaches was a prolonged reaction time. Thereby, the microwave-assisted borations of alkynes or alkenes have also been developed, as described by Kappe and co-workers in a one-pot platinum(0)-catalyzed diboration/Suzuki-Miyaura cross-coupling sequence in 1,4-dioxane.[16] Microwave irradiation has also been applied for the dehydrogenative borylations of alkenes in the presence of bis(pinacolato)boron ($B_2(Pin)_2$).[17] Moreover, the microwave-assisted hydroboration of α,β-unsaturated carbonyl compounds has been described in 1,4-dioxane.[11] More recently, it has been shown that microwave irradiation can be used for the hydroboration of alkynes in chloroform in the presence of different boron catalysts.[18]

In this work, we have focused our attention on the synthesis of alkenyl boronates as building blocks under microwave irradiation, using both metal- and solvent-free conditions, an approach that was not described before.

2. Results and Discussion

The hydroboration of phenylacetylene **1a**, was used as a model reaction (Scheme 1). A calibration curve was established using a LC/UV method (see ESI) to determine the yields of boronic ester **2a** in the reaction mixture during the development of the model reaction (Tables 1-5). Isolated yields of all boronic acid pinacol esters **2a-t** were also determined after purification by column chromatography on silica gel.



Scheme 1. Initial conditions for the model hydroboration reaction.

First, the hydroboration reaction of phenylacetylene **1a** was carried out under similar conditions to those described by Jin and co-workers[15] (octane as the solvent at 100 °C) but boronic ester **2a** was only obtained in trace amounts (2%) after 7 hours (Scheme 1). At the same time, **2a** was obtained in 1 otherwise identical reaction conditions. This promising result encouraged us to conduct a methodological study to optimize the reaction conditions. We considered the nature of the solvent, whether or not a solvent was required, the reaction temperature and the reaction time, the nature of the catalyst and its amount.

Considering that octane was not an ideal solvent for microwave irradiation (ε= 1.93 at 30 °C, 1 bar), the reaction was performed in the presence of more polar solvents in which microwave-assisted reactions are reported to proceed more efficiently.[19] Using the converting rules (according to Arrhenius law),[20] the reaction was conducted at 150 °C for 30 minutes in four different solvents as shown in Table 1. Surprisingly, the highest yield of **2a** was still obtained in octane (Table 1, entry 4).

Table 1. Effect of the nature of the solvent.

Entry	Solvent	Yield **2a** (%) ^{a,b}
1	1,4-Dioxane	48
2	Acetonitrile	62
3	Dimethylformamide	3
4	Octane	70

^{a}Reagents and conditions: phenylacetylene **1a** (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), solvent (2.4 mL), 4-(dimethylamino)benzoic acid (5 mol%), microwave irradiation, 150 °C, 30 min. ^{b}Yields were determined using a calibration curve.

This result prompted us to evaluate the importance of the solvent for this hydroboration reaction of alkynes, under metal-free conditions using concomitant microwave irradiation. First, the reaction was carried out at three different temperatures (120 °C, 150 °C and 170 °C) for 15 or 30 minutes, with or without octane for comparison. As shown in Tables 2 and 3, the best result was obtained at 120 °C after 15 minutes irradiation, under neat conditions (77% yield, Table 2 and Table 3, entry 3). However, increasing the reaction time did not improve the yield (Table 3, entries 4-6).

We further investigated the nature of the catalyst for this reaction (Table 4). As Jin and co-workers have shown that the carboxylic group was crucial for the catalytic hydroboration of alkynes with HB(Pin) in octane,[15] different carboxylic acids were evaluated. These results showed that the catalytic activity depends on the acidity of carboxylic acids. The use of stronger acids resulted in lower yields (Table 4, entries 5 and 6). The weaker 4-(dimethylamino)benzoic acid proved to be the best catalyst. It is worth noting that 2-(dimethylamino)benzoic acid was much less efficient under our solvent-free conditions and gave boronic ester **2a** with a very low 4% yield (Table 4, entry 4). This different catalytic activity has previously been reported[15] and could be explained by the formation of an inactive four-coordinate boron species bound to the N and O atoms of 2-(dimethylamino)benzoic acid.

Table 2. Reaction condition optimization in octane or solvent-free medium under microwave irradiation.

	Octane (Yield **2a**, %)^{a,b}			No solvent (Yield **2a**, %)^{a,b}		
	120 °C	**150 °C**	**170 °C**	**120 °C**	**150 °C**	**170 °C**
15 min	14	63	62	77	50	30
30 min	15	70	52	48	20	2

^{a}Reagents and conditions: phenylacetylene **1a** (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), octane (2.4 mL), 4-(dimethylamino)benzoic acid (5 mol%), microwave irradiation. ^{b} Yields of **2a** were determined using a calibration curve after a complete conversion of the substrate **1a**, under microwave conditions at different temperatures and reaction time, in the presence or absence of octane.

Table 3. Microwave-assisted reaction time optimization under solvent-free conditions.

Entry	Time (min)	Yield **2a** (%) ^{a,b}
1	5	38
2	10	57
3	15	77
4	20	64
5	25	54
6	30	48

^{a}Reagents and conditions: phenylacetylene **1a** (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), 4-(dimethylamino)benzoic acid (5 mol%), microwave irradiation, 120 °C. ^{b}Yields were determined using a calibration curve.

Table 4. Influence of various carboxylic acids as catalysts on the hydroboration of phenylacetylene **1a** with HB(Pin).

Entry	Catalyst (pKa)	Yield **2a** (%) ^{a,b}
1	4-nitrobenzoic acid (3.44)	63
2	benzoic acid (4.20)	66
3	4-(dimethylamino)benzoic acid (5.03)	77
4	2-(dimethylamino)benzoic acid (8.42)	4
5	trifluoroacetic acid (0.52)	44
6	formic acid (3.75)	41
7	acetic acid (4.76)	62

^{a}Reagents and conditions: phenylacetylene **1a** (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), carboxylic acid catalyst (5 mol%), microwave irradiation, 120 °C, 15 minutes. ^{b} Yields were determined using a calibration curve.

Finally, we observed that the maximum yield of boronic ester **2a** was observed with 5 mol% of 4-(dimethylamino)benzoic acid (Table 5, entry 3). It is worth noting that an increase of the catalyst amount did not increase the reaction yields (Table 4).

Table 5. Effect of the amount of 4-(dimethylamino)benzoic acid as a catalyst.

Entry	4-(dimethylamino) benzoic acid (mol%)	Yield **2a** (%) ^{a,b}
1	1	31
2	4	64
3	5	77
4	6	71
5	10	70

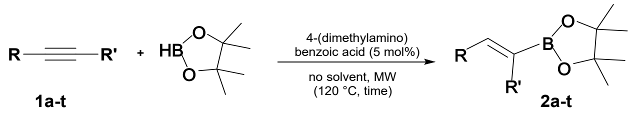
^{a}Reagents and conditions: phenylacetylene **1a** (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), 4-(dimethylamino)benzoic acid (from

1 to

determined using a calibration curve.

At this stage, these new combined solvent- and metal-free hydroboration conditions were applied to a wide scope of aromatic or aliphatic alkynes to obtain the corresponding boronic esters **2a-t** in moderate to excellent yields (Table 6). This reaction proceeded through an *anti*-Markovnikov and *syn*-addition of HB(Pin) to the alkynes.

Table 6. Solvent- and metal-free hydroboration of various aryl- or alkyl-alkynes under microwave irradiation.



Boronic esters	Time (min.)	R	R`	Yield **2** (%) [a,b]
2a	15	Ph	H	62 (77) [c]
2b	15	3-(MeO)C_6H_4	H	60
2c	15	4-(MeO)C_6H_4	H	58
2d	15	$PhCH_2$	H	79
2e	15	Ph	Ph	28
2f	15	3-(MeO_2C)C_6H_4	H	65
2g	15	4-(MeO_2C)C_6H_4	H	48
2h	-	CH_2NH_2	H	0
2i	-	CH_2NHCH_3	H	0
2j	15	CH_2OCH_3	H	34
2k	15	3-Cl-C_6H_4	H	55
2l	15	4-Cl-C_6H_4	H	92
2m	30	$(CH_2)_nCH_3$ n=2	H	35
2n	30	n=3	H	54
2o	30	n=4	H	64
2p	30	n=5	H	58
2q	30	n=6	H	50
2r	30	n=7	H	62
2s	30	n=8	H	61
2t	30	n=9	H	88

[a]Reagents and conditions: alkyne (1 eq, 2.36 mmol), pinacol borane (4 eq, 9.44 mmol), 4-(dimethylamino)benzoic acid (5 mol%), microwave irradiation, 120 °C. [b] Isolated yields. [c] Yield shown in parentheses was determined using a calibration curve. Estimated and isolated yields could differ because boronate **2a** is volatile.

As shown in Table 6, this procedure was compatible with many functional groups such as ethers, esters or chlorine atoms. In the case of the hydroboration of methyl propargyl ether or pent-1-yne, the corresponding boronic esters **2j** and **2m** were obtained with poor isolated yields. In both cases, purification by column chromatography was challenging because the Rf values of the alkyne and the corresponding boronic ester were very close. Moreover, it is worth noting that the hydroboration did not proceed when propargyl amines **2h** and **2i** were used as starting materials. In this case, the reaction resulted in gas release, which was presumably hydrogen, produced after a dehydrocoupling reaction between pinacol borane and amine functionalities.[21]

This method also allowed us to obtain the more sterically hindered *(Z)*-stilbeneboronic acid pinacol ester **2e** from diphenylacetylene and HB(Pin) in a moderate 28% yield. The ^1H NMR spectral characteristics of **2e** were identical to that previously published,[22] attesting to the *syn* addition of HB(Pin) onto the triple bond.

This new method was also applied to alkyl alkynes with a minor adjustment concerning the reaction time. It was observed that the best yields were obtained at 120 °C for 30 min for alkynes having various chain lengths (i.e. C5-C12): the corresponding aliphatic boronic esters **2m-t** were obtained with moderate to good yields. It is important to note that the alkenyl boronic esters **2p-r** were obtained in

ried

out in octane under otherwise identical reaction conditions.

All of the final boronic esters prepared from terminal alkynes (R` = H), were stereoselectively obtained with a *trans* double bond whose stereochemistry was checked by ^1H NMR (the coupling constant $^3J_{HH}$, measured from the displacements of alkenyl protons, was approximately equal to 18 Hz).

3. Conclusion

In this paper, we have developed a solvent- and metal-free approach to synthesize boronic esters under microwave irradiation, which significantly reduced the reaction time from hours to minutes. This simple and eco-friendlier procedure has been applied on a wide scope of aromatic and aliphatic alkynes to lead to the corresponding boronate esters.

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Graphical Abstract

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