

Borylation

International Edition: DOI: 10.1002/anie.201511255
German Edition: DOI: 10.1002/ange.201511255

Transition-Metal-Free Borylation of Allylic and Propargylic Alcohols

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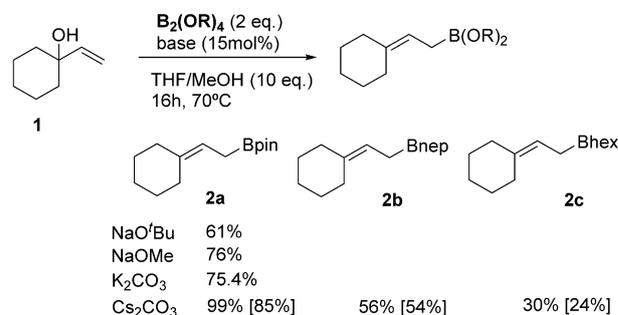
Abstract: The base-catalyzed allylic borylation of tertiary allylic alcohols allows the synthesis of 1,1-disubstituted allyl boronates, in moderate to high yield. The unexpected tandem performance of the Lewis acid–base adduct, $[\text{Hbase}]^+[\text{MeO-B}_2\text{pin}_2]^-$ favored the formation of 1,2,3-triborylated species from the tertiary allylic alcohols and 1-propargylic cyclohexanol at 90 °C.

Allyl boron compounds have become one of the most important reagents for the regio- and stereoselective allylation of carbonyl compounds.^[1] Recently, many excellent applications have been reported, including examples for asymmetric synthesis.^[2] Of course, there is a considerable demand for developing efficient selective synthetic procedures that can access a wide variety of functionalized allyl boron compounds.

Despite the fact that the hydroxy group is one of the most reluctant leaving groups in substitution reactions, the borylation of allylic alcohols has become one of the most suitable methods for preparing the corresponding allyl boronates.^[3] From an economic perspective, allylic alcohols are stable and readily available substrates. However, the main allylic borylation reactions have been performed using activated allylic substrates, such as allylic carboxylates, carbonates, and halides, which are themselves usually prepared from the corresponding allylic alcohols.^[4] In this context, some of us were able to develop a palladium-catalyzed allylic displacement reactions from allylic alcohols, opening a new perspective towards the synthesis and one-pot functionalization of the allyl boronates.^[3a,b,5] In addition, the mechanism of the palladium-catalyzed synthesis of allylic boronates from allylic alcohols has also been investigated in detail.^[6] In the last decade, the discovery of the alkoxide-catalyzed β -borylation,^[7] diboration^[8–10] of unsaturated substrates from diboron reagents, as well as borylation of diaryliodonium salts,^[11] led to the development of conceptually new metal-free borylation reactions with total control of the regio-, diastereo-, and enantioselectivity through quaternized diboron reagents.^[12]

Herein, we aim to converge the two challenges into one, by carrying out the catalytic borylation of allylic alcohols only in the presence of the diboron reagents, base, and MeOH. This idea is based on the finding that alkoxides (formed from MeOH and base) might activate the diboron reagent through direct quaternization of one boryl unit to generate the corresponding Lewis acid–base adduct $[\text{Hbase}]^+[\text{MeO-B}_2\text{pin}_2]^-$, which is characterized by an enhanced nucleophilic character of the B(sp²) unit.^[12a–d]

To experimentally verify the above hypothesis, we selected the commercially available tertiary allylic alcohol 1-vinyl-1-cyclohexanol (**1**) as a model substrate to be borylated in the presence of a series of diboron reagents, such as bis(pinacolato)diboron (**B₂pin₂**), bis(neopentylglycolato)diboron (**B₂nep₂**), and bis(hexyleneglycolato)diboron (**B₂hex₂**), by the sole addition of a catalytic amount of base and MeOH (Scheme 1). We initially conducted several reactions with **B₂pin₂** to identify the optimal base source, as well as the temperature required for high yields. The best yields and selectivities for borylation of **1** were achieved with Cs₂CO₃ at 70 °C, leading to **2a** in an isolated yield of 85%, which represents a significant improvement in comparison with the alternative copper-catalyzed hydroboration of the corresponding allene substrate (66%).^[13]



Scheme 1. Optimized reaction conditions for the metal-free allylic borylation of **1**, with **B₂pin₂**, **B₂nep₂**, and **B₂hex₂**. % NMR yields [% Isolated yields].

Owing to the low efficiency of **B₂nep₂** and **B₂hex₂**, we maintained **B₂pin₂** as the reagent of choice and Cs₂CO₃ as the optimal base in our subsequent investigation into the generality of the reaction. Under the optimal reaction conditions for **1** (Table 1, entry 1) we examined the cyclic tertiary allylic alcohol 1-vinyl-1-cycloheptanol (**3**), 1-vinyl-1-cyclooctanol (**5**), and 1-vinyl-1-cyclododecanol (**7**), which were prepared following a general procedure for the synthesis of tertiary allylic alcohols.^[14] The metal-free borylation produced the corresponding cyclic allyl boronates **4**, **6**, and **8** in quantitative NMR yield and high isolated yields (Table 1, entries 2–4).

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<http://dx.doi.org/10.1002/anie.201511255>.

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Table 1: Substrate scope of the transition-metal-free allylic borylation of tertiary allylic alcohols.^[a]

Entry	Substrate	Product	NMR yield [%] ^[b]	Isolated yield [%]
1			99	85
2	3 n=2	4 n=2	92	84
3	5 n=3	6 n=3	97	79
4	7 n=7	8 n=7	99	79
5	9	10	97	55
6	11	12	95	60
7	13	14	71	42

[a] Reaction conditions: tertiary allylic alcohols (0.3 mmol), B_2pin_2 (2 equiv), Cs_2CO_3 (15 mol%), THF (0.5 mL), MeOH (10 equiv), at 70 °C for 16 h. [b] Yields were determined by 1H NMR analysis of the crude reaction mixture with naphthalene as an internal standard, which was added after the reaction. [c] *E/Z* ratio for **14** is 1:1.

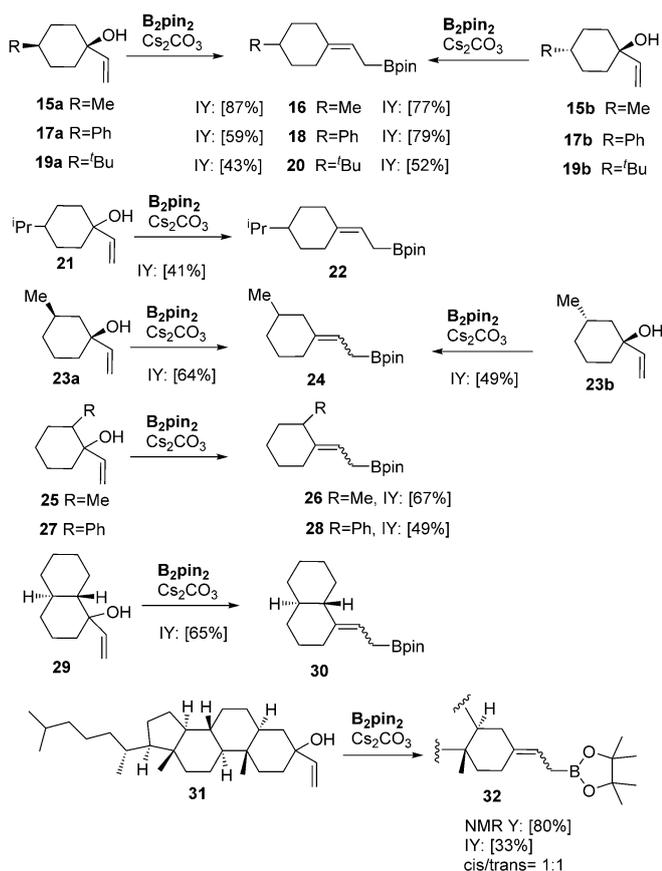
These allyl boronates were synthesized for the first time in this work.

Considering the potentially useful reactivity observed with the cyclic allylic alcohols, we next conducted a series of allylic borylation with acyclic allylic alcohols (Table 1, entries 5–7). Interestingly, under the same reaction conditions, we were able to transform substrates **9**, **11**, and **13** into the corresponding allyl boronates **10**, **12** (as a single diastereoisomer), and **14** (*E/Z* = 1:1). The last reaction was particularly interesting as the allylic borylation was selectively performed over the diboration of the concurrent double bond in substrate **13** (Table 1, entry 7). The synthetic efficiency of the allylboration of tertiary allylic alcohols under the transition-metal-free conditions is comparable to the corresponding methods with palladium catalysis.^[3a,b]

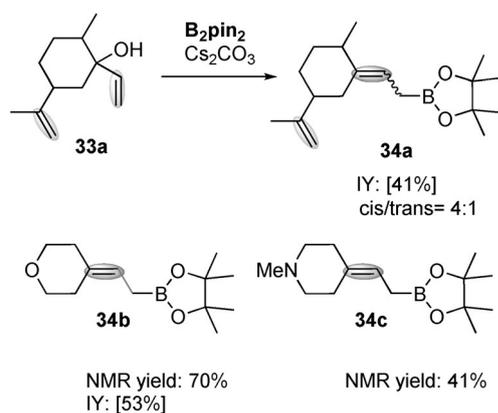
Next, we turned our attention to the substituted cyclohexyl allylic alcohols^[14] to study the influence in the reaction outcome, of the substituents on the cyclic ring (Scheme 2). For these 4-substituted substrates, the two diastereoisomeric alcohols were isolated in pure form,^[15] and in the case of **19b** we obtained the crystal diffraction data to conclude its relative configuration (Supporting Information). Both diastereoisomers (**15a** and **b**) were independently subjected to allylic borylations under the same reaction conditions. Scheme 2 shows an identical product **16** formed in both reactions with similar yields, independently of the relative configuration of **15a** or **15b**. Similar observations were made for the epimeric compounds **17a** and **17b**, as well as **19a** and **19b**. When the cyclohexyl allylic alcohol was 4-substituted with *i*Pr, the mixture of diastereomers could not be separated, so the borylation was carried out directly from substrate **21**, to form the corresponding allyl boronate **22** in moderate yield (Scheme 2). These allyl boronates (**16**, **18**, **20**, **22**) have been reported for the first time in this work.

Moving from 4-substituted to 3- or 2-substituted cyclohexyl allylic alcohols, the transition-metal-free allylic borylation provided mixtures of *cis/trans* allylic boronates. Scheme 2 shows the transformation of the two diastereoisomers of 3-methyl-1-vinyl-1-cyclohexanol (**23a** and **23b**), into the allylic boronate **24** as a 50:50 mixture of isomers. A similar trend was observed for 2-methyl-1-vinyl-1-cyclohexanol (**25**) and 2-phenyl-1-vinyl-1-cyclohexanol (**27**; Scheme 2). The bicyclic substrate **29**, synthesized from decalone in its chiral form, was subjected to the metal-free allylic borylation, and the allylic boronate **30** was isolated in a yield of 65%. The metal-free allylic borylation was also performed for the chiral substrate **31**, prepared from the 5- α -cholestan-3-one, and the corresponding allylic boronate **32** was provided in a 1:1 mixture of *cis/trans* isomers (Scheme 2) with 80% NMR yield, despite the fact it was isolated only in a yield of 33%. All of these allyl boronates (**24**, **26**, **28**, **30**, **32**) were synthesized for the first time in this work.

The tolerance of other functional groups was also studied. We were delighted to see that the allylic borylation was selectively carried out in substrate **33a**, versus the potential metal-free diboration^[8a] of the concurrent double bond (Scheme 3). The reaction was performed under the same optimized reaction conditions, and in this case the *cis/trans* ratio of the product **34a** was 4:1. We also explored the



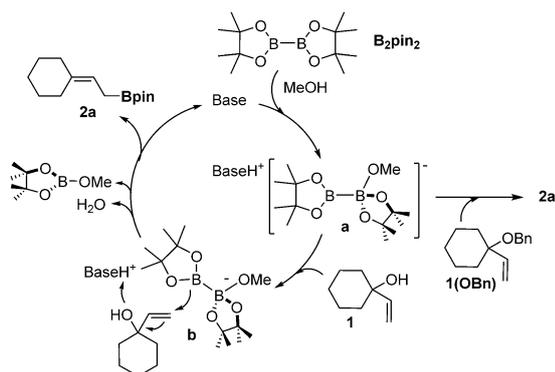
Scheme 2. a) Scope of transition-metal-free allylic borylation of substituted cyclohexyl allylic alcohols (0.3 mmol), B_2pin_2 (2 equiv), Cs_2CO_3 (15 mol%), THF (2.0 mL), MeOH (10 equiv), at 70 °C for 16 h. IY: [%] Isolated yields].



Scheme 3. Transition-metal-free allylic borylation of polyfunctional substituted cyclohexyl allylic alcohols (0.3 mmol), B_2pin_2 (2 equiv), Cs_2CO_3 (15 mol%), THF (0.5 mL), MeOH (10 equiv), at 70 °C for 16 h. [% Isolated yields].

transition-metal-free allylic borylation of N- and O-containing tertiary alcohols. The reactions indeed performed well and showed a high level of functional group compatibility, providing **34b** and **34c** in moderate yield as single isomers (Scheme 3).

The mechanism of this reaction can be best described as an $\text{S}_{\text{N}}2'$ -type process (Scheme 4). Accordingly, the initial step

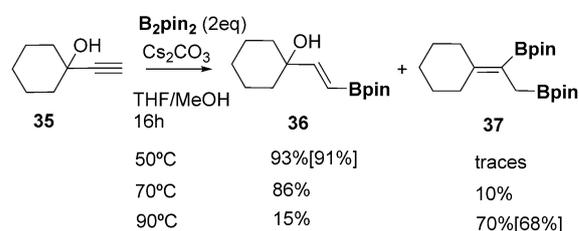


Scheme 4. Suggested mechanism for the metal-free allylic borylation.

is a base-mediated nucleophilic attack by the methoxy group of MeOH on one of the Bpin moieties of B_2pin_2 , to give adduct (**a**). As a consequence, the other Bpin unit becomes nucleophilic,^[12a-d] and attacks the terminal position of alcohol **1**, which leads to C–O bond cleavage in intermediate (**b**). The OH group reacts with the conjugated acid of the base (BaseH^+) to form water and regenerate the base catalyst. Simultaneous formation of the new carbon–boron bond and cleavage of the carbon–oxygen bond of **1** leads to the formation of allyl boronate **2a**. The addition of MeOH and base is a prerequisite for the formation of adduct **a**, and thus for formation of the allyl-Bpin product **2a**. In the absence of MeOH and base, we did not observe any formation of **2a** from **1**. The presence of the unprotected hydroxy group in substrate **1** is also essential. We could not observe any formation of **2a** using benzyl-protected substrate **1(OBn)**

(Scheme 4). A possible explanation for this is that the C–O bond cleavage and/or protonation of the oxygen by BaseH^+ is more difficult in benzyl derivative **1(OBn)** than in **1** with a free hydroxy group. When we carried out the borylation reaction with the secondary alcohol 1-octen-3-ol, the isolated yield was moderate (17%), while the primary alcohol (*E*)-2-octen-1-ol did not react at all. This could be the consequence of the better leaving group ability of a protonated tertiary hydroxy group (such as in **1**) compared to primary or secondary ones. Accordingly, the metal-free borylation method is the most efficient for tertiary allyl alcohols and is limited in scope with primary and secondary allyl alcohol substrates.

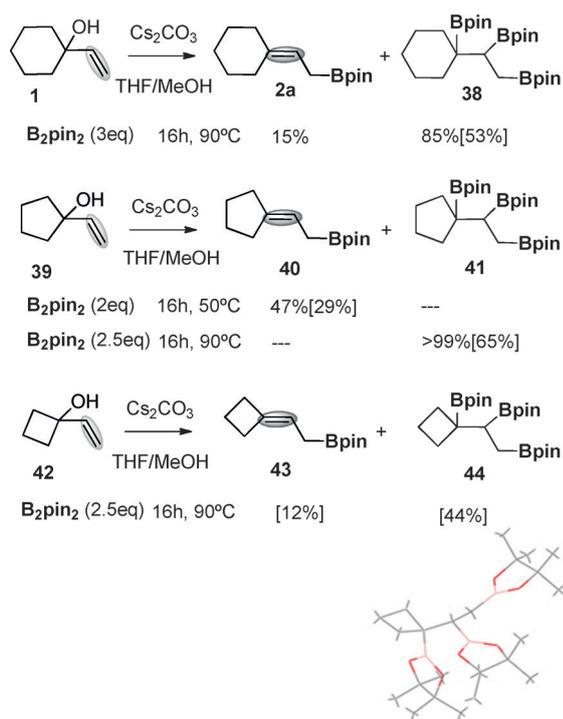
To complement the study, we carried out the metal-free allylic borylation of 1-propargylic cyclohexanol (**35**) and, to our delight, we observed that the main product was the corresponding hydroborated triple bond (**36**), working at 50 °C, with an isolated yield of 91 % (Scheme 5). Interestingly,



Scheme 5. Transition-metal-free allylic borylation of 1-propargylic cyclohexanol (**35**, 0.3 mmol), B_2pin_2 , Cs_2CO_3 (15 mol%), THF (0.5 mL), MeOH (10 equiv), %NMR yields, [% Isolated yields].

by increasing the temperature to 70 or 90 °C, the alkenyl borane **37** was selectively formed, possibly as a consequence of the diboration of the allene intermediate.^[16] Working at 90 °C, it was also possible to observe the allyl boronate **2a** up to 15 % of NMR yield.

Remarkably, the double bond, formed in the allyl boronates during the transition-metal-free allylic borylation, might be susceptible to diboration in the same reaction conditions. Experimentally, when the allylic borylation of the model substrate 1-vinyl-1-cyclohexanol (**1**), is carried out within 90 h at 70 °C, a new product can be identified as the triborated **38** (Scheme 6). Our explanation to understand the in situ formation of **38** is based on the plausible metal-free diboration of product **2a**. This fact was confirmed by a separate study of the metal-free diboration of isolated compound **2a** with 2 equiv of B_2pin_2 and 15 mol % of Cs_2CO_3 at 70 °C for 90 h, leading to **38** in high yields (Supporting Information). This unexpected tandem performance of the Lewis acid–base adduct, $[\text{Hbase}]^+[\text{MeO-B}_2\text{pin}_2]^-$, has not been observed before and it serves as the basis of a new metal-free tandem borylation reaction towards polyborated compounds. Interestingly, when we explored the metal-free tandem allylic borylation/diboration of 1-vinyl-cyclopentanol (**39**) and 1-vinyl-1-cyclobutanol (**42**), the triborylated products were probably mainly formed as a consequence of the



Scheme 6. Transition-metal-free tandem allylic borylation/diboration (0.3 mmol), B₂pin₂, Cs₂CO₃ (15 mol%), THF (0.5 mL), MeOH (10 equiv), % NMR yields, [% Isolated yields]. X-Ray diffraction structure of **44**.

more congested cyclobutane and cyclopentane systems (Scheme 6). The X-ray diffraction structure of 1,2,3-polyborylated product **44** is shown in Scheme 6.^[17]

To conclude, we have developed an unprecedented metal-free allylic borylation of tertiary allylic alcohols that provides access to new allylic boronates. The reactions are carried out in the presence of 15 mol% of Cs₂CO₃ and MeOH to promote the formation of the Lewis acid–base adduct, [Hbase]⁺[MeO-B₂pin₂]⁻, which may also be responsible for the in situ diboration of the allylic double bond that generates 1,2,3-polyborylated products.

Acknowledgements

The present research was supported by the Spanish Ministerio de Economía y Competitividad (MINECO) through project CTQ2013-43395P. KJS thanks the Swedish Reserach Council and the KAW foundation for support. We thank AllyChem for the gift of diboranes.

Keywords: allyl boronates · allylic alcohols · allylic borylation · metal-free · polyboronates

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4303–4307
Angew. Chem. **2016**, *128*, 4375–4379

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- [17] CCDC 1455256 and 1455255 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: December 4, 2015

Revised: February 9, 2016

Published online: March 2, 2016