ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, 55, 458

Received 20th November 2018,
Accepted 5th December 2018

DOI: 10.1039/c8cc09229j

rsc.li/chemcomm

Electrophilic cyanation of allylic boranes: synthesis of β,γ-unsaturated nitriles containing allylic quaternary carbon centers†

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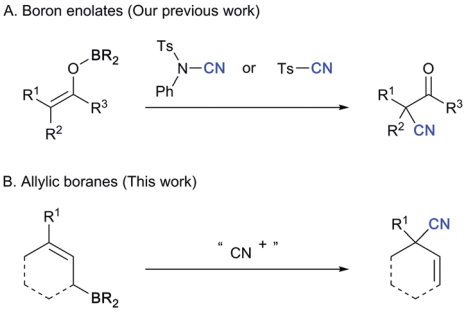
The electrophilic cyanation of allylic boranes, a process that is applicable to the construction of allylic quaternary carbon centers, is reported. The reaction has a broad substrate scope with a high functional group tolerance. The results represent an unprecedented and powerful tool for preparing synthetically useful β,γ-unsaturated nitriles, including derivatives that have been difficult to access using existing methods. The synthetic utility of the method was further demonstrated by functional group interconversions of the cyano group of the products.

Introducing a cyano group into an organic molecule is one of the most fundamental methods for preparing nitriles, an important class of compounds that have wide applications in organic synthesis, pharmaceuticals, and material science.[1] Over the past few decades, considerable efforts have been expended in attempts to develop efficient and selective cyanation methods.[2] Reactions that permit a cyano group to be introduced at allylic positions provide a straightforward access to synthetically versatile β,γ-unsaturated nitriles. Although several methods, such as nucleophilic allylic cyanation[3] and the carbo- and hydrocyanation of dienes,[4,5] have been reported, these reactions often suffer from site selectivity and limited substrate scope. It is particularly noteworthy that a reaction that allows the construction of an allylic quaternary carbon center remains largely undeveloped.

Electrophilic cyanation has emerged as a promising tool for nitrile synthesis.[6] Our group recently reported that dialkylboron enolates could be used in electrophilic cyanation reactions using readily available cyanating reagents, such as *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) and *p*-toluenesulfonyl cyanide (TsCN), providing efficient access to β-ketonitriles containing an α-quaternary carbon center (Scheme 1A).[7] The cyanation was found to proceed *via* an activation process that involved the formation of a six-membered ring transition state, in which a cyano group of the cyanating reagent coordinates to the Lewis acidic boron center of the boron enolate.[7b] This finding prompted us to explore the synthetic potential of the electrophilic cyanation of organoboron nucleophiles in more detail. Herein, we report that the electrophilic cyanation of allylic boranes leads to the formation of β,γ-unsaturated nitriles. The reaction proceeds with complete allylic transposition, thus permitting allylic quaternary carbon centers to be constructed by employing γ,γ-disubstituted allylic boranes (Scheme 1B). Although allylic boranes have found countless applications in the field of organic synthesis,[8,9] the present study appears to be the first example of their use in cyanation and provides a powerful tool for the synthesis of β,γ-unsaturated nitriles.[10]

We began our investigation by examining the electrophilic cyanation of an allylic borane that was prepared by the hydroboration of an allene with 9-BBN.[11] Allene **1a** as a model substrate was treated with 9-BBN at room temperature for 4 h, and the resulting allylic borane **3a** was subsequently subjected to cyanation with NCTS at the same temperature, affording the desired β,γ-unsaturated nitrile **2a** in 78% yield as a single isomer (Table 1, entry 1). This result indicates that an *in situ* generated γ,γ-disubstituted allylic borane **3a** underwent cyanation with complete allylic transposition, which would be



Scheme 1 Electrophilic cyanation of boron nucleophiles.

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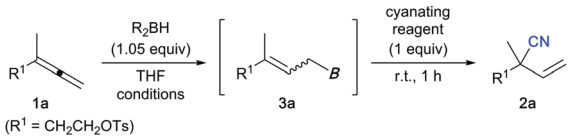
† Electronic supplementary information (ESI) available: Experimental details, characterization data, and spectra. See DOI: 10.1039/c8cc09229j

Table 1 Optimization of reaction conditions[a]

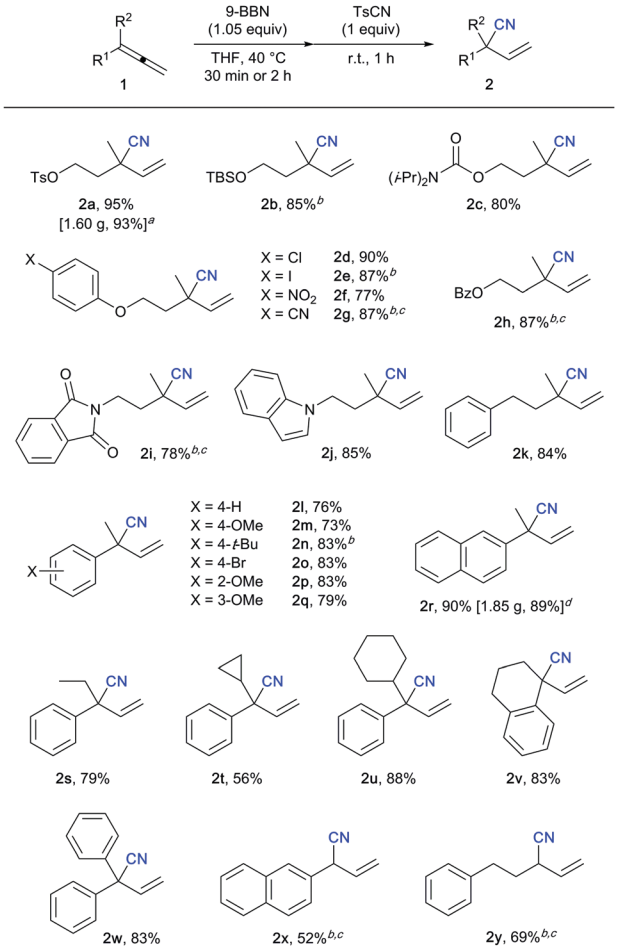


Entry	R_2BH	Conditions	Cyanating reagent	Yield of **2a**[b] [%]
1	9-BBN	r.t., 4 h	NCTS	78
2	Cy_2BH	r.t., 4 h	NCTS	59
3	CatBH	r.t., 4 h	NCTS	0
4	9-BBN	40 °C, 30 min	NCTS	91
5	9-BBN	40 °C, 30 min	TsCN	>95
6	9-BBN	40 °C, 30 min	BrCN	88
7	9-BBN	40 °C, 30 min	BnSCN	59

[a] Reactions were performed on a 0.6 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude product using mesitylene as an internal standard.

predicted to proceed *via* a six-membered ring transition state. The use of dicyclohexylborane (Cy_2BH) resulted in the formation of **2a** in a lower yield than that with 9-BBN (entry 2). Meanwhile, when catecholborane (CatBH) was used (entry 3), the desired product was not obtained and most of the starting material **1a** was recovered. A key to the success of this cyanation method is the use of 9-BBN, leading to the formation of a reactive allylic borane, the boron center of which is sufficiently Lewis acidic to permit a cyanating reagent to be activated.[12] Screening of the reaction conditions, including the reaction temperature and time, revealed that conducting the hydroboration with 9-BBN at 40 °C for 30 min, followed by cyanation, increased the yield of **2a** to 91% (entry 4). It should also be noted that, in addition to NCTS, several commercially available cyanating reagents were found to be applicable for use in this reaction (entries 5–7). TsCN was particularly reactive, leading to the quantitative formation of **2a**.

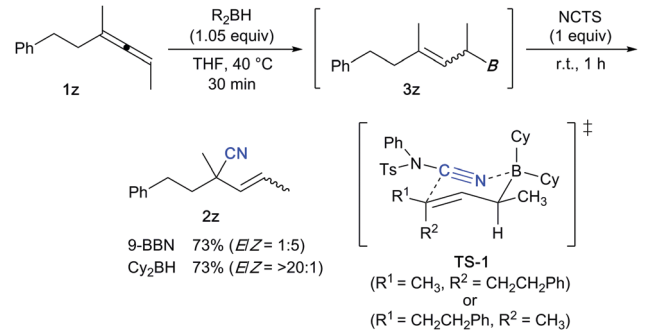
With the optimized reaction conditions identified, we next investigated the substrate scope of the method (Scheme 2). A number of 1,1-disubstituted allenes were subjected to the hydroboration/cyanation sequence, and all of the reactions proceeded with complete regioselectivity, affording the corresponding β,γ-unsaturated nitriles bearing an allylic quaternary carbon center. Such compounds are difficult to access using existing methods.[3–5,13] The synthetic utility of this cyanation was demonstrated by a gram-scale reaction using **1a**, which resulted in the formation of **2a** in excellent yield (1.60 g, 93%). In addition to a tosyl-protected alcohol moiety, a *tert*-butyldimethylsilyl (TBS)-protected one was also well tolerated under the reaction conditions (**2b**). This cyanation was also found to be compatible with various functional groups, which include carbamoyl (**2c**), chloro (**2d**), iodo (**2e**), nitro (**2f**), cyano (**2g**), ester (**2h**), phthaloyl (**2i**), and indolyl (**2j**) groups. It should be noted here that reactions of **1g–i** were conducted with NCTS instead of TsCN, and that all of the reagents were added in succession to avoid side reactions that were observed when the standard stepwise protocol was used, in which *in situ* generated allylic boranes were thought to react with functionalities of those substrates prior to adding a cyanating reagent.



Scheme 2 Scope of terminal allenes. Reactions were performed on a 0.6 mmol scale. Yields are isolated yields. [a] The reaction was conducted on a 6 mmol scale. [b] NCTS was used instead of TsCN. [c] 9-BBN, **1**, THF, and NCTS were added in succession, and the mixture was stirred at 40 °C for 1.5 h. [d] The reaction was conducted on a 10 mmol scale.

Allylic boranes prepared from allenes bearing aromatic substituents also participated in the selective electrophilic cyanation. The reaction appears to be insensitive to electronic and steric effects of the aryl substituents (**2l–q**). The substrate containing a 2-naphthyl group reacted well also on a larger scale reaction, providing **2r** highly efficiently (1.85 g, 89%). The replacement of a methyl group with ethyl (**2s**), cyclopropyl (**2t**), and more sterically hindered cyclohexyl (**2u**) groups at the reaction site had a slight effect on the reaction. Although the yield of **2t** was moderate, no product was produced as a result of the ring-opening of the cyclopropyl group, indicating that the cyanation does not involve a radical process. Using this protocol, it was possible to install a cyano group on a cyclohexane framework (**2v**). 1,1-Diphenyl allene underwent smooth cyanation to provide **2w**. Moreover, mono-substituted allenes could also be used in this cyanation, affording **2x** and **2y** in good yields.

A trisubstituted allene was also found to be a suitable substrate for this cyanation (Scheme 3). When allene **1z** was subjected to the standard reaction conditions using 9-BBN,



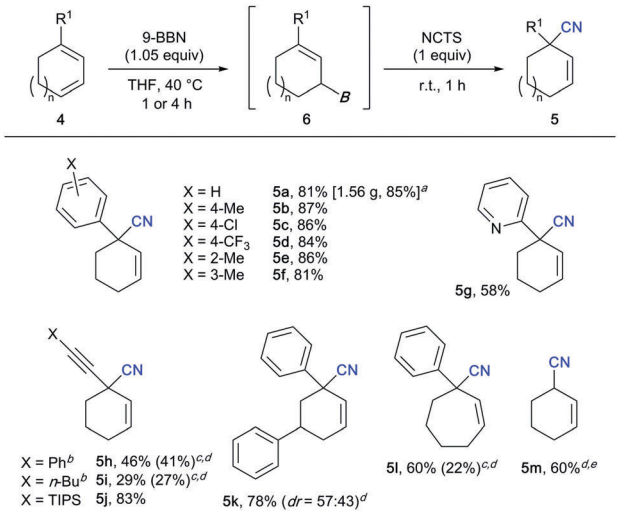
Scheme 3 Reaction using a trisubstituted allene.

the corresponding product **2z** was obtained in good yield but as a mixture of geometric isomers (*E*/*Z* = 1 : 5). After a brief screening of boranes, we were pleased to find that the use of Cy_2BH instead of 9-BBN led to (*E*)-**2z** being produced as a single isomer. These stereoselectivities can be explained by the formation of a chair-like six-membered ring transition state in the cyanation step.[7b,10] The reaction using Cy_2BH would proceed through **TS-1**, in which a methyl group at the α-position of the allylic borane **3z** adopts an equatorial position, leading to the formation of the (*E*)-isomer, while the methyl group would be expected to adopt an axial position to minimize steric repulsion between the methyl group and the 9-BBN backbone when 9-BBN is employed.[14,15]

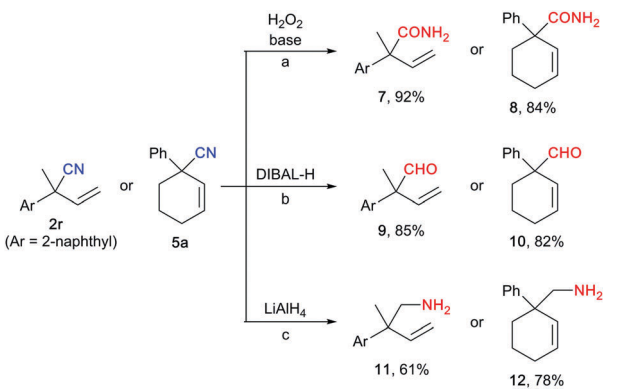
To expand the scope of this electrophilic cyanation, allylic boranes prepared from cyclic 1,3-dienes by hydroboration with 9-BBN were next examined (Scheme 4).[16] Cyclic alk-1-enecarbonitrile derivatives, which can be synthesized by the present reaction, are also attractive synthetic intermediates for preparing potential bioactive compounds.[13l] The treatment of 1-phenyl cyclohexa-1,3-diene (**4a**) with 9-BBN at 40 °C for 1 h, followed by cyanation with NCTS at room temperature, afforded the desired **5a** in 81% yield as a single product. This result clearly indicates that the site-selective hydroboration at the sterically less hindered alkene moiety of **4** provided the allylic borane **6** that then underwent cyanation. This reaction system was successfully applied to various 1-substituted cyclohexa-1,3-dienes. The electronic and steric effects of aryl substituents at the 1-position had no noticeable effect on the yield (**5a–f**). The cyanation proceeded well even in the presence of a Lewis-basic pyridine moiety (**5g**). An alkyne functionality was incompatible with the standard stepwise protocol, leading to a complex mixture, while the method, in which all of the reagents are added in succession, provided **5h** and **5i** in low yields along with several unidentified byproducts and the recovered starting materials. A sterically hindered (triisopropylsilyl)ethynyl group remained intact to afford the desired product **5j** in high yields. A phenyl substituent at the 5-position did not affect the reactivity and regioselectivity, and a diastereomeric mixture of nitrile **5k** was obtained in a 78% combined yield. In addition to cyclohexa-1,3-dienes, a cyclohepta-1,3-diene derivative was also a suitable substrate for this cyanation process (**5l**). Using this method, cyclohexa-1,3-diene was converted to **5m** in a moderate yield.

The synthesized β,γ-unsaturated nitriles could be readily converted into other useful compounds through functional group interconversions, as shown in Scheme 5. For example, the hydrolysis of **2r** and **5a** using hydrogen peroxide in the presence of a catalytic amount of a base proceeded effectively to afford amides **7** and **8**, respectively. In addition, the nitriles were readily partially reduced by DIBAL-H leading to aldehydes (**9** and **10**) and full reduction by $LiAlH_4$ led to the formation of amines (**11** and **12**). These products can also serve as platforms for further chemical elaborations, illustrating the synthetic utility of this cyanation.

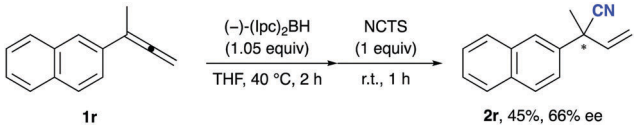
Finally, the enantioselective version of this electrophilic cyanation was investigated by employing a chiral allylic borane



Scheme 4 Scope of cyclic 1,3-dienes. Reactions were performed on a 0.6 mmol scale. Yields are isolated yields. [a] The reaction was conducted on a 10 mmol scale. [b] The reaction was conducted on a 1 mmol scale. 9-BBN, **4**, THF, and NCTS were added in succession, and the mixture was stirred at 40 °C for 2 h. [c] Recovered starting materials. [d] Determined by the ^1H NMR analysis of the crude product. [e] Cy_2BH was used instead of 9-BBN, and the hydroboration was conducted at r.t. for 4 h.



Scheme 5 Functional group interconversions of β,γ-unsaturated nitrile products. (a) For **2r**: H_2O_2 (aq., 2.2 equiv.), NaOH (aq., 0.3 equiv.), DMSO, 0 °C to r.t., 5 h. For **5a**: H_2O_2 (aq., 2.2 equiv.), K_2CO_3 (0.16 equiv.), DMSO, 0 °C to r.t., 16 h. (b) DIBAL-H (1.2 equiv.), toluene, 0 °C, 24 h. (c) $LiAlH_4$ (1 equiv. for **2r** and 2 equiv. for **5a**), Et_2O, 0 °C to r.t., 3 h.



Scheme 6 Enantioselective electrophilic cyanation using a chiral allylic borane.

prepared from diisopinocampheylborane [(−)-(Ipc)$_2$BH] and **1r**, and the cyanation resulted in the formation of (*S*)-**2r** in a 66% enantiomeric excess (Scheme 6).[17,18] This preliminary result, albeit with moderate enantioselectivity, indicates that the present method offers a promising strategy for the construction of quaternary carbon stereogenic centers at an allylic position in acyclic systems, which is an important research topic in synthetic organic chemistry.[19]

In conclusion, we report the electrophilic cyanation of allylic boranes, which can be readily prepared by the hydroboration of allenes and cyclic 1,3-dienes, for the selective and efficient formation of synthetically useful β,γ-unsaturated nitriles. This process is operationally simple, easily scalable, and displays a broad substrate scope with a high functional group tolerance. The present method represents a new entry into synthetic applications of allylic boranes. Further investigations of this method in organic synthesis including enantioselective reactions based on this preliminary result are currently in progress.

This work was supported by the JSPS KAKENHI Grant Number 18K14217.

Conflicts of interest

There are no conflicts to declare.

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