Synthetic methods

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Electrophilic Cyanation of Boron Enolates: Efficient Access to Various β-Ketonitrile Derivatives

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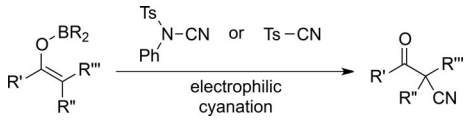
Abstract: *The highly efficient electrophilic cyanation of boron enolates using readily available cyanating reagents, N-cyano-N-phenyl-p-toluenesulfonamide (NCTS) and p-toluenesulfonyl cyanide (TsCN), is reported. Various β-ketonitriles were prepared by this new protocol, which has a remarkably broad substrate scope compared to existing methods. The present method also allowed efficient synthesis of β-ketonitriles containing a quaternary α-carbon center. In addition, a preliminary result with the use of a chiral boron enolate for the enantioselective cyanation reaction is described.*

β-Ketonitriles are important building blocks for the synthesis of various heterocycles such as pyrazoles,[1] pyrimidines,[2] thiophenes,[3] and others,[4] which are frequently found in pharmaceuticals and biologically active compounds. In addition, β-ketonitriles can be converted into optically active β-hydroxy nitriles, by the enantioselective reduction of the carbonyl group,[5] which are also valuable synthetic intermediates in organic synthesis. Therefore, in the past decades considerable effort has been devoted to the development of methodologies for the synthesis of β-ketonitriles.[6] Among them, the condensation of alkyl nitriles with acylating reagents such as esters, Weinreb amides, and *N*-acylbenzotriazoles in the presence of a strong base are currently the most widely employed methods.[7] Nevertheless, these methods usually require an excess amount of the substrate and base. Alternatively, nucleophilic substitution with a cyanide on an α-haloketone has been also used, but the method suffers from several drawbacks such as limited substrate scope and harsh reaction conditions, especially when secondary and tertiary halides are involved.[8] Although the electrophilic cyanation of ketones is also a promising approach to the synthesis of β-ketonitriles, published reports concerning this approach are limited. A practical method for the electrophilic cyanation of ketones often employs enolates or enolate equivalents as the nucleophile.[9] An early report is the reaction of cyclic enamines with the highly toxic cyanogen chloride (ClCN).[10,11] Lithium enolates can react with *p*-toluenesulfonyl cyanide (TsCN) and phenyl cyanate,[12] but these methods were also limited to the use of cyclic ketone derivatives. Although the reaction of silyl enolates with a hypervalent-iodine-based cyanating reagent has recently been reported,[13] the method still remains limited to a narrow substrate scope and low efficiency.[14,15]

Meanwhile, boron Lewis-acid-promoted electrophilic cyanation has emerged in recent years as a useful strategy for introducing a cyano group into a nucleophilic substrate.[16,17] In this context, we envisioned that boron enolates, in which the boron center can interact with the cyano group of a cyanating reagent, would be a promising nucleophile for electrophilic cyanation. Herein, we report on the highly efficient electrophilic cyanation of boron enolates with either *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS)[18,19] or TsCN as a cyanating reagent, thus affording β-ketonitriles (Scheme 1). Various types of boron enolates, prepared by the



Scheme 1. Electrophilic cyanation of boron enolates. Ts = *p*-toluenesulfonyl.

1,4-hydroboration of α,β-unsaturated ketones and the base-mediated enolization of simple ketones, were applicable to this new protocol. β-Ketonitriles bearing a quaternary α-carbon center, which is difficult to access by existing methods, could also be prepared by this method.

We initially chose NCTS, which has been employed in electrophilic cyanation reactions promoted by boron Lewis acids,[16a,b] as a cyanating reagent to investigate the cyanation of boron enolates derived from chalcone (**1a**; Table 1).[20] A brief screening of borane derivatives revealed that the boron enolate prepared using 9-borabicyclo-[3.3.1]nonane (9-BBN) reacted smoothly with NCTS in THF at ambient temperature, thus affording the desired product **2a** in 84% yield, along with a small amount of the boron complex **2a′** as a by-product (entry 1).[21] In contrast, the cyanation of both of the boron enolates prepared, using dicyclohexylborane ($HBCy_2$) and catecholborane (HBcat), were largely suppressed (entries 2 and 3). The product distribution between **2a** and **2a′** was dramatically changed by the choice of solvent, although the nature of this solvent effect on this reaction is not clear at this stage. For example, the reaction with the 9-BBN-based enolate in Et_2O provided **2a** and **2a′** in 75 and 10% yields, respectively (entry 4), while higher yields of **2′** were obtained when toluene and CH_2Cl_2 were used as solvents, thus lowering the yield of **2a** (entries 5 and 6). When the reaction was conducted in MeCN, the hydroboration was incomplete, and

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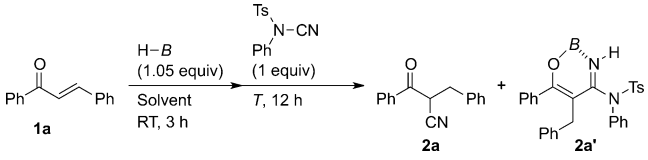
Table 1: Optimization of the cyanation of boron enolates prepared by the 1,4-hydroboration of chalcone.[a]

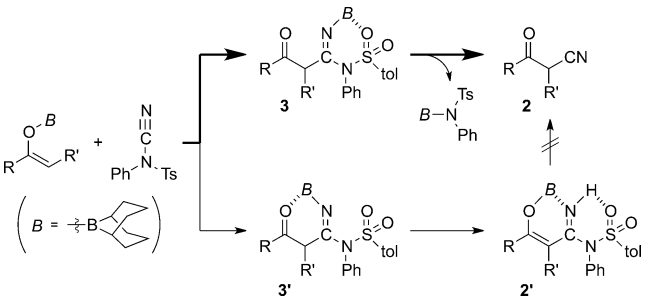


Entry	H-*B*	Solvent	*T* [°C]	Yield [%][b]	
				2a	**2a′**
1	9-BBN	THF	RT	84	7
2	$HBCy_2$	THF	RT	8	0
3	HBcat	THF	RT	0	17
4	9-BBN	Et_2O	RT	75	10
5	9-BBN	toluene	RT	58	24
6	9-BBN	CH_2Cl_2	RT	42	45
7	9-BBN	MeCN	RT	26	14
8	9-BBN	THF	40	90	< 5
9[c]	9-BBN	THF	40	93 (84)	< 5

[a] Reaction conditions: **1a** (0.5 mmol), borane (0.525 mmol), solvent (1 mL), NCTS (0.5 mmol), RT. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. The value within parentheses refers to the yield of the isolated product. [c] 9-BBN, **1a**, NCTS, and THF were added in succession.

50% of **1a** was recovered (entry 7). When the reaction temperature was increased to 40 °C in THF, the production of **2a′** was suppressed, and the yield of **2a** was increased to 90% (entry 8). Furthermore, the highest yield of **2a** (84% yield) was obtained when all of the reagents were added in succession, thus demonstrating that the prior in situ preparation of the boron enolate is not required for this reaction (entry 9). In addition, an examination of other electrophilic cyanogen sources revealed that TsCN was also a suitable reagent, but cyanogen bromide, thiocyanate, and hypervalent iodine reagents gave lower yields of **2a**.[22]

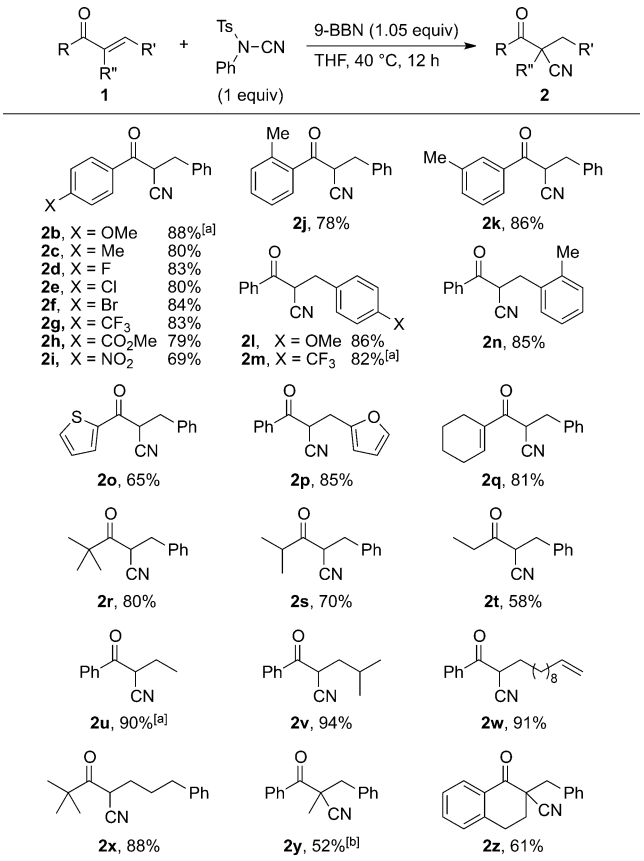
Control experiments using the corresponding silyl enolate, instead of the boron enolate derived from **1a**, failed to give the cyanated product **2a** in both the absence and presence of a boron Lewis acid. The corresponding lithium enolate gave **2a** but the yield was moderate.[22] These results clearly show that the use of a boron enolate is crucial for the success of this conversion. Although details of the reaction mechanism are not yet clear, we postulate the following reaction pathway: The reaction is assumed to be triggered by the sufficient activation of NCTS by the coordination of its cyano group to the strained and Lewis-acidic boron center of the 9-BBN-based boron enolate. This coordination would enhance the nucleophilicity of the boron enolate, thus promoting the addition to the cyano group of NCTS.[23] However, no direct evidence for the interaction between the cyano group and the boron center has been obtained at this stage.[24] After the nucleophilic attack of a boron enolate to the cyanao group of NCTS, two types of intermediates, namely, **3** and **3′**, would be generated (Scheme 2). When the intermediate **3**, the boron center of which is coordinated by the sulfonyl group, is generated, the elimination of the amide moiety occurs, thus leading to the formation of the cyanated product **2**. The Lewis-acidic boron center would also be expected to play a key role in this elimination step. The



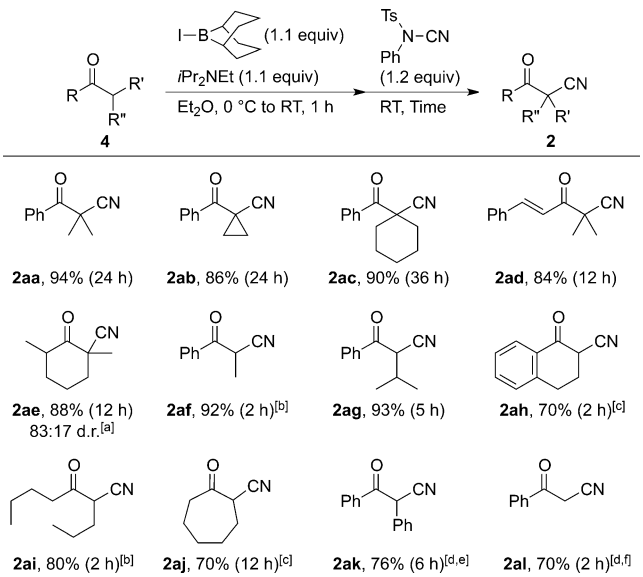
Scheme 2. Plausible reaction pathway.

product **2′** would be generated by the minor pathway. In contrast to the intermediate **3**, the formation of **3′**, the boron center of which is coordinated by the carbonyl group, did not induce the elimination of the amide moiety. Thus **3′** undergoes isomerization to give the highly stable product **2′**. Indeed, isolated boron complex **2a′** was not converted into the **2a** when exposed to the above reaction conditions (40 °C in THF), thus indicating that **2′** is not an intermediate for this cyanation.[22]

With the optimized reaction conditions identified (Table 1, entry 9), we next investigated the substrate scope of the cyanation (Scheme 3). A number of chalcone derivatives bearing a variety of substituents were examined. Substrates bearing electron-donating and electron-withdrawing groups in the *para* positions on the phenyl ring at the 2-position provided the corresponding cyanated products in high yields (**2b–h**), although highly electron-deficient substrates with a nitro group gave a relatively low yield (**2i**). The effects of methyl substituents on either the *ortho* or *meta* positions were negligible (**2j** and **2k**). This cyanation appears to be insensitive to electronic and steric effects by aryl substituents at the 4-position (**2l–n**). In addition, electron-rich heteroaromatics such as thiophene and furan moieties are well tolerated (**2o** and **2p**). In the reaction of an enone containing two types of conjugated alkene moieties, one in an *s-cis* and the other in an *s-trans* geometry, the *s-cis*-moiety predominantly underwent hydroboration, thus leading to the formation of the cyanated product **2q**. In addition, enones possessing aliphatic substituents at the 2- and 4-positions were also applicable to this cyanation (**2r–x**). In those reactions, steric bulk of the aliphatic substituents at the 2-positions is crucial for the selectivity between 1,2- and 1,4-hydroboration. The presence of a bulky *tert*-butyl group afforded the product **2r** in high yield by selective generation of the boron enolate through 1,4-hydroboration. In contrast, a smaller ethyl group resulted in a lower yield of the cyanated product because of the competitive 1,2-hydroboration, and thus the delivery of the corresponding allylic alcohol.[22] To the contrary, steric effects of aliphatic substituents at the 4-position had negligible effects in this system (**2u–x**). Notably, the use of α-substituted enones also proceeded effectively to afford β-ketonitriles bearing a quaternary α-carbon center (**2y** and **2z**), which would be otherwise difficult to access, although a certain amount of 1,2-hydroboration products were also formed.[22]



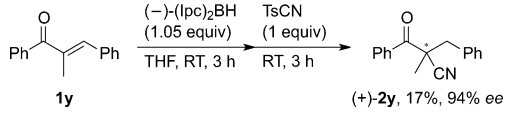
Scheme 3. Substrate scope of enones. Unless otherwise noted, reaction conditions: **1** (0.5 mmol), 9-BBN (0.525 mmol), NCTS (0.5 mmol), THF (1 mL), 40 °C, 12 h. Yields denoted are those of the isolated products. [a] **1** (1.2 equiv) and 9-BBN (1.26 equiv) were used. [b] The boron enolate was prepared by premixing enone **1** and 9-BBN in THF at RT for 3 h prior to addition of NCTS.



Scheme 4. Substrate scope of ketones. Unless otherwise noted, reaction conditions: **4** (0.5 mmol), *B*-I-9-BBN (1 M in hexane) (0.55 mL, 0.55 mmol), *N*,*N*-diisopropylethylamine (0.55 mmol), NCTS (0.6 mmol), Et_2O (1 mL), RT. The value within parentheses refers to reaction time. Yields denoted are those of the isolated products. [a] The d.r. value was determined by ^1H NMR analysis of the crude product. [b] Et_2O (2 mL) was used. [c] Dimethoxyethane (DME) (2 mL) was used instead of Et_2O. [d] TsCN was used instead of NCTS. [e] Reaction performed at 0 °C. [f] Reaction performed at −78 °C to RT.

To expand the scope of this electrophilic cyanation, boron enolates prepared from simple ketones by treatment with *B*-iodo-9-borabicyclo-[3.3.1]nonane (*B*-I-9-BBN) and *N*,*N*-diisopropylethylamine were examined (Scheme 4).[25] A brief screening of solvents revealed that the use of Et_2O was suitable for this system.[22] The method was successfully applied to the cyanation of α,α-disubstituted ketones to furnish the corresponding β-ketonitriles (**2aa**–**ae**), compounds which would be difficult to produce by our method described above, as well as by existing methods. In comparison with the reaction employing 1,4-hydroboration, this protocol allowed the selective synthesis of **2ad** bearing a conjugated alkene moiety. This result is a clear demonstration of the switchable selectivity of the introduction of a cyano group by the preparation of a boron enolate. This cyanation was also applicable to various types of α-monosubstituted ketones, including propiophenone, isovalerophenone, tetralone, and fully aliphatic ketones, thus providing the corresponding products in good to high yields (**2af**–**aj**). However, when the reaction was carried out using phenyl benzyl ketone, the cyanated product **2ak** was obtained in low yield (28% NMR yield) because of the formation of the corresponding boron complex **2′**. Gratifyingly, the use of TsCN instead of NCTS suppressed the production of **2′**, thus improving the yield of **2ak** to 76%. Similarly, an α-unsubstituted ketone underwent cyanation in case where TsCN was used. Taken together, the present electrophilic cyanation of boron enolates demonstrates the extremely broad substrate scope of the reaction and enables the versatile synthesis of a wide variety of β-ketonitrile derivatives.

Lastly, the enantioselective version of this electrophilic cyanation was investigated by employing a chiral boron enolate prepared from diisopinocampheylborane [(−)-$(Ipc)_2BH$] and **1y** (Scheme 5). Although the use of NCTS resulted in no cyanated product being produced, the use of TsCN was found to afford the desired product in excellent enantioselectivity, thereby indicating that the present method is potentially promising for the synthesis of optically active β-ketonitriles, albeit in low yield at this stage.



Scheme 5. Enantioselective electrophilic cyanation using chiral boron enolate.

In conclusion, we report on the development of a new class of electrophilic cyanation reactions in which boron enolates are reacted with either readily available NCTS or TsCN as cyanating reagent. The reaction has a remarkably broad substrate scope with good functional-group compatibility. Boron enolates derived from various types of ketones,

including α,β-unsaturated ketones, can be applied to this cyanation to afford a wide variety of synthetically useful β-ketonitriles. In addition, the present method represents a new entry into an oxidative functionalization of boron enolates.[26] Further investigations of the mechanism and applications of this method to organic synthesis including enantioselective reactions based on this preliminary result are currently in progress.

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Keywords: boron · cyanation · nucleophilic addition · reaction mechanisms · synthetic methods

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[22] See the Supporting Information for details.

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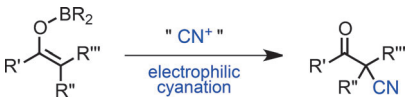
S. Minakata* _____ ■■■■–■■■■

Electrophilic Cyanation of Boron Enolates: Efficient Access to Various β-Ketonitrile Derivatives



Plus CN: The title reaction proceeds with readily available cyanating reagents, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide and *p*-toluenesulfonyl cyanide. Various β-ketonitriles can be prepared by this new protocol, which shows a remarkably broad substrate scope compared to existing methods. The present method also allowed efficient synthesis of β-ketonitriles bearing a quaternary α-carbon center.