Doctoral Dissertation

Electrophilic Cyanation of Enolate Equivalents Utilizing Lewis Acidity of Boron

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Department of Applied Chemistry

Graduate School of Engineering

Osaka University

Electrophilic Cyanation of Enolate Equivalents Utilizing Lewis Acidity of Boron

（ホウ素のルイス酸性を活用したエノラート類の求電子的シアノ化反応）

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Preface

The studies presented in this thesis were conducted under the supervision of Professor Dr. Satoshi Minakata, Department of Applied Chemistry, Graduate School of Engineering, Osaka University during the period of 2013-2019.

The objects of this thesis are electrophilic cyanation of enolate equivalents utilizing Lewis acidity of boron. The author hopes sincerely that the fundamental work described in this thesis contributes to further development of synthetic methods of nitriles and other related fields of chemistry.

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Contents

General Introduction

1. Utility of β-Ketonitriles

Nitriles are distributed across a wide range of molecules, from simple synthetic intermediates to biologically active molecules and functional materials.[1] Among them, β-ketonitriles are an important class of building blocks for the synthesis of various heterocycles such as pyrazoles,[2] pyrimidines,[3] thiophenes,[4] and others,[5] which are frequently found in pharmaceuticals and biologically active compounds (Figure 1). In addition, β-ketonitriles can be converted to optically active β-hydroxy nitriles via the enantioselective reduction of the carbonyl group,[6] which are also valuable synthetic intermediates in organic synthesis.

Therefore, considerable efforts have been devoted to the development of methods for the synthesis of β-ketonitriles in the past decades.[7]

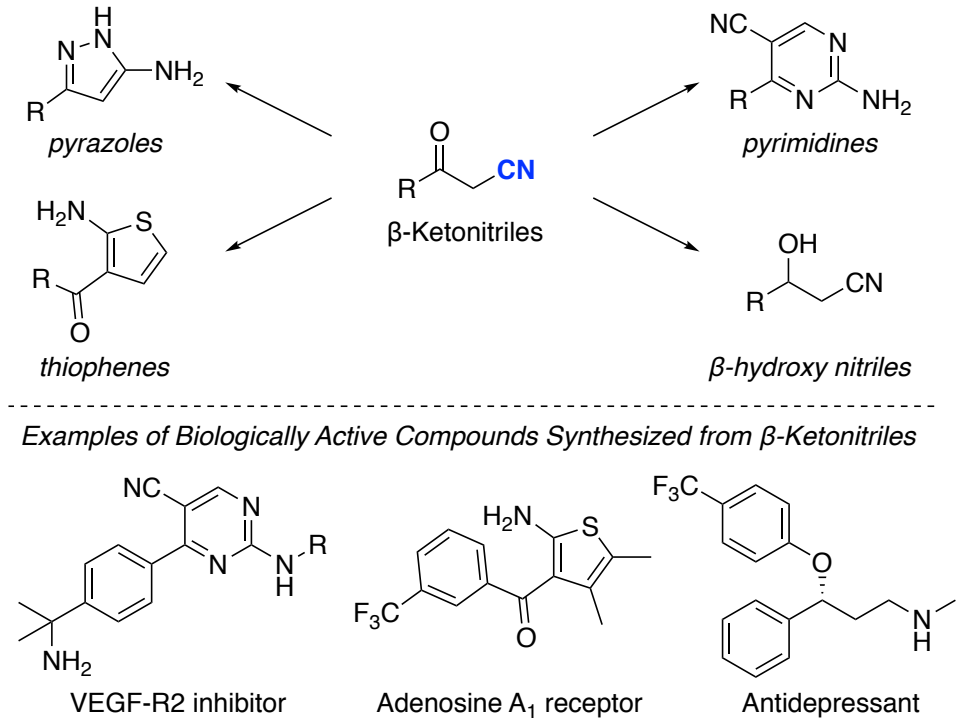
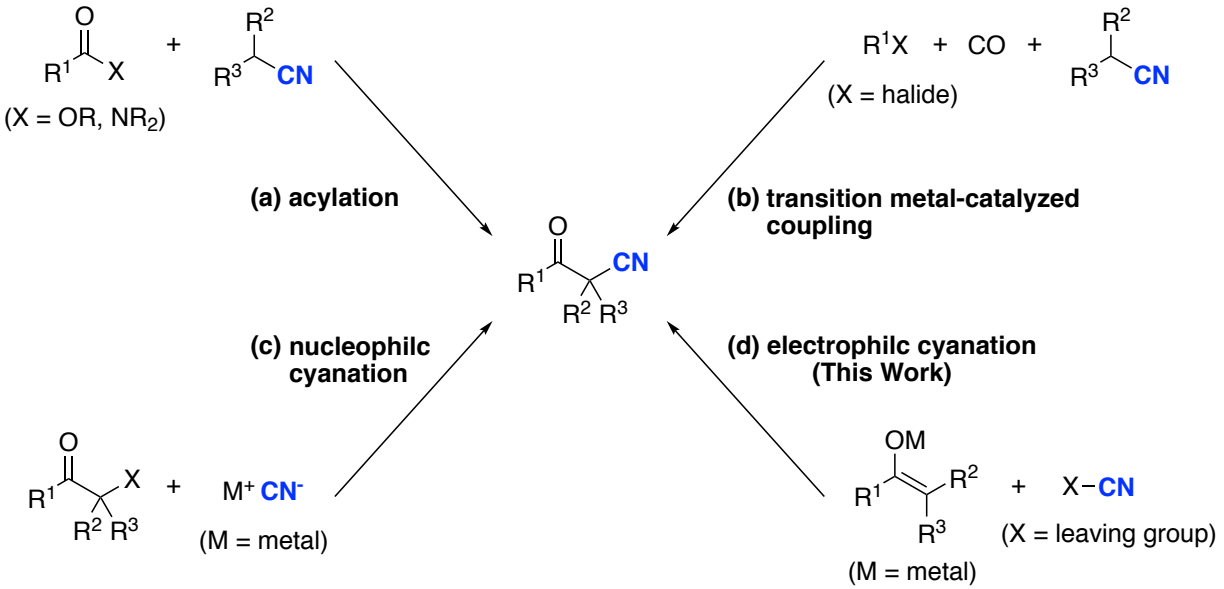


Figure 1. β-Ketonitriles as Useful Synthetic Intermediates

2. Synthetic Methods of β-Ketonitriles

For the synthesis of β-ketonitriles, acylation of alkyl nitriles is widely employed (Scheme 1a). 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 used.[8] Nevertheless, those methods usually require an excess amount of the substrate and base. Although transition metal-catalyzed carbonylative coupling reaction has been also reported in recent years, these methods are applicable only to the synthesis of aromatic β-ketonitriles (Scheme 1b).[9,10] Meanwhile, cyanation of the α-position of carbonyls is also a promising strategy for the synthesis of β-ketonitriles. As such an approach, nucleophilic substitution with a cyanide on an α-haloketones has been developed (Scheme 1c).[11] However, the method suffers from limited substrate scope and harsh reaction conditions especially when

secondary and tertiary halides are involved because of the side reaction where a cyanide attacks the carbonyl carbon. To avoid this problem, electrophilic cyanation of enolate equivalents should be an attractive approach to the synthesis of β-ketonitriles (Scheme 1d).

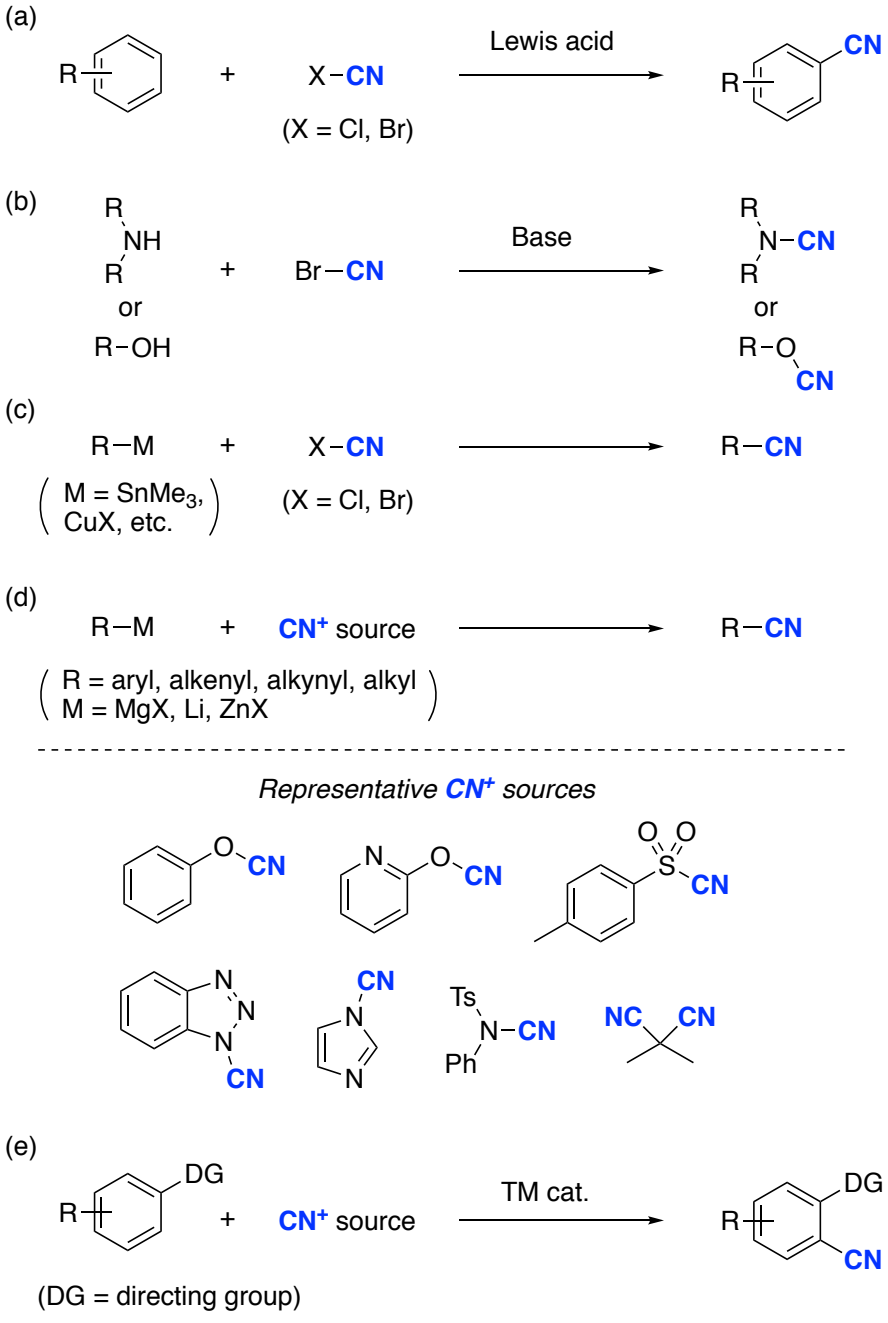


Scheme 1. Representative Synthetic Methods of β-Ketonitriles

3. Electrophilic Cyanation

Electrophilic cyanation of heteroatom-based nucleophiles, organometallic reagents, enolates, and so on, using formal CN^+ species as electrophiles, provides complementary synthetic strategy to the reaction using conventional cyanides (CN^-).[12] An early report is Friedel-Crafts-type cyanation of aromatic compounds with cyanogen halides (XCN, X = Cl or Br) in the presence of a stoichiometric amount of Lewis acid (Scheme 2a).[13] Amines,[14a] alcohols,[14b] and organometallic reagents[14c-e] also react with cyanogen halides to provide the corresponding products (Scheme 2b and 2c). However, the methods are suffered from the use of toxic cyanogen halides and competitive halogenation reaction especially when organometallic reagents are employed as a nucleophile. To address these issues, electrophilic cyanating reagents, which contain heteroatom–CN bond or carbon–CN bond, have been

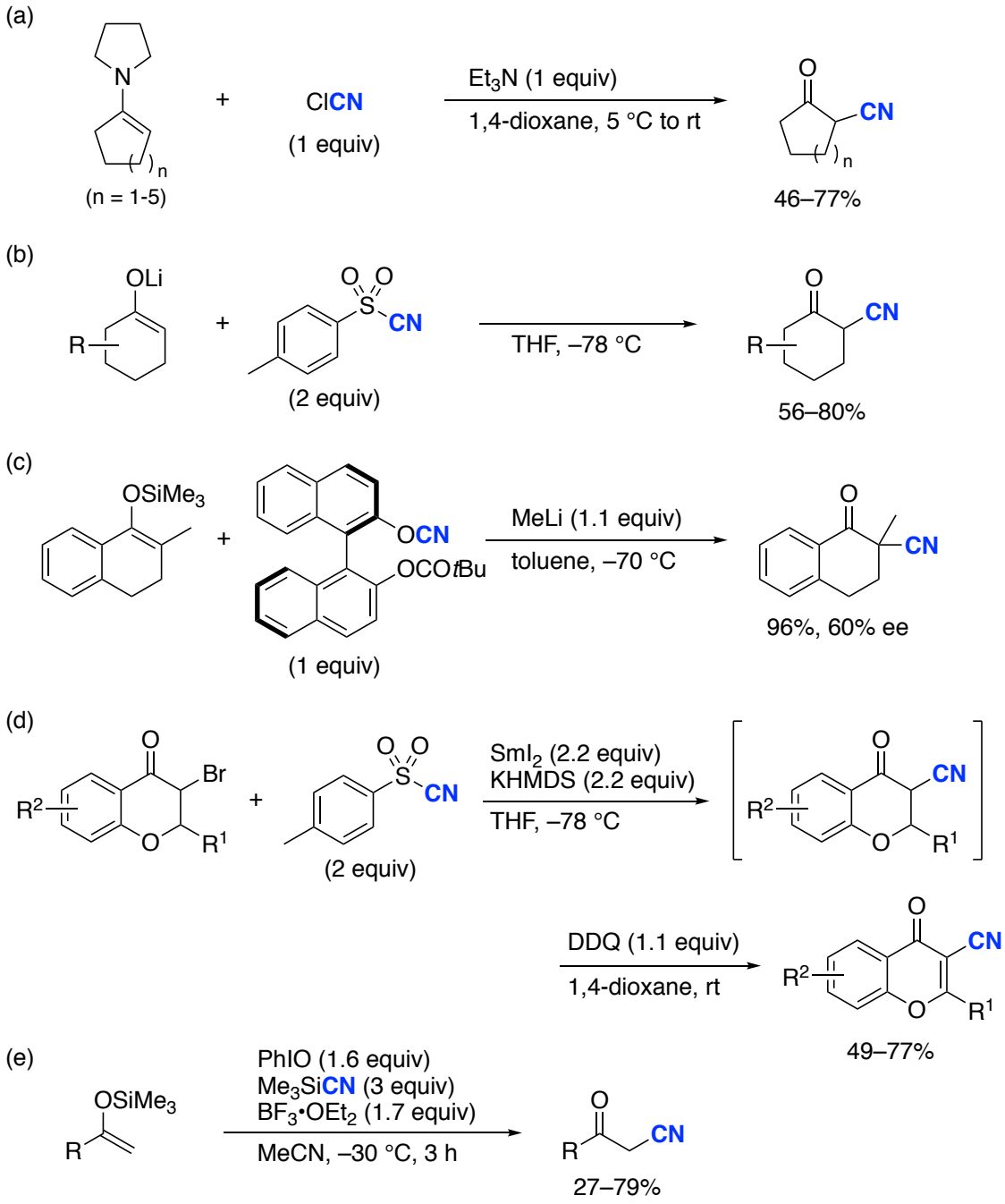
synthesized and utilized in electrophilic cyanation. For instance, cyanates,[15] cyanamides,[16] *p*-toluenesulfonyl cyanide,[17] and dimethylmalononitrile[18] have been developed to achieve efficient electrophilic cyanation of organometallic reagents, such as organomagnesium, organolithium, and organozinc compounds (Scheme 2d). These reagents are also used in transition metal-catalyzed C-H cyanation reactions of aromatic compounds in recent years (Scheme 2e).[12d]



Scheme 2. Representative Electrophilic Cyanation Reactions

4. Electrophilic Cyanation of Enolate Equivalents

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.[19] An early report is the reaction of cyclic enamines with the cyanogen



Scheme 3. Synthetic Methods of β-Ketonitriles by Electrophilic Cyanation

chloride (ClCN) and *p*-toluenesulfonyl cyanide (TsCN) (Scheme 3a).[20,21] Cyclic lithium enolates react with TsCN and phenyl cyanate (Scheme 3b and c).[22] Reformatsky-type electrophilic cyanation reaction using TsCN is also reported (Scheme 3d).[23] However, these methods were limited to the use of cyclic ketone derivatives. Although the reaction of silyl enol ethers with a hypervalent iodine-based cyanating reagent has recently been reported, the method was applicable only to α-unsubstituted silyl enol ethers (Scheme 3e).[24,25] Therefore, efficient method for the synthesis of β-ketonitriles by electrophilic cyanation is still highly desired.

5. Optically Active β-Ketonitriles

Chiral β-ketonitriles bearing a stereogenic carbon center at the α-position are useful precursors of chiral 1,3-aminoalcohols and β-hydroxy nitriles, which are ubiquitous building blocks for a variety of biologically active compounds and natural products (Figure 2).[26] Therefore, the development of efficient methods for the synthesis of chiral β-ketonitriles represents an important research topic in organic chemistry.

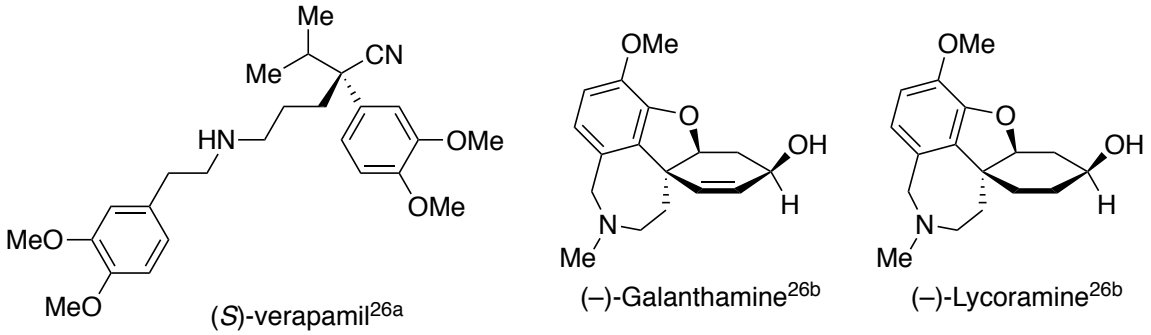
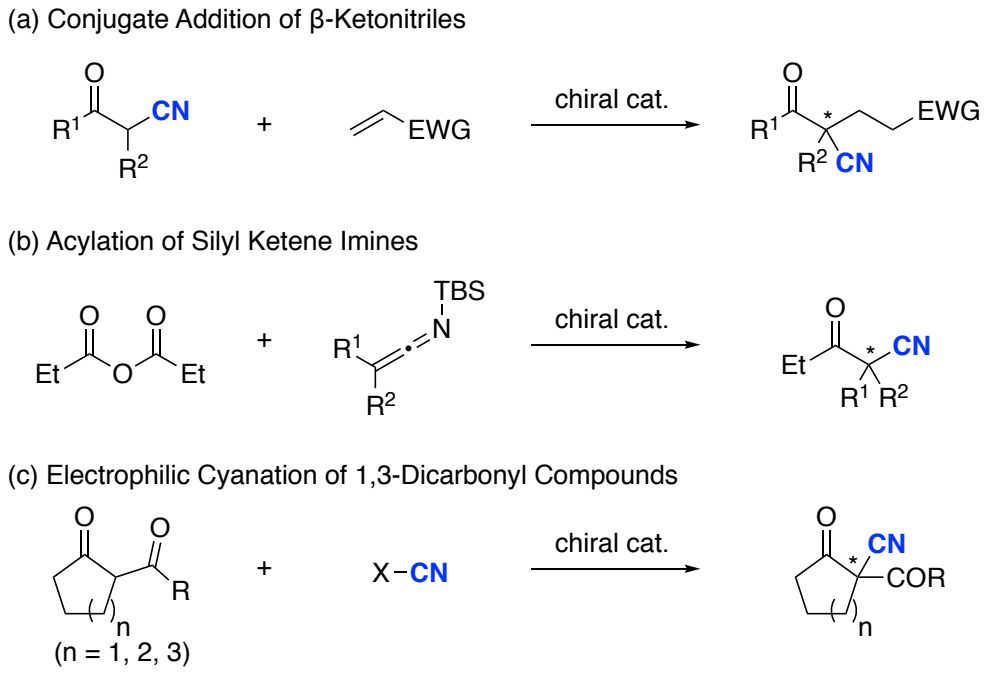


Figure 2. Biologically Active Compounds and Natural Products Prepared from Chiral β-Ketonitriles

For the synthesis of chiral β-ketonitriles, the catalytic enantioselective α-alkylation of β-ketonitriles, which includes the conjugate addition of β-ketonitriles, is the most widely used approaches (Scheme 4a).[26b,27-29] Meanwhile, the enantioselective acylation of silyl ketene

imines has also been reported (Scheme 4b).[26a,30] In addition to these transformations using β-ketonitriles or alkyl nitrile equivalents as a starting material, enantioselective cyanation, the direct introduction of a cyano group into the α-position of a ketone, is also a promising strategy for preparing a variety of chiral β-ketonitriles. To achieve such reactions, the enantioselective electrophilic cyanation of ketone enolate equivalents has been developed in recent years. However, the methods reported to date are limited to the cyanation of cyclic 1,3-dicarbonyl compounds (Scheme 4c)[31] with the only one exception, in which the reaction of tetralone-derived lithium enolates proceeded with moderate enantioselectivity (Scheme 3c).[22b] Therefore, the enantioselective electrophilic cyanation of ketone-derived enolates remains largely undeveloped and continues to be a challenging task.



Scheme 4. Synthetic Models of Optically Active β-Ketonitriles

6. Boron Lewis Acid-Promoted Electrophilic Cyanation

Boron Lewis acids can activate a cyano group by the coordination of a nitrogen atom of a cyano group to a Lewis acidic boron center (Figure 3).[32] This reactivity has been successfully applied to electrophilic cyanation in recent years as a useful strategy for introducing a cyano group into a nucleophilic substrate.[33] For instance, BF_3•OEt_2-catalyzed electrophilic cyanation of indoles with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) was reported (Scheme 5a).[33a] Moreover, $B(C_6F_5)_3$-mediated intramolecular aminocyanation of olefins[33b] and BF_3•OEt_2-catalyzed cyanation of electron rich aromatic compounds[33c] were also achieved (Scheme 5b and c).

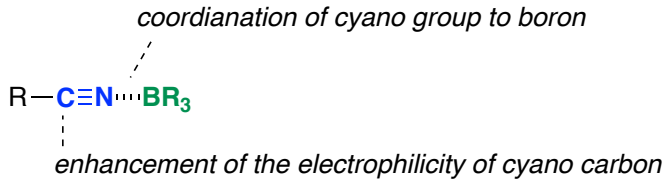
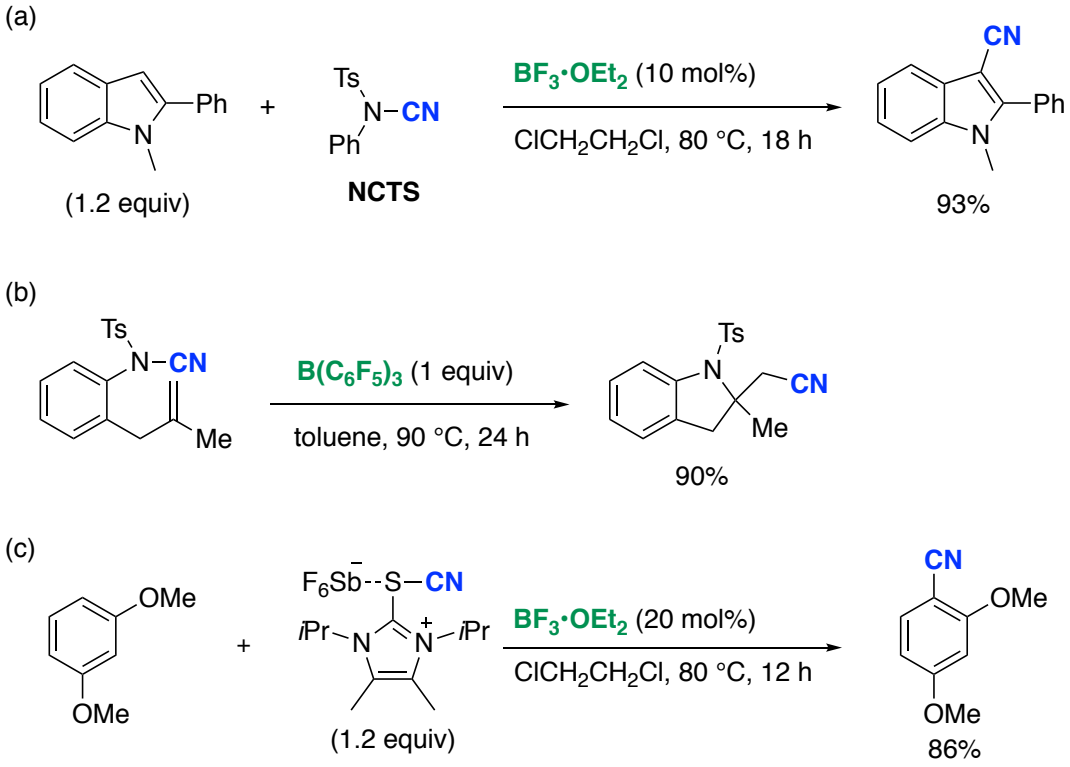


Figure 3. Activation of Cyano Group with a Boron Lewis Acid



Scheme 5. Electrophilic Cyanation Using Boron Lewis Acids

7. Synopsis of This Thesis

On the basis of these backgrounds, the author has developed the synthetic methods of β-ketonitriles by electrophilic cyanation utilizing the Lewis acidity of boron (Figure 4). This thesis consists of General Introduction, three Chapters, and Conclusion.

In Chapter 1, $B(C_6F_5)_3$-catalyzd electrophilic cyanation of silyl enol ethers with 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (CDBX) is described.

In Chapter 2, electrophilic cyanation of 9-BBN-based boron enolates with NCTS is described.

In Chapter 3, enantioselective electrophilic cyanation of Ipc_2B-based boron enolates with TsCN is described.

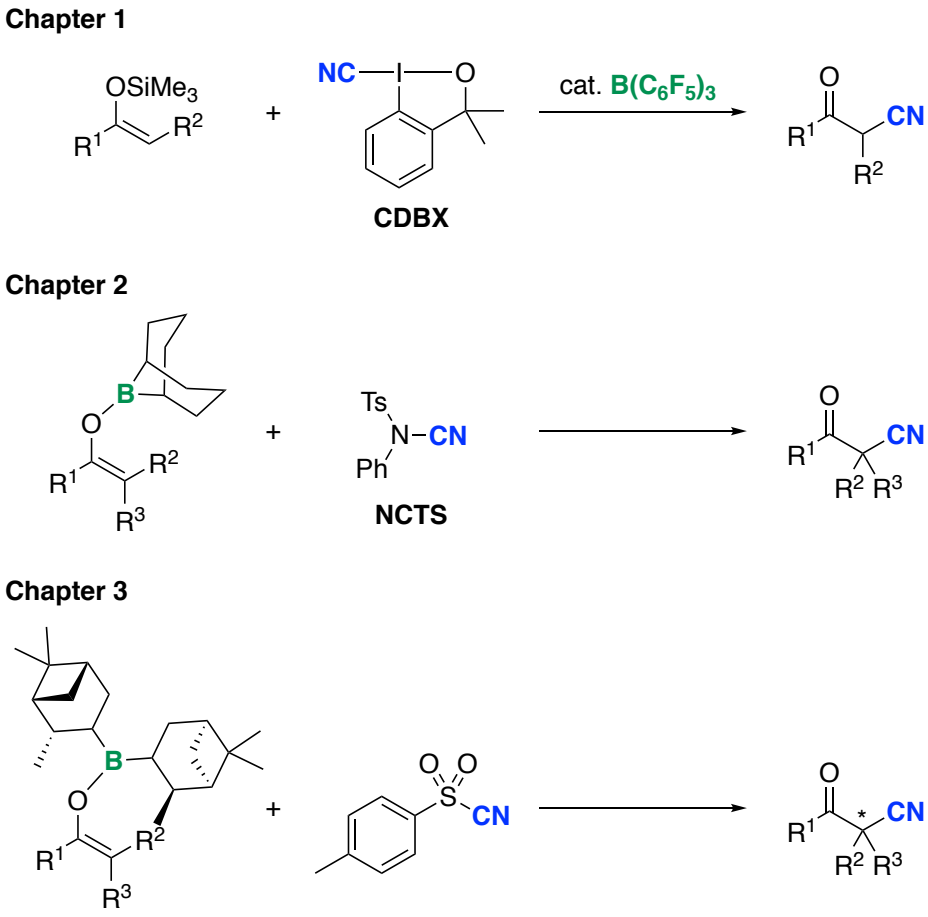


Figure 4. Summary of This Thesis

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Chapter 1

$B(C_6F_5)_3$-Catalyzed Electrophilic Cyanation of Silyl Enol Ethers

1-1. Introduction

Electrophilic cyanating reagents generally contain a heteroatom–CN bond and include cyanates,[1] cyanamides,[2] and *p*-toluenesulfonyl cyanide (TsCN),[3] etc.[4] Although cyanogen halides (XCN, X = Cl, Br, or I) may also be useful reagents for electrophilic cyanation reactions, the use of these reagents often suffers from several drawbacks including their high toxicity and competitive electrophilic halogenation reactions that occur, rather than cyanation.[5] To address these issues, hypervalent iodine(III) reagents possessing a transferable cyano group has emerged as a promising electrophilic cyanating reagent. In the 1990s, non-cyclic hypervalent iodine reagents, such as phenyl(cyano)iodonium triflate (**1a**) and (dicyanoiodo)benzene (**1b**), were synthesized by Zhdankin and Stang (Figure 1).[6] However, neither **1a** nor **1b** are frequently used in electrophilic cyanation reactions.[7] A few years later, Zhdankin developed some relatively stable and easy-to-handle cyclic analogues, including 1-cyano-1,2-benziodoxol-3-(1*H*)-one (CBX, **1c**) and 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxol (CDBX, **1d**), which were used in the $C(sp^3)$–H cyanation of *N*,*N*-dialkylarylamines.[8] Although several examples of electrophilic cyanation reactions employing **1c** and **1d**, including the cyanation of thiols[9] and β-ketoesters[10] under basic conditions, have

been reported, these reagents continue to have limited applications in electrophilic cyanation reactions[11] and have never been used for cyanation of ketone enolates, probably because of their low reactivity. In this context, the development of a robust activation system would be desirable.

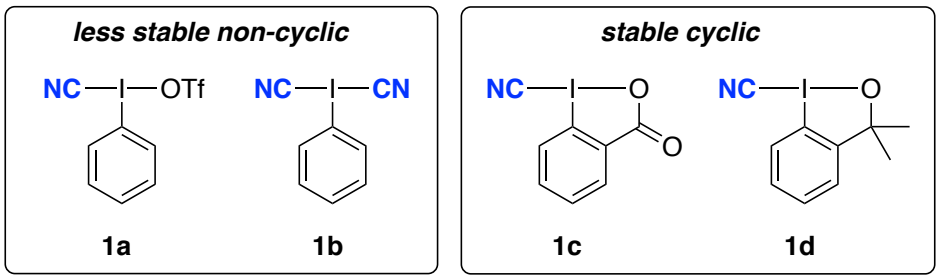


Figure 1. Hypervalent Iodine Reagents Possesing a Transferable Cyano Group

Based on the background described in general introduction, the author hypothesized that the activation of the cyano group of hypervalent iodine with a boron Lewis acid would provide highly reactive electrophilic cyanating reagent, thus reacting with silyl enol ethers to afford β-ketonitriles efficiently (Figure 2). Chapter 1 describes $B(C_6F_5)_3$-catalyzed electrophilic cyanation of silyl enol ethers with CDBX.

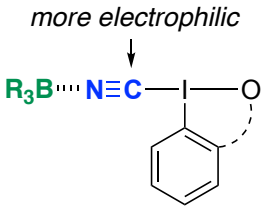


Figure 2. Activation of the Cyano Group by Boron Lewis Acids

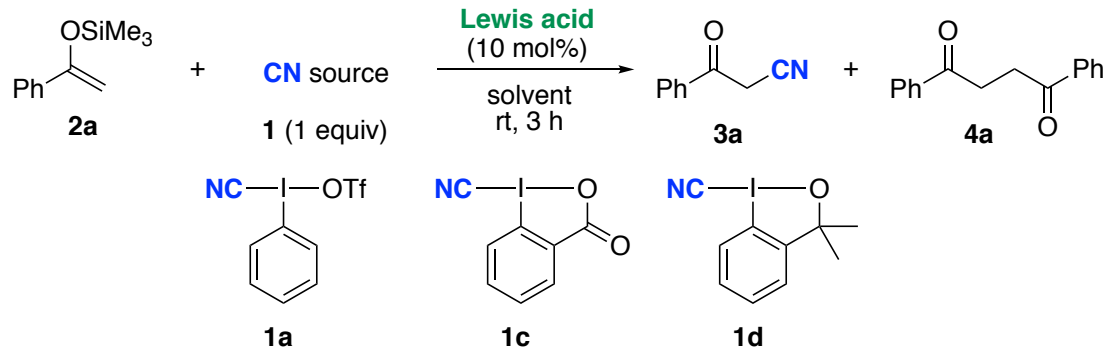
1-2. Results and Discussion

1-2-1. Reaction of Silyl Enol Ether 2a with Hypervalent Iodine

Electrophilic cyanation of trimethyl(1-phenylvinyloxy)silane (**2a**) was examined as the model reaction, and a series of Lewis acid catalysts were screened (Table 1). A brief screening of boron Lewis acids indicated that the cyanation proceeded effectively when 10 mol% of $B(C_6F_5)_3$ was added to the reaction using **1d** in CH_2Cl_2 at room temperature, thus affording the corresponding β-ketonitrile **3a** in 84% yield, along with a small amount of **4a** as a byproduct (entry 1).[12] Meanwhile, both BF_3•OEt_2 and BEt_3 failed to promote the cyanation (entries 2 and

3), and when BF_3•OEt_2 was used in the reaction, **4a** was formed predominantly (31% yield). Reactions using other hypervalent iodine reagents, such as **1a** and **1c**, resulted in quite low yields of **3a** (entries 4 and 5). Control experiments revealed that this reaction did not proceed

Table 1. Screening of Reaction Parameters for the Electrophilic Cyanation of **2a**[a]



entry	CN source	Lewis acid	solvent	yield (%)[b]	
				3a	**4a**
1	**1d**	$B(C_6F_5)_3$	CH_2Cl_2	84	6
2	**1d**	BF_3•OEt_2	CH_2Cl_2	<5	31
3	**1d**	BEt_3[c]	CH_2Cl_2	<5	<5
4	**1a**	$B(C_6F_5)_3$	CH_2Cl_2	<5	38
5[d]	**1c**	$B(C_6F_5)_3$	CH_2Cl_2	7	<5
6	**1d**	none	CH_2Cl_2	<5	<5
7[e]	**1d**	$B(C_6F_5)_3$	CH_2Cl_2	32	<5
8	**1d**	$AlMe_2Cl$[c]	CH_2Cl_2	<5	<5
9	**1d**	$AlMe_3$[c]	CH_2Cl_2	<5	<5
10	**1d**	$InCl_3$	CH_2Cl_2	<5	<5
11	**1d**	Me_3SiOTf	CH_2Cl_2	<5	48
12	**1d**	$Zn(OTf)_2$	CH_2Cl_2	<5	52
13	**1d**	$Cu(OTf)_2$	CH_2Cl_2	<5	54
14	**1d**	$Cu(OTf)_2$	CH_2Cl_2	<5	63
15	**1d**	$B(C_6F_5)_3$	MeCN	69	8
16	**1d**	$B(C_6F_5)_3$	$MeNO_2$	43	20
17	**1d**	$B(C_6F_5)_3$	toluene	<5	<5
18	ICN	$B(C_6F_5)_3$	CH_2Cl_2	<5	<5
19	BrCN	$B(C_6F_5)_3$	CH_2Cl_2	<5	<5

[a] Reaction conditions: **2a** (0.2 mmol), cyanating reagent (0.2 mmol), Lewis acid (10 mol %), solvent (2 mL), rt, 3 h. [b] Determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c] Lewis acid (1 M in hexane) was used. [d] Reaction was run for 14 h. [e] $B(C_6F_5)_3$ (5 mol %) was used.

in the absence of $B(C_6F_5)_3$, and decreasing the catalyst loading to 5 mol% resulted in a low yield of the product (entries 6 and 7). Furthermore, other group 13 Lewis acids, such as $AlMe_2Cl$, $AlMe_3$, and $InCl_3$, showed no catalytic activity (entries 8−10). The author also tested some commonly used Lewis acids, such as Me_3SiOTf, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Sc(OTf)_3$, but in all reactions, no cyanation products were detected, and the oxidative dimerization of **2a** proceeded exclusively to give **4a** (entries 11−14). Screening a series of solvents revealed that CH_2Cl_2 was the best medium for this transformation (entries 15−17). Only electrophilic halogenation, which leads to α-halogenated products, proceeded exclusively when cyanogen halides (ICN and BrCN) were used instead of hypervalent iodine reagents (entries 18 and 19).[13] These results clearly demonstrate that the use of **1d** with $B(C_6F_5)_3$ is specifically effective in this electrophilic cyanation reaction.

1-2-2. IR and NMR measurements

To obtain additional insights into the activation mode of **1d** with $B(C_6F_5)_3$, spectroscopic analysis of a mixture of **1d** and 1 equiv of $B(C_6F_5)_3$ in dichloromethane were carried out. In a previous report,[14] the coordination between the cyano group of ICN to $B(C_6F_5)_3$ was confirmed by IR spectroscopy. According to the literature, the CN stretching vibrational band of ICN was shifted significantly from 2169 to 2267 cm^{-1} when the complex of ICN with $B(C_6F_5)_3$ was formed. Indeed, when 1 equiv of $B(C_6F_5)_3$ was added to a solution of **1d** in CH_2Cl_2, a significant shift in the CN stretching vibrational band of **1d**, from 2137 to 2216 cm^{-1}, was observed (Figure 3), strongly suggesting that the cyano group of **1d** coordinates to $B(C_6F_5)_3$. Furthermore, control experiments using Lewis acids, which provided **4a** rather than **3a**, were carried out. The IR spectra of **1d** were essentially unchanged on the addition of BF_3•OEt_2, Me_3SiOTf, $Zn(OTf)_2$, and $Sc(OTf)_3$.[15] These results clearly demonstrate that $B(C_6F_5)_3$ is specifically effective for activating **1d** through coordination, which results in the generation of

a highly electrophilic species. To gain additional insights into the activation mode, a mixture of **1d** and $B(C_6F_5)_3$ was monitored by ^{13}C NMR spectroscopy (Figure 4). When **1d** and 1 equiv of $B(C_6F_5)_3$ were mixed in CD_2Cl_2, the signal corresponding to the cyano group (98.4 ppm) was significantly shifted to a lower field (111.1 ppm) (Figure 4). In addition, the signal corresponding to the tertiary carbon adjacent to the oxygen atom (80.6 ppm) was also shifted to a lower field (86.8 ppm). These results also provide support for the Lewis acidic activation of

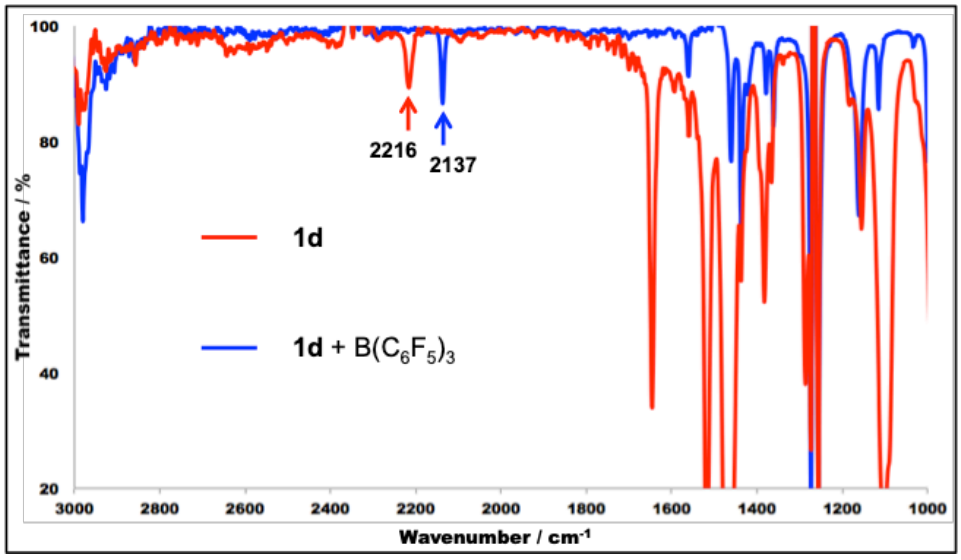


Figure 3. FTIR spectra of **1d** (blue line) and the mixture of **1d** and $B(C_6F_5)_3$ (red line) in CH_2Cl_2

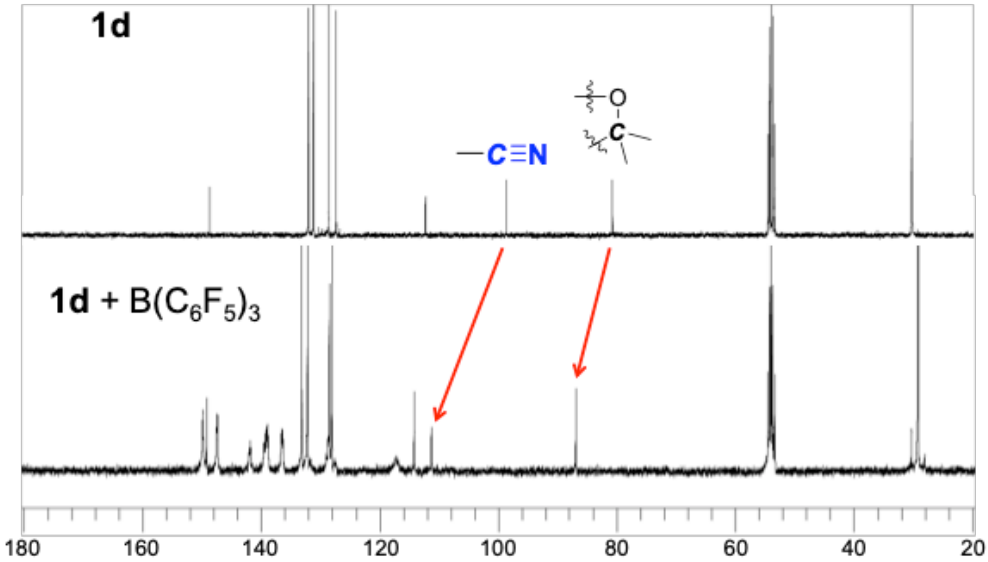
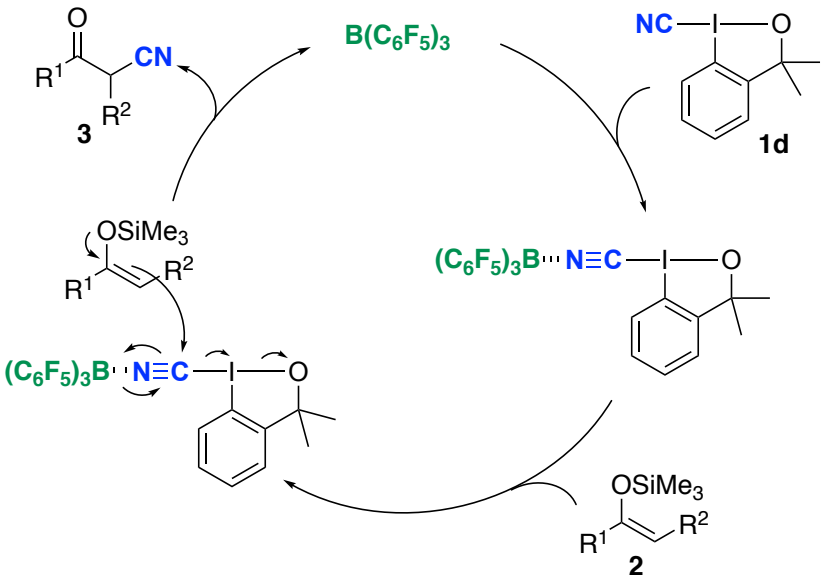


Figure 4. ^{13}C NMR spectra in CD_2Cl_2: i) **1d**. b) The mixture of **1d** and $B(C_6F_5)_3$.

1d, which is different from the generally proposed activation mode of hypervalent iodine reagents by Lewis acids.[16,17]

1-2-3. Proposed Reaction Pathway

On the basis of the IR and NMR data, a plausible reaction pathway is depicted in Scheme 1. The reaction is initiated through the Lewis acidic activation of **1d** through the coordination of its cyano group to $B(C_6F_5)_3$. The silyl enol ether **2** directly attacks the cyano group to provide the product **3** via an addition−elimination pathway.



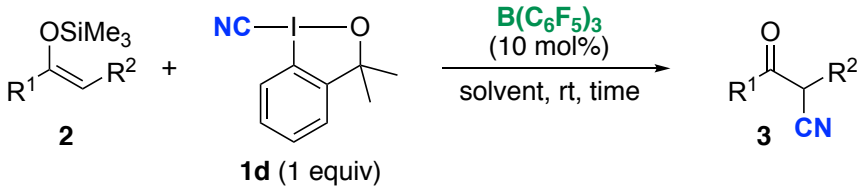
Scheme 1. Proposed Reaction Pathway

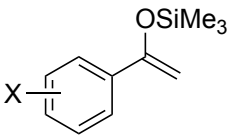
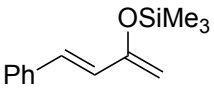
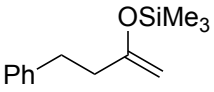
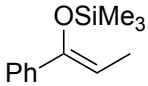
1-2-4. Scope of Silyl Enol Ethers

Finally, the author explored the scope of this electrophilic cyanation reaction (Table 2). In this cyanation, various silyl enol ethers derived from aromatic and aliphatic ketones were efficiently converted into the corresponding β-ketonitriles. Silyl enol ethers derived from acetophenone derivatives containing electron-donationg groups in the *para* position on the phenyl ring, such as methoxy and methyl groups, participated in the reaction to give good product yields. (entries 2 and 3). The presence of a bromo substituent on the phenyl ring

decreased the reactivity, and increasing the amount of $B(C_6F_5)_3$ from 10 to 20 mol% was effective, thus affording **3d** in a higher yield (entry 4). However, the reaction of the electron-deficient **2e** resulted in a low yield when the reaction was conducted in CH_2Cl_2. A brief screening of solvents revealed that the use of $MeNO_2$ improved the efficiency to afford **3e** as the product (entry 5). This cyanation appears to be sensitive to steric effects by aryl

Table 2. Scope of Silyl Enol Ethers for the Electrophilic Cyanation[a]



entry	2	solvent	time (h)	3, yield (%)[b]
				
1	**2a**, X = H	CH_2Cl_2	3	**3a**, 81
2	**2b**, X = 4-MeO	CH_2Cl_2	2	**3b**, 74
3	**2c**, X = 4-Me	CH_2Cl_2	3	**3c**, 75
4[c]	**2d**, X = 4-Br	CH_2Cl_2	3	**3d**, 80
5[c]	**2e**, X = 4-CO_2Me	$MeNO_2$	3	**3e**, 48
6	**2f**, X = 2-Me	MeCN	3	**3f**, 64
7	**2g**, X = 3-Me	CH_2Cl_2	3	**3g**, 89
8	 **2h**	MeCN	3	**3h**, 84
9	 **2i**	CH_2Cl_2	6	**3i**, 58
10[d]	 **2j**	MeCN	5	**3j**, 37

[a] Reactions were conducted on a 0.5 mmol scale (0.1 M). [b] Isolated yield. [c] B(C6F5)3 (20 mol%) was used. [d] MeCN (2 mL) was used.

substituents. For example, a methyl substituent at the *ortho* position resulted in a decreased reactivity to afford **3f** in 64% yield in MeCN (entry 6). A methyl substituent at the *meta* position had no effect on the cyanation reaction, giving high yields of **3g** (entry 7). In addition, silyl enol ethers containing vinyl and alkyl substituents were also applicable to this cyanation (entries 8 and 9). The silyl enol ether **2j** derived from propiophenone gave the corresponding β-ketonitrile, albeit in moderate yield (entry 10).

1-3. Conclusion

The author has developed $B(C_6F_5)_3$-catalyzed electrophilic cyanation of silyl enol ethers with 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (CDBX). The reaction was applicable to α-monosubstituted silyl enol ether **2j**, which could not be applied to the previously reported electrophilic cyanation.[18] The Lewis acidic activation of CDBX through the coordination of the cyano group to the boron center was confirmed by IR and NMR studies.

1-4. Experimental Section

General Remarks

New compounds were characterized by ^{1}H, ^{13}C, IR, MS, and HRMS. ^{1}H, and ^{13}C NMR spectra were recorded on a JEOL JMTC-400/54/SS spectrometer (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz). ^{1}H NMR chemical shifts were determined relative to Me_4Si (0.00 ppm) as an internal standard. ^{13}C NMR chemical shifts were determined relative to solvent signal ($CDCl_3$ at 77.0 ppm or CD_2Cl_2 at 53.8 ppm) as an internal standard. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR spectrometer. Mass spectra were obtained on a SHIMADZU GCMS-QP2010 and a JEOL JMS-700 mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer (magnetic sector type mass spectrometer). Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. All reactions were carried out under nitrogen.

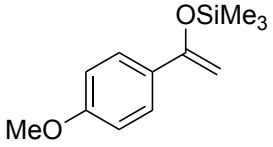
Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or aluminium oxide (Merck, 90 active stage I, 0.063–0.200 mm). Analytical thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (Merck silica gel 60 F_{254} and Fuji Silysia Chromatorex NH, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

Materials

Dehydrated dichloromethane was used as obtained. Dehydrated acetonitrile was used from a solvent purification system. Cyanating reagents **1a**,[6a] **1c**,[9] **1d**,[9] and ICN[19] were prepared according to literature procedures. Silyl enol ethers **2b**,[20] **2c**,[20] **2d**,[18] **2e**,[18] **2f**,[18] **2g**,[18] **2h**,[18] **2i**,[21] and **2j**[22] were prepared according to literature procedures. Analytical data for **2c**,[23] **2h**,[24] **2i**,[25] and **2j**[26] were in excellent agreement with reported data. Silyl enol ether **2a** was purchased and purified by flash column chromatography on silica gel (hexane) before using. All other solvents and reagents were purchased and used as obtained.

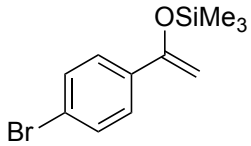
Spectral data of silyl enol ethers

[1-(4-methoxyphenyl)vinyloxy]trimethylsilane (2b)



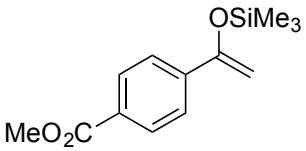
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.80 (d, *J* = 2.0 Hz, 1H), 4.33 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 155.3, 130.1, 126.5, 113.3, 89.4, 55.2, 0.07; IR: (ATR) 1607 cm^{-1}; MS: (EI) *m*/*z* 222 (M^+, 69), 221 (100), 207 (76), 191 (86), 75 (40); HRMS: (EI) calcd for ($C_{12}H_{18}O_2Si$) 222.1076 (M^+). found 222.1073

[1-(4-bromophenyl)vinyloxy]trimethylsilane (2d)



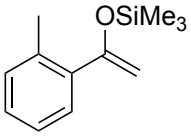
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.40 (m, 4H), 4.90 (d, *J* = 2.0 Hz, 1H), 4.44 (d, *J* = 2.0 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 136.4, 131.2, 126.8, 122.2, 91.5, 0.03; IR: (ATR) 1614 cm^{-1}; MS: (EI) *m*/*z* 272 ($[M+2]^+$, 13) 270 (M^+, 13), 191 (100), 75 (63), 73 (32); HRMS: (EI) calcd for ($C_{11}H_{15}BrOSi$) 270.0076 (M^+) found *m*/*z* 270.0074

methyl 4-[(1-trimethylsilyloxy)vinyl]benzoate (2e)



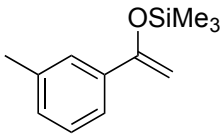
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 5.03 (d, *J* = 2.0 Hz, 1H), 4.54 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 154.6, 141.7, 129.6, 129.4, 125.0, 93.1, 52.0, –0.04; IR: (ATR) 1722, 1611 cm^{-1}; MS: (EI) *m*/*z*; 250 (M^+, 15), 237 (37), 235 (34), 193 (20), 191 (100), 163 (21); HRMS: (EI) calcd for ($C_{13}H_{18}O_3Si$) 250.1025 (M^+) found *m*/*z* 250.1029

trimethyl[1-(2-methylphenyl)vinyloxy]silane (2f)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.3 Hz, 1H), 7.24–7.10 (m, 3H), 4.53 (d, *J* = 1.0 Hz, 1H), 4.40 (d, *J* = 1.0 Hz, 1H), 2.39 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 138.9, 135.8, 130.3, 128.7, 128.0, 125.4, 94.8, 20.5, 0.05; IR: (ATR) 1622 cm^{-1}; MS: (EI) *m*/*z* 206 (M^+, 31), 191 (100), 75 (29); HRMS: (EI) calcd for ($C_{12}H_{18}OSi$) 206.1127 (M^+) found *m*/*z* 206.1128

trimethyl[1-(3-methylphenyl)vinyloxy]silane (2g)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.37 (m, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.90 (d, *J* = 1.5 Hz, 1H), 4.41 (d, *J* = 1.5 Hz, 1H), 2.35 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 137.5, 137.4, 129.0, 128.0, 125.9, 122.4, 91.0, 21.5, 0.08; IR: (ATR) 1616, 1601 cm^{-1}; MS: (EI) *m*/*z* 206 (M^+, 42), 205 (38), 191 (100), 119 (21), 75 (34); HRMS: (EI) calcd for ($C_{12}H_{18}OSi$) 206.1127 (M^+) found *m*/*z* 206.1124

Experimental procedure for FTIR monitoring of a mixture of CDBX and $B(C_6F_5)_3$

In a glove box, an oven dried reaction flask was charged with $B(C_6F_5)_3$ (0.050 mmol). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, CH_2Cl_2 (0.5 mL) and CDBX (0.050 mmol) were added. The solution was transferred to IR liquid cell.

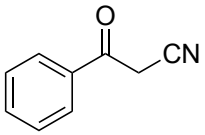
Experimental procedure for ^{13}C NMR monitoring of a mixture of CDBX and $B(C_6F_5)_3$

In a glove box, an oven dried reaction flask was charged with $B(C_6F_5)_3$ (0.050 mmol). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, CD_2Cl_2 (0.5 mL) and CDBX (0.050 mmol) were added. The solution was transferred to NMR tube.

Typical procedure for the electrophilic cyanation of silyl enol ethers and product data

In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with $B(C_6F_5)_3$ (0.050 mmol). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, solvent (5 mL), CDBX (0.500 mmol), and silyl enol ether (0.500 mmol) were added to the flask, and the solution was stirred at room temperature. After the indicated time, the reaction was quenched by sat. $NaHCO_3$ aq. (5 mL) and $Na_2S_2O_3$ aq. (1 M, 5 mL), and solution was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to give a crude product, which was analyzed by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the pure product.

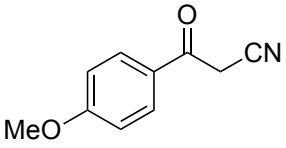
3-oxo-3-phenylpropanenitrile (3a)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.4 mg, 0.050 mmol), CH_2Cl_2 (5 mL), CDBX (144.2 mg, 0.502 mmol), and trimethyl(1-phenylvinyloxy)silane (96.7 mg, 0.503 mmol) was conducted at room temperature for 3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a pale yellow solid (58.9 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 134.6, 134.1, 129.0, 128.4, 113.9, 29.4

The analytical data for this compound were in excellent agreement with the reported data.[27]

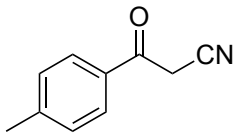
3-(4-methoxyphenyl)-3-oxopropanenitrile (3b)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.4 mg, 0.050 mmol), CH_2Cl_2 (5 mL), CDBX (143.3 mg, 0.499 mmol), and [1-(4-methoxyphenyl)vinyloxy]trimethylsilane (112.1 mg, 0.504 mmol) was conducted at room temperature for 2 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a pale yellow solid (64.5 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.3 Hz, 2H), 6.98 (d, *J* = 9.3 Hz, 2H), 4.02 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 164.7, 130.9, 127.3, 114.3, 114.0, 55.7, 29.0

The analytical data for this compound were in excellent agreement with the reported data.[27]

3-oxo-3-*p*-tolylpropanenitrile (3c)

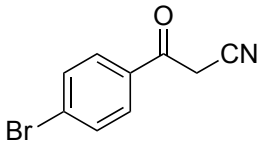


According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.3 mg, 0.049 mmol), CH_2Cl_2 (5 mL), CDBX (144.0 mg, 0.502 mmol), and trimethyl[1-(4-methylphenyl)vinyloxy]silane (104.1 mg, 0.504 mmol) was conducted at room temperature for

3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a pale yellow solid (60.1 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 4.09 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 145.9, 131.7, 129.8, 128.5, 114.0, 29.3, 21.7

The analytical data for this compound were in excellent agreement with the reported data.[27]

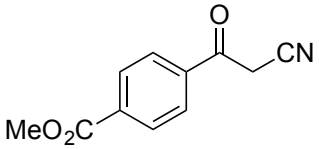
3-(4-bromophenyl)-3-oxopropanenitrile (3d)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (51.9 mg, 0.101 mmol), CH_2Cl_2 (5 mL), CDBX (144.1 mg, 0.502 mmol), and [1-(4-bromophenyl)vinyloxy]trimethylsilane (135.1 mg, 0.498 mmol) was conducted at room temperature for 3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a yellow solid (89.0 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 2H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 132.9, 132.6, 130.3, 129.8, 113.4, 29.4

The analytical data for this compound were in excellent agreement with the reported data.[27]

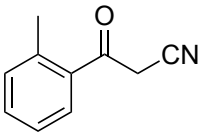
methyl 4-(2-cyanoacetyl)benzoate (3e)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (52.0 mg, 0.102 mmol), $MeNO_2$ (5 mL), CDBX (144.1 mg, 0.502 mmol), and methyl 4-[(1-trimethylsilyloxy)vinyl]benzoate (125.0 mg, 0.499 mmol) was conducted at room temperature for 3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a yellow solid (48.9 mg, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 4.12 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 165.7, 137.2, 135.3, 130.3, 128.4, 113.3, 52.7, 29.7

The analytical data for this compound were in excellent agreement with the reported data.[27]

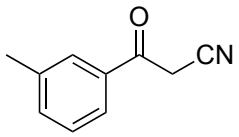
3-oxo-3-*o*-tolylpropanenitrile (3f)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (26.0 mg, 0.051 mmol), MeCN (5 mL), CDBX (143.6 mg, 0.500 mmol), and trimethyl[1-(2-methylphenyl)vinyloxy]silane (102.9 mg, 0.499 mmol) was conducted at room temperature for 3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a pale yellow solid (50.8 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.39–7.30 (m, 2H), 4.07 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 140.4, 133.7, 133.3, 132.7, 129.3, 126.1, 114.1, 31.4, 21.8

The analytical data for this compound were in excellent agreement with the reported data.[27]

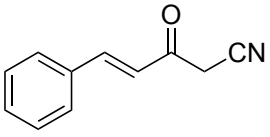
3-oxo-3-*m*-tolylpropanenitrile (3g)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.9 mg, 0.051 mmol), CH_2Cl_2 (5 mL), CDBX (144.5 mg, 0.503 mmol), and trimethyl[1-(3-methylphenyl)vinyloxy]silane (102.7 mg, 0.498 mmol) was conducted at room temperature for 3 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a pale yellow solid (70.3 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.68 (m, 2H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 4.11 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 139.1, 135.5, 134.2, 128.9, 128.8, 125.6, 113.9, 29.4, 21.2

The analytical data for this compound were in excellent agreement with the reported data.[27]

(*4E*)-3-oxo-5-phenyl-4-pentenenitrile (3h)

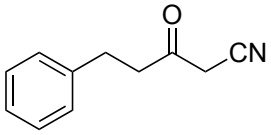


According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.7 mg, 0.050 mmol), MeCN (5 mL), CDBX (144.2 mg, 0.502 mmol), and 4-phenyl-2-trimethylsilyloxy-1,3(*E*)-butadiene (109.4 mg, 0.501 mmol) was conducted at room temperature for 3 h. Purification by flash

column chromatography on silica gel (hexane/EtOAc) gave the product as a yellow solid (72.4 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.1 Hz, 1H), 7.59 (d, *J* = 6.3 Hz, 2H), 7.50–7.38 (m, 3H), 6.87 (d, *J* = 16.1 Hz, 1H), 3.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 146.5, 133.3, 131.7, 129.1, 128.8, 122.3, 114.0, 30.8

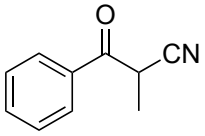
The analytical data for this compound were in excellent agreement with the reported data.[28]

3-oxo-5-phenylpentanenitrile (3i)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (26.0 mg, 0.058 mmol), CH_2Cl_2 (5 mL), CDBX (144.2 mg, 0.502 mmol), and trimethyl[(4-phenylbut-1-en-2-yl)oxy]silane (109.5 mg, 0.497 mmol) was conducted at room temperature for 6 h. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the product as a yellow solid (50.1 mg, 58% yield). mp: 69.0–71.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 3.41 (s, 2H), 2.98–2.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 139.6, 128.7, 128.3, 126.6, 113.6, 43.6, 32.2, 29.3; IR: (ATR) 2263, 1724 cm^{-1}; MS (EI) *m*/*z* 173 (M^+, 86), 133 (26), 105 (69), 104 (25), 91 (100); HRMS: (EI) calcd for ($C_{11}H_{11}NO$) 173.0841 (M^+), found *m*/*z* 173.0841

2-methyl-3-oxo-3-phenylpropanenitrile (3j)



According to the typical procedure, the reaction using $B(C_6F_5)_3$ (25.5 mg, 0.050 mmol), MeCN (2 mL), CDBX (144.1 mg, 0.502 mmol), and [(*Z*)-1-phenylprop-1-enyloxy]trimethylsilane (102.0 mg, 0.494 mmol) was conducted at room temperature for 5 h. Purification by flash column chromatography on neutral alumina (EtOAc/MeOH) and silica gel (hexane/EtOAc) gave the product as a colorless liquid (29.0 mg, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 1H), 1.66 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 134.5, 133.6, 129.0, 128.7, 118.1, 33.6, 14.9

The analytical data for this compound were in excellent agreement with the reported data.[29]

1-5. References and Notes

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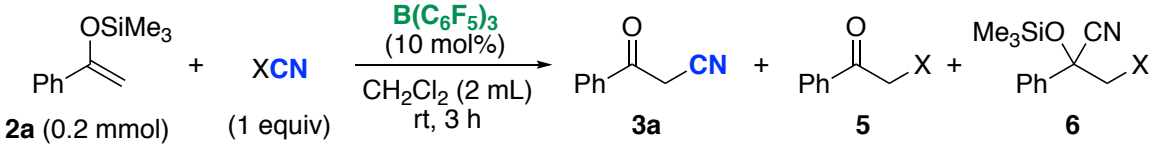
13. When the reaction of **2a** with cyanogen iodide (ICN) was carried out in the presence of 10 mol% of $B(C_6F_5)_3$ in CH_2Cl_2 at room temperature for 3 h, α-iodinated products **6** and **7** were obtained (Table 3, entry 1). In addition, the reaction using cyanogen bromide (BrCN) provided similar results (entry 2).

Table 3. Detail of Reaction of **1a** with Cyanogen Halides



entry	XCN	yield (%)[a]		
		3a	**5**	**6**
1	ICN	<5	11	19
2	BrCN	<5	33	32

[a] Determined by ^{1}H NMR.

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15. When 1 equiv of BF_3•OEt_2 was added to a solution of **1d** in CH_2Cl_2, the CN stretching vibrational band of **1d** was slightly shifted from 2137 to 2162 cm^{-1}. In addition, in the ^{13}C NMR spectrum, the signal corresponding to the cyano group was shifted upfield from 98.4 ppm to 78.1 ppm.

16. For reactions via Lewis acidic activation of hypervalent iodine reagents, see: (a) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4332. (b) Vita, M. V.; Waser, J. *Org. Lett.* **2013**, *15*, 3246. (c) Ilchenko, N. O.; Tasch, B. O. A.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 12897. (d) Yuan, W.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 8533. (e) Geary, G. C.; Hope, E. G.; Stuart, A. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14911. (f) Ilchenko, N. O.; Cortés, M. A.; Szabó, K. J. *ACS Catal.* **2016**, *6*, 447. (g) Zhou, B.; Yan, T.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2016**, *18*, 6128. (h) Zhang, J.; Szabó, K. J.; Himo, F. *ACS Catal.* **2017**, *7*, 1093. (i) Zhou, B.; Xue, X.-S.; Cheng, J.-P. *Tetrahedron Lett.* **2017**, *58*, 1287. (j) Ilchenko, N. O.; Hedberg, M.; Szabó, K. J. *Chem. Sci.* **2017**, *8*, 1056.

17. Although the Lewis acidic activation of a hypervalent fluoroiodine(III) reagent through the coordination of its fluorine atom to a Lewis acid has recently been revealed (references 16g–i), this type of activation mode for the related cyanoiodine(III) reagent has never been reported.

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Chapter 2

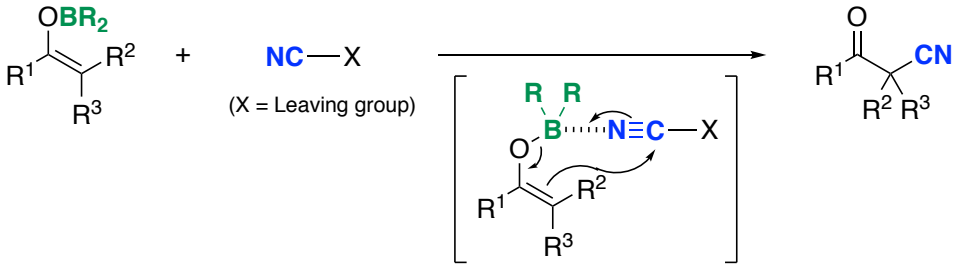
Electrophilic Cyanation of Boron Enolates

2-1. Introduction

β-Ketonitriles are an important building block for the synthesis of various heterocycles such as pyrazoles,[1] pyrimidines,[2] thiophenes,[3] and others,[4] that are frequently found in pharmaceuticals and biologically active compounds. In addition, β-ketonitriles can be converted to optically active β-hydroxy nitriles via the enantioselective reduction of the carbonyl group,[5] which are also valuable synthetic intermediates in organic synthesis. Therefore, considerable efforts have been devoted to the development of methodology for the synthesis of β-ketonitriles in the past decades.[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, those methods usually require an excess amount of the substrate and base. Alternatively, nucleophilic substitution with a cyanide on an α-haloketones 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 an enolate equivalent 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] By using this concept, the author found that electrophilic cyanation of silyl enol ethers with CDBX in the presence of $B(C_6F_5)_3$ catalyst as mentioned in Chapter 1. Although this method has a broad substrate scope compared to the previously reported electrophilic cyanation of silyl enol ethers, the method still suffered from low efficiency when the α-monosubstituted silyl enol ether was used. In Chapter 2, the author envisioned that boron enolates, the boron center of which can interact with the cyano group of a cyanating reagent, would be a promising nucleophile for electrophilic cyanation (Scheme 1).



Scheme 1. Utilization of Boron Enolates

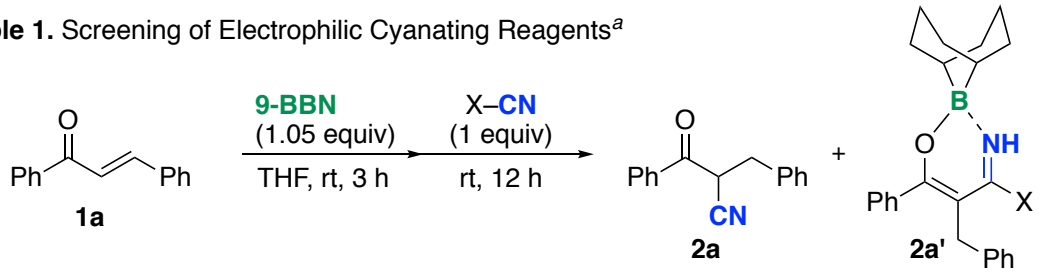
2-2. Results and Discussion

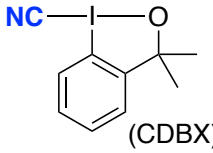
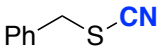
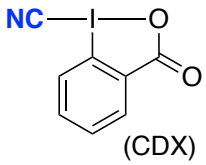
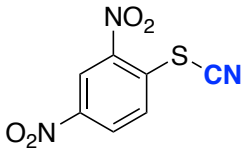
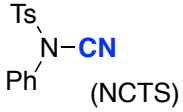
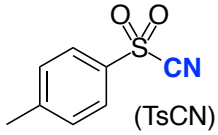
2-2-1. Electrophilic Cyanation of a Boron Enolate with Electrophilic Cyanating Reagents

At first, the reaction of a boron enolate, which was prepared from chalcone (**1a**) and 9-BBN, with various electrophilic cyanating reagents in THF at room temperature was

investigated (Table 1).[18] Although the use of CDBX did not provide cyanated product **2a**, the cyanation proceeded to give **2a** in 48% when CDX was used (entries 1 and 2). Further screening of cyanating reagents revealed that NCTS is a suitable reagent to provid **2a** in 84% (entry 3). In this reaction, boron complex **2a'** was also obtained in 7%. The reaction using cyananogen bromide resulted in the formation of **2a** in low yield, and the α-brominated product was obtained as a byproduct (entry 4). Only boron complex **2a'** was produced when benzyl thiocyanate was used, while the use of 2,4-dinitrophenyl thiocyanate gave a mixture of **2a** and **2a'** (entries 5 and 6). The reaction using TsCN proceeded effectively, affording **2a** in 85% yield (entry 7). Because of its ease of preparation,[19] NCTS was chosen as the best cyanating reagent for this reaction and further optimization of reaction conditions was carried out.

Table 1. Screening of Electrophilic Cyanating Reagents[a]



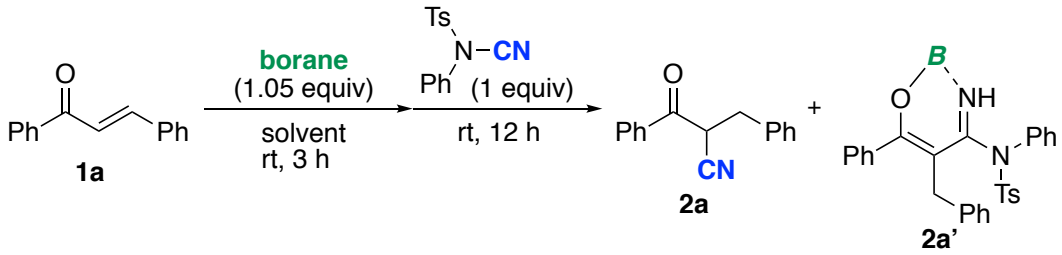
Entry	X–CN	yield (%)[b] 2a	2a'	Entry	X–CN	yield (%)[b] 2a	2a'
1	 (CDBX)	<5	<5	4[c]	Br–CN	24	<5
				5		<5	>95
2	 (CDX)	48	<5	6		42	40
3	 (NCTS)	84	7	7	 (TsCN)	85	<5

[a] Reaction conditions: **1a** (0.5 mmol), 9-BBN (0.525 mmol), solvent (1 mL), cyanating reagent (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. [c] α-Brominated product was obtained in 39% yield.

2-2-2. Electrophilic Cyanation of Boron Enoaltes with NCTS

The reaction of various boron enolates with NCTS was investigated. In contrast to the 9-BBN-based boron enolate, the cyanation of both of the boron enolates prepared using dicyclohexylborane ($HBCy_2$) and catecholborane (HBcat), respectively, were largely suppressed (Table 2, 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 **2a'** 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 50% of **1a** was recovered (entry 7). When the reaction temperature was

Table 2. Optimization of Reaction Conditions[a]



entry	borane	solvent	temp. (°C)	yield (%)[b]	
				2a	**2a'**
1	9-BBN	THF	rt	84	7
2	$HBCy_2$	THF	rt	8	<5
3	HBcat	THF	rt	<5	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

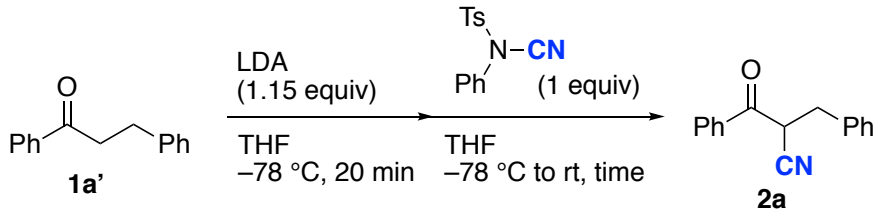
[a] Reaction conditions: **1a** (0.5 mmol), borane (0.525 mmol), solvent (1 mL), NCTS (0.5 mmol). [b] Determined by ^1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. The value within parentheses refers to the yield of the isolated product. [c] 9-BBN,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

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% isolated yield) was obtained when all of the reagents were added in succession, demonstrating that the prior in situ preparation of the boron enolate was not required for this reaction (entry 9).

2-2-3. Reaction of NCTS with Other Enolate Equivalents

To demonstrate the superiority of a boron enolate, control experiments using the other enolate equivalents were carried out. The reaction of a lithium enolate, which was prepared from ketone **1a'** and LDA, with NCTS resulted in the formation of **2a** in a moderate yield (Table 3). The corresponding silyl enolate failed to provide the cyanated product **2a** in the

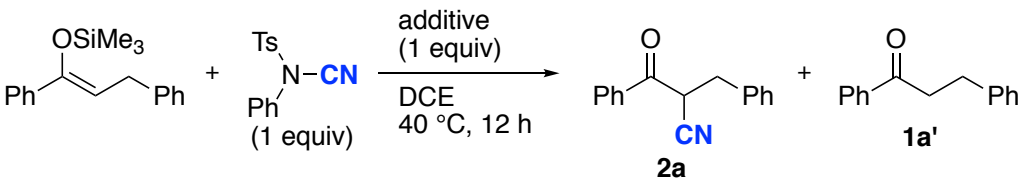
Table 3. Reaction of Lithium Enolate with NCTS



entry	time	yield (%)[a]	recovery of **1a'** (%)[a]
1	10 min	48	33
2	1 h	39	27

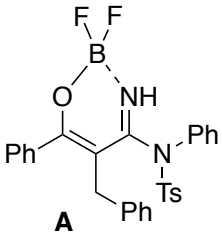
[a] Determined by ^{1}H NMR.

Table 4. Reaction of Silyl Enol Ethers with NCTS



entry	additive	yield (%)[a]		recovery of silyl enol ether (%)[a]
		2a	**1a'**	
1	none	0	12	85
2[b]	BF_3•OEt_2	0	53	0

[a] Determined by ^{1}H NMR. [b] Compound **A** was obtained in 32% yield.

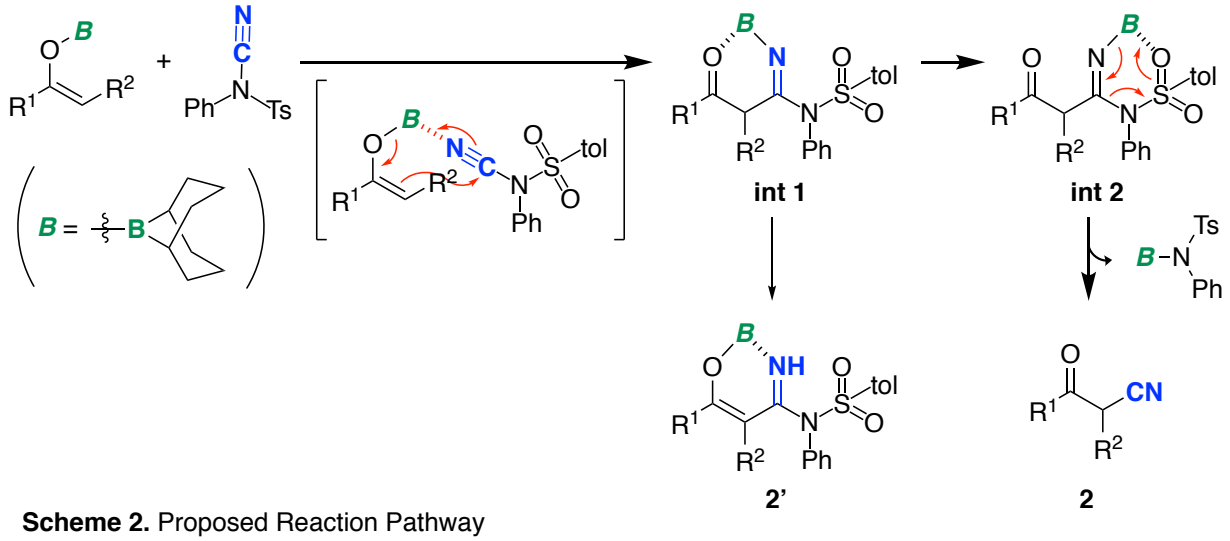


A

absence and presence of a boron Lewis acid (Table 4). These results clearly show that the use of boron enolate is crucial for the success of this cyanation.

2-2-4. Proposed Reaction Pathway

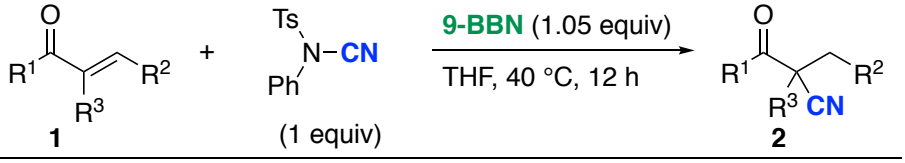
The proposed reaction pathway is depicted in Scheme 2. The reaction is assumed to be triggered by the sufficient activation of NCTS via the coordination of its cyano group to the strained and Lewis acidic boron center of the 9-BBN-based boron enolate. This coordination would enhance the nucleophilicity of the boron enolate, thus promoting the addition to the cyano group of NCTS. After the nucleophilic attack of a boron enolate to the cyanao group of NCTS, **int 1** would be genetrated. When **int 1** isomerizes to **int 2**, in which the boron center is coordinated by the sulfonyl group, the elimination of the amide moiety occurs, 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. In contrast, keto-enol tautomerization of **int 1** leads to the stable product **2'**. Isolated boron complex **2a'** was not converted to the ketonitrile **2a** when exposed to the standard reaction conditions (40 °C in THF), indicating that **2'** is not an intermediate for this cyanation.

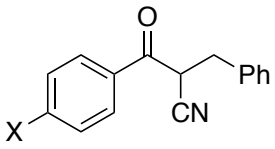


Scheme 2. Proposed Reaction Pathway

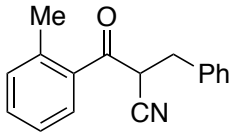
2-2-5. Scope of α,β-Unsaturated Ketones

With the optimized reaction conditions identified (Table 2, Entry 9), the author 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 -withdrawing groups in the *p*-positions on the phenyl ring at the 2-position provided the corresponding cyanated products in high yields (**2b**–**2h**), although highly electron-deficient substrates with a nitro group gave a relatively low yield (**2i**). The effects of methyl substituents on the *o*- or *m*-positions were negligable (**2j** and **2k**). This cyanation appears to be insensitive to electronic and steric effects by aryl substituents at the 4-position (**2l**–**2n**). In addition, electron-rich hetero aromatics 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, each of which prefers a *s-cis* and *s-trans* geometry, respectively, the *s-cis*-moiety predominantly underwent hydroboration, leading to the formation of the cyanated product **2q**. In addition, enones possessing aliphatic substituents at the 2- and/or 4-positions were also applicable to this cyanation (**2r**–**2x**). In those reactions, steric hindrance of 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 via the selective generation of the boron enolate by 1,4-hydroboration, while a smaller ethyl group resulted in a lower yield of the cyanated product, since competitive 1,2-hydroboration occurred, giving rise to the corresponding allylic alcohol.[20] To the contrary, steric effects of aliphatic substituents at the 4-position had negligible effects in this system (**2u**–**2x**). 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.[20]

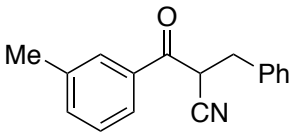




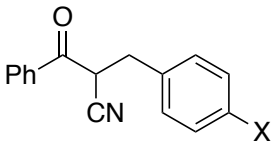
2b, X = OMe 88%[a]
2c, X = Me 80%
2d, X = F 83%
2e, X = Cl 80%
2f, X = Br 84%
2g, X = CF_3 83%
2h, X = CO_2Me 79%
2i, X = NO_2 69%



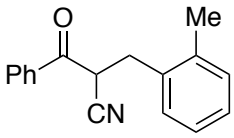
2j, 78%



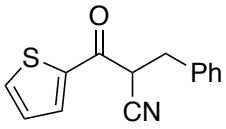
2k, 86%



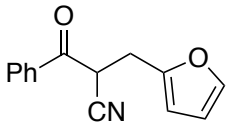
2l, X = OMe 86%
2m, X = CF_3 82%[a]



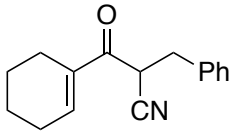
2n, 85%



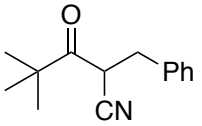
2o, 65%



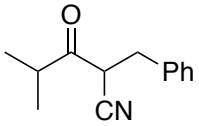
2p, 85%



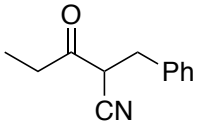
2q, 81%



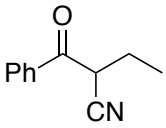
2r, 80%



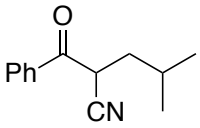
2s, 70%



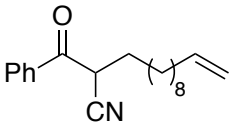
2t, 58%



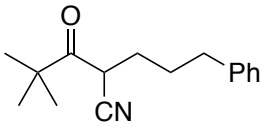
2u, 90%[a]



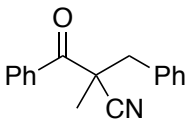
2v, 94%



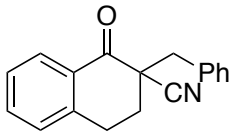
2w, 91%



2x, 88%



2y, 52%[b]

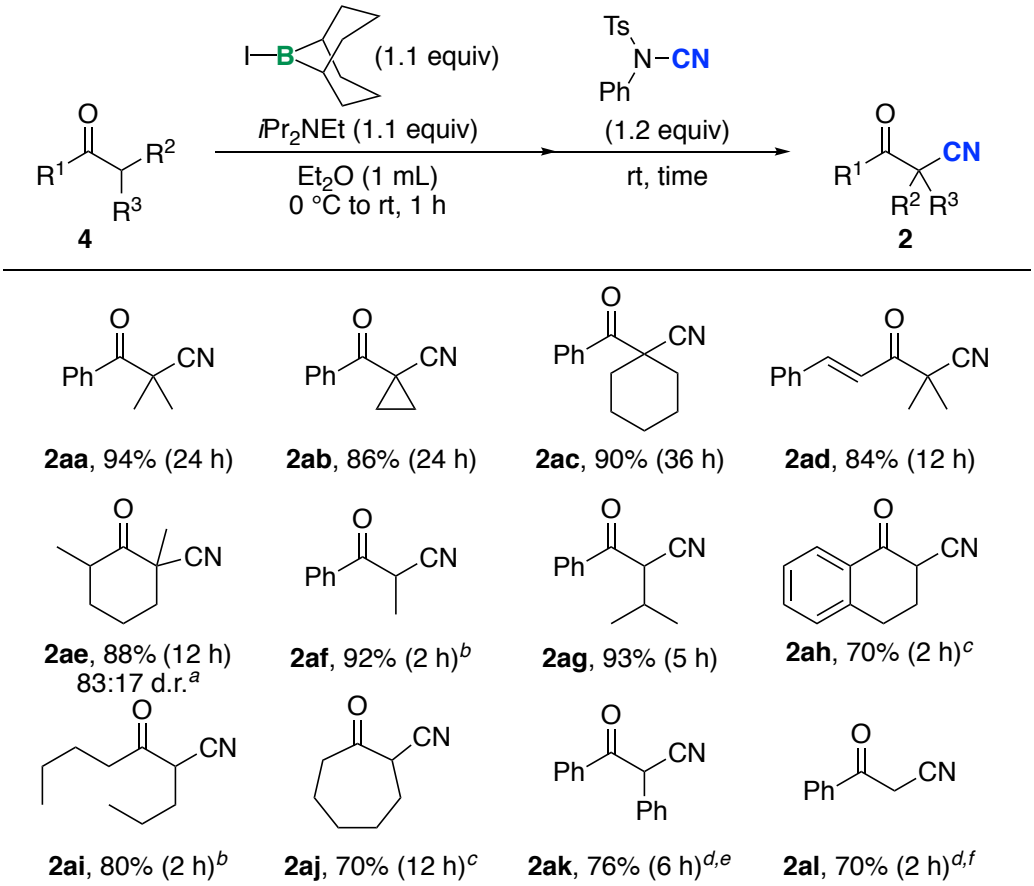


2z, 61%

Scheme 3. Substrate scope of α,β-unsaturated ketones. 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.

2-2-6. Reaction of Boron Enolates Prepared from Ketones

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).[21] A brief screening of solvents revealed that the use of Et_2O was suitable for this system. The method was successfully applied to the cyanation of α,α-disubstituted ketones to furnish the corresponding β-ketonitriles (**2aa**–**2ae**), compounds that would be difficult to produce by our method described above as well as 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 via 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, providing the corresponding products in good to high yields (**2af**–**2aj**). 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.



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.

2-3. Conclusion

In conclusion, the author developed a new class of electrophilic cyanation reactions in which boron enolates are reacted with readily available NCTS as a cyanating reagent. Boron enolates derived from various types of ketones including α,β-unsaturated ketones could be applied to this cyanation. Various β-ketonitriles were synthesized by this protocol, which has a remarkably broad substrate scope compared to existing methods. This method also allowed efficient synthesis of β-ketonitriles containing a quarternary α-carbon center.

2-4. Experimental Section

General Remarks

New compounds were characterized by ^{1}H, ^{13}C, ^{19}F, IR, MS, and HRMS. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL JMTC-400/54/SS spectrometer (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz; ^{11}B NMR, 128 MHz; ^{19}F NMR, 377 MHz). ^{1}H NMR chemical shifts were determined relative to Me_4Si (0.0 ppm) as an internal standard. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ (77.0 ppm). ^{11}B NMR chemical shifts were determined relative to BF_3•OEt_2 (0.0 ppm) as an external standard. ^{19}F NMR chemical shifts were determined relative to C_6F_6 (-164.9 ppm) as an external standard. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR Spectrometer. Mass spectra were obtained on a SHIMADZU GCMS-QP2010 and a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-DX303HF mass spectrometer. Melting points were determined on a Stanford Research Systems MPA100 OptiMelt Automated Melting Point System. X-ray crystal data were collected by a Rigaku RAXIS-RAPID Imaging Plate diffractometer. All reactions were carried out under nitrogen. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or Chromatorex NH (Fuji Silysia Chemical Ltd.). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel glass plates (Merck silica gel 60 F_{254} and Fuji Silysia Chromatorex NH, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating.

Materials

Dehydrated tetrahydrofurane and diethyl ether were used from a solvent purification system. Dehydrated 1,2-dimethoxyethane was used as obtained. α,β-Unsaturated ketones **1b**,[22] **1c**,[22] **1d**,[23] **1e**,[22] **1f**,[24] **1g**,[25] **1i**,[24] **1j**,[26] **1k**,[26] **1m**,[27] **1n**,[22] **1o**,[28] **1p**,[28] **1q**,[29] **1r**,[30] **1u**,[30] **1v**,[31] **1x**,[31] **1y**,[30] and **1z**[28] were prepared by known methods. Analytical data for **1c**,[32] **1f**,[22] **1o**,[33] **1n**,[32] and **1x**[34] were in excellent agreement with reported data. 9-Borabicyclo- [3.3.1]nonane (9-BBN) dimer and *B*-iodo-9-borabicyclo-[3.3.1]nonane (*B*-I-9-BBN) (1 M in hexane) were purchased and used as obtained. Dicyclohexylborane was prepared by known method.[35] *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) was prepared by known method.[36] *p*-Toluenesulfonyl cyanide (TsCN) was purchased and used as obtained. All other solvents and reagents were purchased and used as obtained.

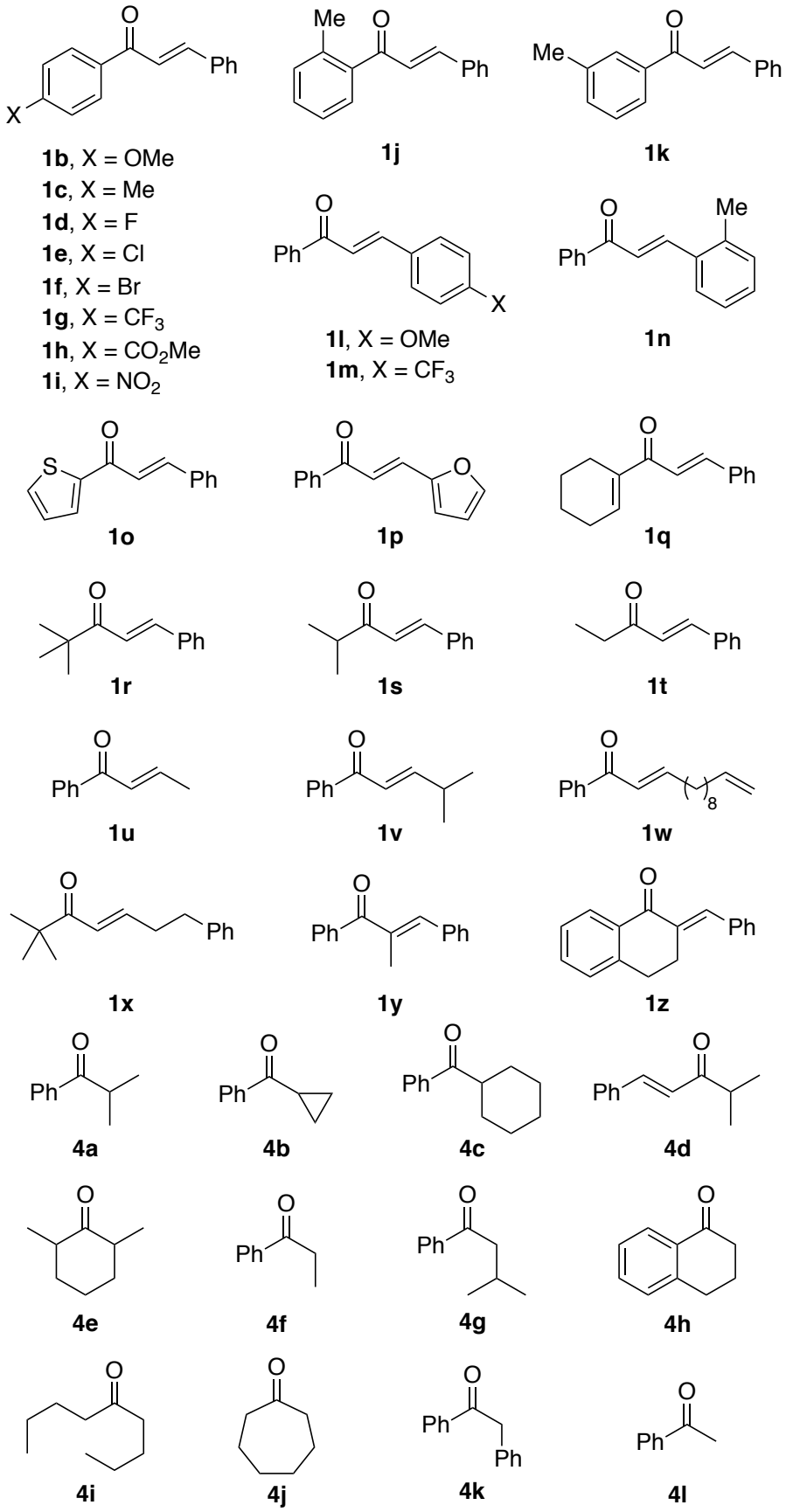
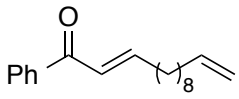


Figure 1. List of substrates

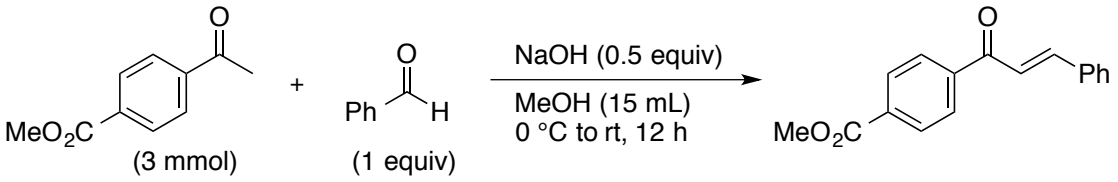
Preparation of α,β-unsaturated ketones

(*E*)-1-phenyldodeca-2,12-dien-1-one (1w)



The compounds was prepared by known methods.[31] ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.11–7.02 (m, 1H), 6.88 (d, *J* = 15.1 Hz, 1H), 5.87–5.75 (m, 1H), 5.13–4.88 (m, 2H), 2.32 (dt, *J* = 7.2, 7.2 Hz, 2H), 2.04 (dt, *J* = 6.8, 6.8 Hz, 2H), 1.58–1.45 (m, 2H), 1.42–1.20 (m, 10H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.0, 150.2, 139.2, 138.0, 132.6, 128.50, 128.48, 125.8, 114.1, 33.8, 32.9, 29.3, 29.2, 29.1, 28.9, 28.1 (one sp^3 signal was not observed because of overlapping); IR: (ATR) 1670, 1620 cm^{-1}; MS: (EI) *m*/*z* 270 (M^+, 3), 120 (22), 105 (100), 77 (46), 55 (42) HRMS: (EI) calcd for ($C_{19}H_{26}O$) 270.1984 (M^+) found *m*/*z* 270.1986

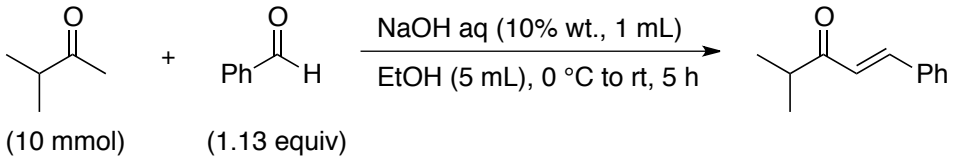
methyl 4-cinnamoylbenzoate (1h)



A solution of benzaldehyde (0.3 mL, 3 mmol) in methanol (15 mL) was cooled to 0 °C. Then, NaOH (60 mg, 1.5 mmol) and methyl 4-acetylbenzoate (535 mg, 3 mmol) were added to the solution. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 12 h. The reaction mixture was diluted with water, and the precipitate formed was collected by filtration, washed with water and diethyl ether to give the product as a yellow solid (533 mg, 67%).

The analytical data for this compound were in excellent agreement with the reported data.[37]

(*E*)-4-methyl-1-phenylpent-1-en-3-one (1s)

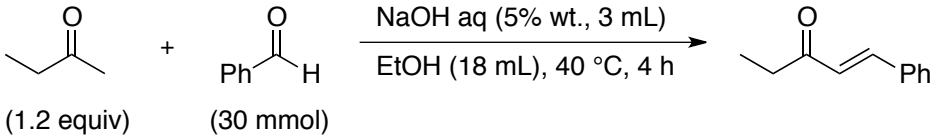


(10 mmol) (1.13 equiv)

The compound was prepared following the reported procedure,[38] with a slight modification. A solution of benzaldehyde (1.2 mL, 11.3 mmol) and 3-methylbutan- 2-one (1.1 mL, 10 mmol) in EtOH (5 mL) was cooled to 0 °C. Then, NaOH aq. (10% wt., 1 mL) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 5 h. The reaction mixture was diluted with water and extracted with diethyl ether (3 x 20 mL). The collected organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product. Purification was performed by column chromatography on silica gel (hexane/EtOAc) and reprecipitaiton from hexane under -40 °C to give the product as a pale yellow solid, which is a pale yellow liquid at room temperature (520 mg, 30%).

The analytical data for this compound were in excellent agreement with the reported data.[39]

(*E*)-1-phenylpent-1-ene-3-one (1t)



(1.2 equiv) (30 mmol)

The compounds was prepared following a slight modification of the reported procedure.[40] NaOH aq. (5% wt., 3 mL) was added to a solution of benzaldehyde (3.0 mL, 30 mmol) and methyl ethyl ketone (3.2 mL, 36 mmol) in EtOH (18 mL) at 40 °C, and the mixture was stirred for 4 h. The reaction was diluted with water and extracted with EtOAc (3 x 30 mL). The collected organic layers were washed with brine (2 x 20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product. Purification was performed by column chromatography on silica gel (hexane/EtOAc) and reprecipitation from hexane under -40 °C to give the product as a white solid (621 mg, 13%).

The analytical data for this compound were in excellent agreement with the reported data.[41]

Typical procedure for the cyanation of boron enolates

Procedure A (Table 1 and Table 2, Entries 1–8)

In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with borane (0.525 mmol) (or 9-BBN dimer (0.263 mmol)). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, solvent (1 mL) and chalcone (0.500 mmol) were added to the flask. The mixture was stirred for 3 h at room temperature before NCTS (0.500 mmol) was added. The mixture was stirred for 12 h, and the reaction was then quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product, which was analyzed by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Procedure B (Table 2, Entry 9 and Scheme 3)

In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with 9-BBN dimer (0.263 mmol). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, α,β-unsaturated ketone (0.500 mmol), NCTS (0.500 mmol), and THF (1 mL) were added to the flask, and the solution was stirred at 40 °C for 12 h. The reaction was then quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product, which was analyzed by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Purification by flash column chromatography on silica gel (hexane/EtOAc) or GPC ($CHCl_3$) gave the product.

Procedure C (Scheme 4)

A flame-dried reaction flask containing a magnetic stir bar was charged with ketone (0.500 mmol), *i*Pr_2NEt (0.550 mmol), and Et_2O (1 mL) under nitrogen. *B*-I-9-BBN (1 M in hexane, 0.550 mmol) was added slowly at 0 °C to the solution. The mixture was warmed to room temperature and stirred for 1 h before NCTS (0.600 mmol) was added. The mixture was stirred

for the indicated time, and the reaction was then quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product, which was analyzed by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Purification by flash column chromatography on silica gel (hexane/EtOAc) or GPC ($CHCl_3$) gave the product.

Procedure for the reactions of lithium enolate with NCTS (Table 3)

The lithium enolate was prepared as follows. To a solution of *N*,*N*-diisopropylamine (0.575 mmol) in THF (0.5 mL), *n*BuLi (1.6 M in hexane, 0.575 mmol) was added dropwise at -78 °C. The mixture was stirred for 10 min at -78 °C and then 10 min at room temperature. The mixture was cooled to -78 °C, and a solution of 1,3-diphenylpropan-1-one (0.500 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred for 20 min at -78 °C.

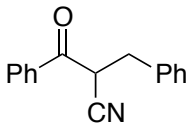
The solution of freshly prepared lithium enolate was added dropwise to a solution of NCTS (0.500 mmol) in THF (1 mL) at -78 °C. The cryobath was removed, and the mixture was stirred for 10 min or 1 h. The reaction was quenched by adding sat. NH_4Cl aq. (10 mL). The mixture was extracted with diethyl ether (3 x 20 mL), and combined organic layers were dried over Na_2SO_4. The solution was concentrated under reduced pressure to give the crude product, which was analyzed by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard.

Procedure for the reactions of silyl enol ether with NCTS (Table 4)

The silyl enolate (0.5 mmol) (and BF_3•OEt_2 (0.500 mmol)) was added to a solution of NCTS (0.500 mmol) in 1,2-dichloroethane (1 mL) at room temperature. The mixture was stirred for 12 h at 40 °C, and the reaction was then quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product, which was analyzed by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Product data

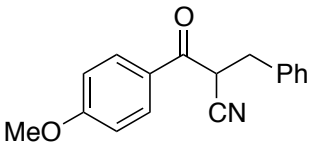
2-benzyl-3-oxo-3-phenylpropanenitrile (2a)



According to the procedure B, the reaction using (*E*)-chalcone (104.8 mg, 0.503 mmol), 9-BBN dimer (64.0 mg, 0.262 mmol), and NCTS (136.2 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (98.5 mg, 84% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.39–7.18 (m, 5H), 4.52 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.37 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.25 (dd, *J* = 14.1, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.9, 135.9, 134.6, 134.0, 129.1, 129.0, 128.9, 128.8, 127.6, 116.9, 41.8, 35.4

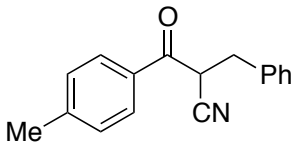
The analytical data for this compound were in excellent agreement with the reported data.[7e]

2-benzyl-3-(4-methoxyphenyl)-3-oxopropanenitrile (2b)



According to the procedure B, the reaction using (*E*)-1-(4-methoxyphenyl)-3- phenylprop-2-en-1-one (142.5 mg, 0.598 mmol), 9-BBN dimer (77.3 mg, 0.317 mmol), and NCTS (135.7 mg, 0.498 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) gave the product as a pale yellow solid (116.2 mg, 88% yield). mp: 92.3–93.1 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.39–7.20 (m, 5H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.45 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.89 (s, 3H), 3.35 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.24 (dd, *J* = 14.1, 9.3 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 188.2, 164.6, 136.1, 131.2, 129.0, 128.8, 127.5, 126.9, 117.3, 114.3, 55.6, 41.3, 35.5; IR: (ATR) 2251, 1672 cm^{-1}; MS: (EI) *m/z* 265 (M^+, 29), 207 (20), 135 (100), 77 (27); HRMS: (EI) calcd for ($C_{17}H_{15}NO_2$) 265.1103 (M^+), found *m/z* 265.1104

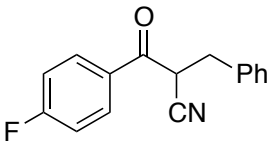
2-benzyl-3-(4-methylphenyl)-3-oxopropanenitrile (2c)



According to the procedure B, the reaction using (*E*)-3-phenyl-1-*p*-tolylprop-2-en-1-one (111.2 mg, 0.500 mmol), 9-BBN dimer (64.2 mg, 0.263 mmol), and NCTS (136.2 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a pale yellow solid (99.5 mg, 80% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.39–7.19 (m, 7H), 4.49 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.35 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.24 (dd, *J* = 14.1, 9.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.5, 145.8, 136.0, 131.5, 129.7, 129.0, 128.9, 128.8, 127.5, 117.1, 41.6, 35.5, 21.7

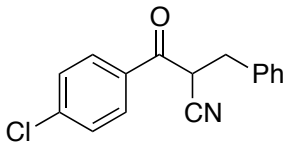
The analytical data for this compound were in excellent agreement with the reported data.[42]

2-benzyl-3-(4-fluorophenyl)-3-oxopropanenitrile (2d)



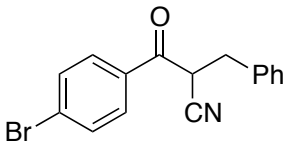
According to the procedure B, the reaction using (*E*)-1-(4-fluorophenyl)-3- phenylprop-2-en-1-one (113.3 mg, 0.501 mmol), 9-BBN dimer (64.1 mg, 0.263 mmol), and NCTS (136.4 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (105.4 mg, 83% yield). mp: 72.3–73.1 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.03–7.90 (m, 2H), 7.39–7.08 (m, 7H), 4.46 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.36 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.25 (dd, *J* = 14.1, 8.5 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 188.4, 166.5 (d, J_{CF} = 256.9 Hz), 135.8, 131.6 (d, J_{CF} = 9.9 Hz), 130.5 (d, J_{CF} = 2.5 Hz), 129.0, 128.9, 127.7, 116.8, 116.4 (d, J_{CF} = 22.2 Hz), 41.7, 35.4; ^{19}F NMR: (377 MHz, $CDCl_3$) δ -105.0; IR: (ATR) 2249, 1682 cm^{-1}; MS: (EI) *m*/*z* 253 (M^+, 12), 124 (47), 123 (100), 95 (98), 91 (42), 77 (21), 75 (43), 65 (21), 51 (23); HRMS: (EI) calcd for ($C_{16}H_{12}FNO$) 253.0903 (M^+), found *m*/*z* 253.0899

2-benzyl-3-(4-chlorophenyl)-3-oxopropanenitrile (2e)



According to the procedure B, the reaction using (*E*)-1-(4-chlorophenyl)-3- phenylprop-2-en-1-one (120.8 mg, 0.498 mmol), 9-BBN dimer (64.6 mg, 0.265 mmol), and NCTS (136.1 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (106.9 mg, 80% yield). mp: 94.1–95.3 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8, 2H), 7.39–7.15 (m, 5H), 4.45 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.36 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.25 (dd, *J* = 14.1, 8.5 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 188.9, 141.2, 135.6, 132.3, 130.1, 129.4, 129.0, 128.9, 127.7, 116.7, 41.7, 35.3; IR: (ATR) 2241, 1695 cm^{-1}; MS: (EI) *m*/*z* 271 ($[M+2]^+$, 2), 269 (M^+, 5), 141 (31), 139 (100), 111 (42), 91 (21), 75 (25); HRMS: (EI) calcd for ($C_{16}H_{12}ClNO$) 269.0607 (M^+), found *m*/*z* 269.0607

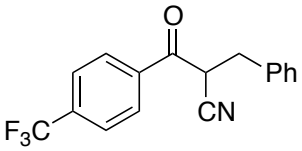
2-benzyl-3-(4-bromophenyl)-3-oxopropanenitrile (2f)



According to the procedure B, the reaction using (*E*)-1-(4-bromophenyl)-3- phenylprop-2-en-1-one (142.9 mg, 0.498 mmol), 9-BBN dimer (64.7 mg, 0.265 mmol), and NCTS (135.1 mg, 0.496 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a white solid (131.5 mg, 84% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.39–7.20 (m, 5H), 4.45 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.35 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.25 (dd, *J* = 13.9, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.1, 135.6, 132.7, 132.4, 130.1, 130.0, 129.0, 128.9, 127.7, 116.7, 41.7, 35.3

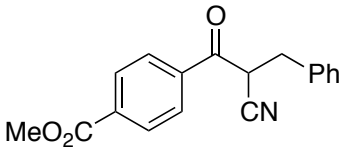
The analytical data for this compound were in excellent agreement with the reported data.[43]

2-benzyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propanenitrile (2g)



According to the procedure B, the reaction using (*E*)-3-phenyl-1- (4-(trifluoromethyl)phenyl)prop-2-en-1-one (137.0 mg, 0.496 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (136.2 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (125.2 mg, 83% yield). mp: 88.6–89.5 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.40–7.20 (m, 5H), 4.50 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.38 (dd, *J* = 13.9, 6.1 Hz, 1H), 3.27 (dd, *J* = 13.9, 8.5 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.4, 136.7, 135.6 (q, J_{CF} = 33.0 Hz), 135.4, 129.1, 128.98, 128.96, 127.8, 126.1 (q, J_{CF} = 3.9 Hz), 123.2 (q, J_{CF} = 273.1 Hz), 116.5, 42.1, 35.2; ^{19}F NMR: (377 MHz, $CDCl_3$) δ -51.8; IR: (ATR) 2247, 1695 cm^{-1}; MS: (EI) *m*/*z* 303 (M^+, 11), 173 (100), 145 (46), 91 (24); HRMS: (EI) calcd for ($C_{17}H_{12}F_3NO$) 303.0871 (M^+), found *m*/*z* 303.0872

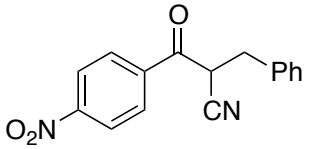
methyl 4-(2-cyano-3-phenylpropanoyl)benzoate (2h)



According to the procedure B, the reaction using methyl 4-cinnamoylbenzoate (132.6 mg, 0.498 mmol), 9-BBN dimer (64.6 mg, 0.265 mmol), and NCTS (136.5 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) and recrystallization from hexane/CH_2Cl_2 gave the product as a white solid (115.8 mg, 79% yield). mp: 135.0 °C (dec.); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.3, 2H), 7.39–7.18 (m, 5H), 4.52 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.96 (s, 3H), 3.37 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.26 (dd, *J* = 13.7, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.7, 165.7, 137.2, 135.6, 135.1, 130.2, 129.0, 129.0, 128.7, 127.8, 116.6, 52.6, 42.1, 35.4; IR: (ATR) 2253, 1719, 1692 cm^{-1}; MS: (EI)

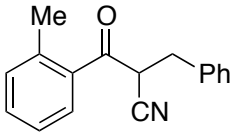
m/*z* 293 (M^+, 7), 163 (100), 104 (20), 103 (20), 91 (31), 76 (24); HRMS: (EI) calcd for ($C_{18}H_{15}NO_3$) 293.1052 (M^+), found *m*/*z* 293.1053

2-benzyl-3-(4-nitrophenyl)-3-oxopropanenitrile (2i)



According to the procedure B, the reaction using (*E*)-1-(4-nitrophenyl)-3- phenylprop-2-en-1-one (127.0 mg, 0.501 mmol), 9-BBN dimer (64.3 mg, 0.263 mmol), and NCTS (136.4 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) gave the product as a pale yellow solid (96.6 mg, 69% yield). mp: 102.5–103.4 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.3 Hz, 2H), 8.09 (d, *J* = 9.3 Hz, 2H), 7.39–7.22 (m, 5H), 4.52 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.39 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.30 (dd, *J* = 14.1, 8.3 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.0, 150.9, 138.5, 135.2, 129.9, 129.1, 129.0, 127.9, 124.2, 116.2, 42.3, 35.3; IR: (ATR) 2257, 1692 cm^{-1}; MS: (EI) *m*/*z* 280 (M^+, 12), 150 (100), 104 (53), 92 (32), 91 (62), 77 (23), 76 (52), 50 (27); HRMS: (EI) calcd for ($C_{16}H_{12}N_2O_3$) 280.0848 (M^+), found *m*/*z* 280.0849

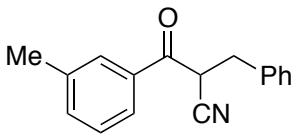
2-benzyl-3-(2-methylphenyl)-3-oxopropanenitrile (2j)



According to the procedure B, the reaction using (*E*)-3-phenyl-1-*o*-tolylprop-2-en-1-one (111.8 mg, 0.503 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (136.2 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) gave the product as a colorless liquid (97.0 mg, 78% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 1H), 7.39–7.20 (m, 7H), 4.46 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.34 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.21 (dd, *J* = 14.1, 8.8 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.8, 139.9, 135.9, 134.5, 132.8, 132.5, 129.0, 128.9, 128.5, 127.6, 126.0, 117.1, 44.0, 35.4, 21.3; IR:

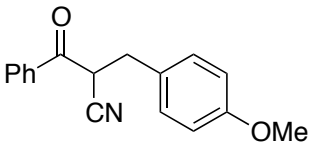
(ATR) 2251, 2208, 1694 cm^{-1}; MS: (EI) *m*/*z* 249 (M^+, 6), 119 (100), 91 (95), 65 (46); HRMS: (EI) calcd for ($C_{17}H_{15}NO$) 249.1154 (M^+), found *m*/*z* 249.1155

2-benzyl-3-(3-methylphenyl)-3-oxopropanenitrile (2k)



According to the procedure B, the reaction using (*E*)-3-phenyl-1-*m*-tolylprop-2- en-1-one (111.0 mg, 0.499 mmol), 9-BBN dimer (64.2 mg, 0.263 mmol), and NCTS (136.5 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (106.8 mg, 86% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.80–7.70 (m, 2H), 7.50–7.21 (m, 7H), 4.52 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.35 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.24 (dd, *J* = 14.1, 8.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.1, 139.1, 136.0, 135.4, 134.1, 129.3, 129.0, 128.93, 128.89, 127.6, 126.0, 117.0, 41.8, 35.5, 21.3; IR: (ATR) 2249, 1692 cm^{-1}; MS: (EI) *m*/*z* 249 (M^+, 9), 119 (100), 91 (55), 65 (23); HRMS: (EI) calcd for ($C_{17}H_{15}NO$) 249.1154 (M^+), found *m*/*z* 249.1159

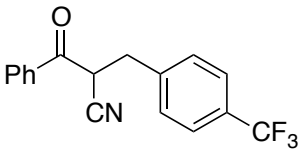
2-(4-methoxyphenylmethyl)-3-oxo-3-phenylpropanenitrile (2l)



According to the procedure B, the reaction using (*E*)-3-(4-methoxyphenyl)-1- phenylprop-2-en-1-one (119.7 mg, 0.502 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (135.9 mg, 0.499 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) and GPC ($CHCl_3$) gave the product as a pale yellow liquid (114.3 mg, 86% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.49 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.79 (s, 3H), 3.31 (dd, *J* = 14.1, 5.4 Hz, 1H), 3.20 (dd, *J* = 14.1, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.2, 158.9, 134.4, 134.0, 130.1, 129.0, 128.7, 127.7,

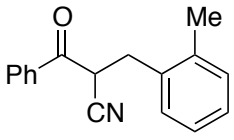
117.0, 114.2, 55.2, 42.1, 34.7; IR: (ATR) 2249, 1692 cm^{-1}; MS: (EI) *m*/*z* 265 (M^+, 7), 121 (100), 105 (49), 77 (53); HRMS: (EI) calcd for ($C_{17}H_{15}NO_2$) 265.1103 (M^+), found *m*/*z* 265.1104

3-oxo-3-phenyl-2-(4-(trifluoromethyl)phenylmethyl)propanenitrile (2m)



According to the procedure B, the reaction using (*E*)-1-phenyl-3- (4-(trifluoromethyl)phenyl)prop-2-en-1-one (165.3 mg, 0.598 mmol), 9-BBN dimer (77.1 mg, 0.316 mmol), and NCTS (136.3 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by silica gel column chromatography (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a pale yellow solid (124.3 mg, 82% yield). mp: 88.5–89.2 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 4.52 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.43 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.32 (dd, *J* = 14.1, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.4, 139.9, 134.7, 133.7, 129.8 (q, J_{CF} = 32.1 Hz), 129.5, 129.1, 128.7, 125.8 (q, J_{CF} = 3.6 Hz), 123.9 (q, J_{CF} = 272.3 Hz), 116.6, 41.1, 34.8; ^{19}F NMR: (377 MHz, $CDCl_3$) δ -65.2; IR: (ATR) 2247, 1695 cm^{-1}; MS: (EI) *m*/*z* 303 (M^+, 3), 105 (100), 77 (47); HRMS: (EI) calcd for ($C_{17}H_{12}F_3NO$) 303.0871 (M^+), found *m*/*z* 303.0872

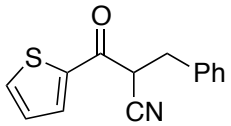
2-(2-methylphenylmethyl)-3-oxo-3-phenylpropanenitrile (2n)



According to the procedure B, the reaction using (*E*)-3-(2-methylphenyl)-1- phenylprop-2-en-1-one (111.5 mg, 0.502 mmol), 9-BBN dimer (64.2 mg, 0.263 mmol), and NCTS (136.3 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a yellow liquid (106.4 mg, 85% yield). ^{1}H

NMR: (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.31–7.10 (m, 4H), 4.51 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.38 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.28 (dd, *J* = 14.1, 9.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.2, 136.2, 134.6, 134.12, 134.06, 130.8, 129.7, 129.1, 128.8, 127.7, 126.5, 117.0, 40.3, 32.6, 19.5; IR: (ATR) 2251, 1690 cm^{-1}; MS: (EI) *m*/*z* 249 (M^+, 5), 105 (100), 77 (48); HRMS: (EI) calcd for ($C_{17}H_{15}NO$) 249.1154 (M^+) found *m*/*z* 249.1153

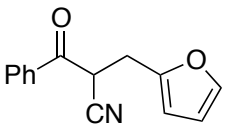
2-benzyl-3-oxo-3-(thiophen-2-yl)propanenitrile (2o)



According to the procedure B, the reaction using (*E*)-3-phenyl-1-(2-thienyl)prop-2- en-1-one (107.0 mg, 0.499 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (136.1 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) gave the product as an orange liquid (77.9 mg, 65% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.9 Hz, 1H), 7.78 (d, *J* = 4.9 Hz, 1H), 7.38–7.21 (m, 5H), 7.17 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.33 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.38 (dd, *J* = 13.9, 6.3 Hz, 1H), 3.28 (dd, *J* = 13.9, 8.8 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 182.5, 140.8, 136.3, 135.7, 133.8, 129.0, 128.9, 128.7, 127.7, 116.9, 42.8, 35.9

The analytical data for this compound were in excellent agreement with the reported data.[42]

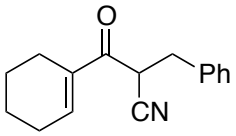
2-(2-furylmethyl)-3-oxo-3-phenylpropanenitrile (2p)



According to the procedure B, the reaction using (*E*)-3-(2-furyl)-1-phenylprop-2- en-1-one (119.1 mg, 0.601 mmol), 9-BBN dimer (76.7 mg, 0.314 mmol), and NCTS (136.2 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a yellow liquid (95.2 mg, 85% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.53 (t,

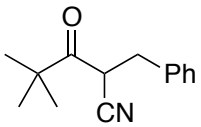
J = 7.6 Hz, 2H), 7.35 (d, *J* = 1.0 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.0 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 4.69 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.42 (dd, *J* = 15.1, 6.1 Hz, 1H), 3.33 (dd, *J* = 15.1, 8.5 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.5, 149.2, 142.4, 134.6, 133.9, 129.1, 128.8, 116.6, 110.7, 108.4, 38.7, 28.1; IR: (ATR) 2243, 1694 cm^{-1}; MS: (EI) *m*/*z* 225 (M^+, 7), 105 (100), 81 (37), 77 (52); HRMS: (EI) calcd for ($C_{14}H_{11}NO_2$) 225.0790 (M^+), found *m*/*z* 225.0791

2-benzyl-3-(2-cyclohexen-1-yl)-3-oxopropanenitrile (2q)



According to the procedure B, the reaction using (*E*)-1-(cyclohex-1-enyl)-3-phenylprop- 2-en-1-one (106.1 mg, 0.500 mmol), 9-BBN dimer (64.1 mg, 0.263 mmol), and NCTS (136.6 mg, 0.502 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a yellow solid (96.6 mg, 81% yield). mp: 63.0–63.8 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40–7.13 (m, 5H), 7.00–6.90 (m, 1H), 4.23 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.22 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.15 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.40–2.13 (m, 4H), 1.71–1.45 (m, 4H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.3, 144.0, 137.6, 136.3, 129.0, 128.8, 127.5, 117.5, 39.8, 35.7, 26.4, 23.3, 21.5, 21.1; IR: (ATR) 2241, 1676 cm^{-1}; MS: (EI) *m*/*z* 239 (M^+, 17), 109 (100), 91 (20), 81 (62), 79 (27); HRMS: (EI) calcd for ($C_{16}H_{17}NO$) 239.1310 (M^+), found *m*/*z* 239.1312

2-benzyl-4,4-dimethyl-3-oxopentanenitrile (2r)

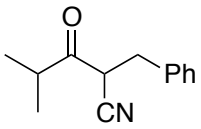


According to the procedure B, the reaction using (*E*)-4,4-dimethyl-1-phenylpent-1- en-3-one (94.0 mg, 0.499 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (135.8 mg, 0.499 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a pale yellow liquid (85.9 mg, 80% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 3H), 7.20 (d, *J* = 6.3 Hz, 2H), 4.01 (dd, *J*

= 7.3, 7.3 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.3 Hz, 1H), 3.14 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 204.8, 136.1, 129.0, 128.8, 127.5, 117.0, 45.4, 38.7, 35.9, 25.5

The analytical data for this compound were in excellent agreement with the reported data.[44]

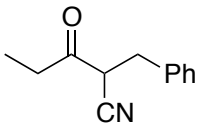
2-benzyl-4-methyl-3-oxopentanenitrile (2s)



According to the procedure B, the reaction using (*E*)-4-methyl-1-phenylpent-1-en-3-one (87.8 mg, 0.504 mmol), 9-BBN dimer (64.0 mg, 0.262 mmol), and NCTS (135.7 mg, 0.498 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a colorless liquid (70.4 mg, 70% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 3.73 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.23 (dd, *J* = 13.9, 6.3 Hz, 1H), 3.11 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.89 (qq, *J* = 7.1, 7.1 Hz, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 204.0, 135.9, 129.0, 128.8, 127.6, 117.2, 43.8, 40.2, 35.0, 18.0, 17.8

The analytical data for this compound were in excellent agreement with the reported data.[7e]

2-benzyl-3-oxopentanenitrile (2t)

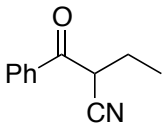


According to the procedure B, the reaction using (*E*)-1-phenylpent-1-en-3-one (79.8 mg, 0.498 mmol), 9-BBN dimer (63.8 mg, 0.261 mmol), and NCTS (135.9 mg, 0.499 mmol) in THF (1 mL) was carried out. Purification by GPC ($CHCl_3$) gave the product as a colorless liquid (54.3 mg, 58% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 3.63 (dd, *J* = 8.5, 5.6 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.11 (dd, *J* = 13.7, 8.5 Hz, 1H), 2.70–2.56 (m, 2H), 1.07

(dd, *J* = 7.3, 7.3 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 201.1, 135.6, 129.0, 128.9, 127.7, 117.3, 45.5, 35.3, 35.0, 7.3

The analytical data for this compound were in excellent agreement with the reported data.[7e]

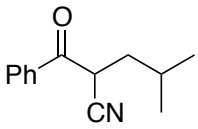
2-ethyl-3-oxo-3-phenylpropanenitrile (2u)



According to the procedure B, the reaction using (*E*)-1-phenylbut-2-en-1-one (87.6 mg, 0.599 mmol), 9-BBN dimer (76.5 mg, 0.313 mmol), and NCTS (136.4 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (78.1 mg, 90% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 4.30 (dd, *J* = 8.3, 5.9 Hz, 1H), 2.16–1.97 (m, 2H), 1.18 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.8, 134.4, 133.9, 129.0, 128.6, 117.2, 41.4, 23.5, 11.4

The analytical data for this compound were in excellent agreement with the reported data.[45]

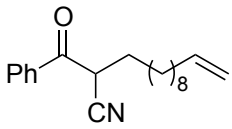
2-(2-methypropyl)-3-oxo-3-phenylpropanenitrile (2v)



According to the procedure B, the reaction using (*E*)-4-methyl-1-phenylpent-2-en-1-one (87.3 mg, 0.501 mmol), 9-BBN dimer (64.3 mg, 0.263 mmol), and NCTS (135.8 mg, 0.499 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (94.6 mg, 94% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 2H), 4.38 (dd, *J* = 9.8, 5.4 Hz, 1H), 2.00–1.88 (m, 2H), 1.85–1.75 (m, 1H), 1.09–0.95 (m, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.9, 134.4, 133.9, 129.1, 128.7, 117.4, 38.5, 38.3, 26.4, 22.7,

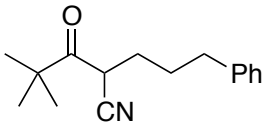
21.3; IR: (ATR) 2249, 1694 cm^{-1}; MS: (CI) *m*/*z* 202 ($[M+H]^+$, 100); HRMS: (EI) calcd for ($C_{13}H_{15}NO$) 201.1154 (M^+), found *m*/*z* 201.1150

3-oxo-3-phenyl-2-(undec-10-enyl)propanenitrile (2w)



According to the procedure B, the reaction using (*E*)-1-phenyldodeca-2,12-dien-1-one (134.1 mg, 0.496 mmol), 9-BBN dimer (64.2 mg, 0.263 mmol), and NCTS (136.7 mg, 0.502 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a yellow liquid (133.7 mg, 91% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 8.3 Hz, 2H), 5.88–5.76 (m, 1H), 5.02–4.90 (m, 2H), 4.33 (dd, *J* = 7.3, 7.3 Hz, 1H), 2.09–1.92 (m, 4H), 1.66–1.44 (m, 2H), 1.42–1.19 (m, 12H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.9, 139.1, 134.4, 134.0, 129.1, 128.7, 117.4, 114.1, 40.0, 33.7, 29.9, 29.3, 29.1, 29.0, 28.9, 28.8, 27.0 (one sp^3 signal was not observed because of overlapping); IR: (ATR) 2249, 1695 cm^{-1}; MS: (CI) *m*/*z* 298 ($[M+H]^+$, 100); HRMS: (CI) calcd for ($C_{20}H_{28}NO$) 298.2171 ($[M+H]^+$) found *m*/*z* 298.2171

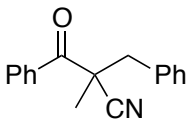
4,4-dimethyl-3-oxo-2-(3-phenylpropyl)pentanenitrile (2x)



According to the procedure B, the reaction using (*E*)-2,2-dimethyl-7-phenylhept-4- en-3-one (108.0 mg, 0.499 mmol), 9-BBN dimer (64.4 mg, 0.264 mmol), and NCTS (136.4 mg, 0.501 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a colorless liquid (106.9 mg, 88% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.24–7.15 (m, 3H), 3.77 (dd, *J* = 8.3, 5.9 Hz, 1H), 2.67 (t, *J* = 7.1 Hz, 2H), 1.96–1.65 (m, 4H), 1.21 (s, 9H); ^{13}C NMR: (100

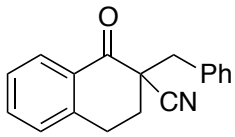
MHz, $CDCl_3$) δ 205.4, 140.9, 128.5, 128.3, 126.2, 117.3, 45.4, 36.8, 35.1, 29.3, 28.7, 26.0; IR: (ATR) 2241, 1721 cm^{-1}; MS: (EI) *m*/*z* 243 (M^+, 2), 57 (100); HRMS: (EI) calcd for ($C_{16}H_{21}NO$) 243.1623 (M^+) found *m*/*z* 243.1623

2-benzyl-2-methyl-3-oxo-3-phenylpropanenitrile (2y)



According to the procedure A, the reaction using (*E*)-2-methyl- 1,3-diphenylprop-2- en-1-one (108.2 mg, 0.487 mmol), 9-BBN dimer (64.2 mg, 0.263 mmol), and NCTS (135.7 mg, 0.498 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (63.4 mg, 52% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.36–7.28 (m, 5H), 3.49 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.8, 134.6, 134.3, 133.5, 130.4, 129.1, 128.54, 128.51, 127.8, 121.6, 47.5, 43.8, 24.0; IR: (ATR) 2237, 1689 cm^{-1}; MS: (EI) *m*/*z* 249 (M^+, 5), 105 (100), 91 (21), 77 (47); HRMS: (EI) calcd for ($C_{17}H_{15}NO$) 249.1154 (M^+), found *m*/*z* 249.1154

2-benzyl-2-cyano-3,4-dihydronaphthalen-1(*2H*)-one (2z)

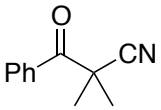


According to the procedure B, the reaction using 3,4-dihydro-2-(phenylmethylene) naphthalen-1(*2H*)-one (116.7 mg, 0.498 mmol) and 9-BBN dimer (64.5 mg, 0.264 mmol) and NCTS (136.1 mg, 0.500 mmol) in THF (1 mL) was carried out. Purification by column chromatography on silica gel (hexane/EtOAc = 9:1) and NH silica gel (hexane/EtOAc = 8:2) gave the product as a colorless liquid (78.9 mg, 61% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.59–7.51 (m, *J* = 7.4, 1.3 Hz, 1H), 7.40–7.25 (m, 7H), 3.51 (d, *J* = 13.7 Hz, 1H), 3.27–3.18 (m, 1H), 3.11–3.02 (m, 1H), 3.09 (d, *J* = 13.7 Hz, 1H), 2.40–2.31 (m,

1H), 2.13–2.08 (m, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 189.9, 142.8, 134.6, 134.2, 130.4, 130.0, 128.92, 128.91, 128.6, 127.7, 127.4, 118.6, 48.8, 39.3, 30.9, 25.6

The analytical data for this compound were in excellent agreement with the reported data.[12b]

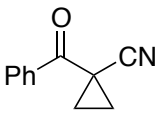
2,2-dimethyl-3-oxo-3-phenylpropanenitrile (2aa)



According to the procedure C, the reaction using isobutyrophenone (75.0 mg, 0.506 mmol), *i*Pr_2NEt (71.3 mg, 0.552 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.550 mmol), and NCTS (163.7 mg, 0.601 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a colorless liquid (82.0 mg, 94% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 193.9, 133.8, 133.5, 129.3, 128.7, 122.6, 40.7, 25.6

The analytical data for this compound were in excellent agreement with the reported data.[46]

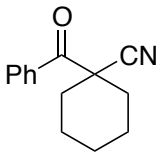
1-benzoylcyclopropanecarbonitrile (2ab)



According to the procedure C, the reaction using cyclopropyl phenyl ketone (73.4 mg, 0.502 mmol), *i*Pr_2NEt (71.7 mg, 0.555 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (164.2 mg, 0.603 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (73.5 mg, 86% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 1.95–1.82 (m, 2H), 1.82–1.65 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.5, 135.6, 133.7, 128.7, 128.6, 121.0, 20.3, 18.1; IR: (ATR) 2239, 1684 cm^{-1}; MS:

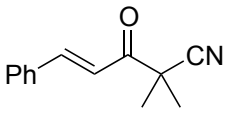
(EI) *m*/*z* 171 (M^+, 14), 105 (100), 77 (68), 51 (32); HRMS: (EI) calcd for ($C_{11}H_9NO$) 171.0684 (M^+) found *m*/*z* 171.0685

1-benzoylcyclohexanecarbonitrile (2ac)



According to the procedure C, the reaction using cyclohexyl phenyl ketone (94.4 mg, 0.501 mmol), *i*Pr_2NEt (70.6 mg, 0.546 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (163.2 mg, 0.599 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (96.4 mg, 90% yield). mp: 48.0–48.9 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 2.35–2.18 (m, 2H), 1.92–1.70 (m, 7H), 1.35–1.19 (m, 1H): ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.4, 134.2, 133.6, 129.2, 128.6, 120.8, 48.0, 33.6, 24.8, 22.3; IR: (ATR) 2236, 1688 cm^{-1}; MS: (CI) *m*/*z* 214 ($[M+H]^+$, 100); HRMS: (CI) calcd for ($C_{14}H_{16}NO$) 214.1232 ($[M+H]^+$) found *m*/*z* 214.1231

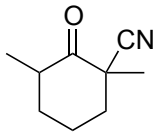
(*4E*)-2,2-dimethyl-3-oxo-5-phenylpent-4-enenitrile (2ad)



According to the procedure C, the reaction using (*E*)-4-methyl-1-phenylpent-1-en-3-one (86.8 mg, 0.498 mmol), *i*Pr_2NEt (70.5 mg, 0.545 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (163.3 mg, 0.600 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1 and CH_2Cl_2) gave the product as a pale yellow solid (83.8 mg, 84% yield). mp: 61.1–61.9 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.48–7.20 (m, 3H), 7.29 (d, *J* = 15.6 Hz, 1H), 1.60 (s, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.5, 147.0, 133.8, 131.4, 129.0, 128.9,

122.1, 119.1, 43.1, 23.8; IR: (ATR) 2247, 1680 cm^{-1}; MS: (EI) *m*/*z* 199 (M^+, 1), 131 (100), 103 (66), 77 (53), 51 (24); HRMS: (EI) calcd for ($C_{13}H_{13}NO$) 199.0997 (M^+) found *m*/*z* 199.0999

1,3-dimethyl-2-oxocyclohexanecarbonitrile (2ae)

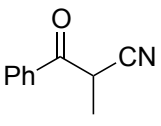


According to the procedure C, the reaction using 2,6-dimethylcyclohexanone (62.8 mg, 0.498 mmol), *i*Pr_2NEt (71.0 mg, 0.549 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (164.2 mg, 0.603 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave major isomer as a colorless liquid (58.1 mg, 77% yield). Further purification by GPC ($CHCl_3$) gave minor isomer as a colorless liquid (8.1 mg, 11%).

Major isomer: ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.10–3.00 (m, 1H), 2.41–2.32 (m, 1H), 2.25–2.10 (m, 2H), 1.90–1.81 (m, 1H), 1.64–1.55 (m, 1H), 1.47–1.32 (m, 1H), 1.43 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 204.8, 121.1, 46.2, 42.8, 41.3, 37.0, 22.6, 20.3, 14.5; IR: (ATR) 2232, 1730 cm^{-1}; MS: (EI) *m*/*z* 151 (M^+, 14), 68 (100), 56 (74), 55 (20); HRMS: (EI) calcd for ($C_9H_{13}NO$) 151.0997 (M^+) found *m*/*z* 151.1000

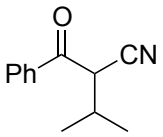
Minor isomer: ^{1}H NMR: (400 MHz, $CDCl_3$) δ 2.71–2.60 (m, 1H), 2.24–2.19 (m, 2H), 2.14–2.05 (m, 1H), 1.93–1.80 (m, 2H), 1.64 (s, 3H), 1.54–1.41 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 205.7, 120.8, 47.8, 40.5, 38.3, 35.2, 21.9, 19.8, 14.9; IR: (ATR) 2243, 1715 cm^{-1}; MS: (EI) *m*/*z* 151 (M^+, 13), 68 (100), 56 (72); HRMS: (EI) calcd for ($C_9H_{13}NO$) 151.0997 (M^+) found *m*/*z* 151.0995

2-methyl-3-oxo-3-phenylpropanenitrile (2af)



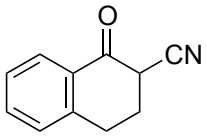
According to the procedure C, the reaction using propiophenone (67.4 mg, 0.502 mmol), *i*Pr_2NEt (71.5 mg, 0.553 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (163.1 mg, 0.599 mmol) in Et_2O (2 mL) was carried out. Purification by GPC ($CHCl_3$) and flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (73.3 mg, 92% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 1H), 1.66 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 190.8, 134.5, 133.6, 129.0, 128.7, 118.1, 33.6, 14.9; IR: (ATR) 2253, 1694 cm^{-1}; MS: (CI) *m*/*z* 160 ([M+H]$^+$, 100); HRMS: (EI) calcd for ($C_{10}H_9NO$) 159.0684 (M^+) found *m*/*z* 159.0684

2-isopropyl-3-oxo-3-phenylpropanenitrile (2ag)



According to the procedure C, the reaction using isovalerophenone (81.0 mg, 0.499 mmol), *i*Pr_2NEt (71.2 mg, 0.551 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (162.5 mg, 0.597 mmol) in Et_2O (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (86.5 mg, 93% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 4.29 (d, *J* = 5.4 Hz, 1H), 2.53–2.40 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 191.1, 134.3, 129.0, 128.6, 116.1, 47.8, 29.8, 21.3, 18.6 (one sp^2 signal was not observed because of overlapping); IR: (ATR) 2247, 1694 cm^{-1}; MS: (CI) *m*/*z* 188 ([M+H]$^+$, 100); HRMS: (EI) calcd for ($C_{12}H_{13}NO$) 187.0997 (M^+) found *m*/*z* 187.0997

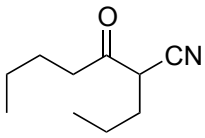
2-cyano-3,4-dihydronaphthalen-1(*2H*)-one (2ah)



According to the procedure C, the reaction using α-tetralone (72.3 mg, 0.494 mmol), *i*Pr_2NEt (71.3 mg, 0.552 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (163.6 mg, 0.601 mmol) in DME (2 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (59.0 mg, 70% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 3.76 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.20–3.02 (m, 2H), 2.62–2.42 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.9, 142.9, 134.8, 130.3, 129.0, 128.2, 127.4, 116.7, 40.7, 27.8, 27.6

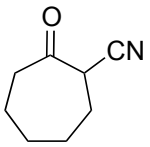
The analytical data for this compound were in excellent agreement with the reported data.[47]

3-oxo-2-propylheptanenitrile (2ai)



According to the procedure C, the reaction using 5-nonanone (70.9 mg, 0.498 mmol), *i*Pr_2NEt (71.6 mg, 0.554 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (162.7 mg, 0.597 mmol) in Et_2O (2 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc and CH_2Cl_2) gave the product as a colorless liquid (66.7 mg, 80% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.40 (dd, *J* = 7.1, 7.1 Hz, 1H), 2.76–2.62 (m, 2H), 1.89–1.78 (m, 2H), 1.66–1.41 (m, 4H), 1.39–1.28 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 201.2, 117.6, 43.8, 40.7, 30.8, 25.3, 22.0, 20.2, 13.7, 13.3; IR: (ATR) 2243, 1726 cm^{-1}; MS: (CI) *m*/*z* 168 ($[M+H]^+$, 100); HRMS: (CI) calcd for ($C_{10}H_{18}NO$) 168.1388 ($[M+H]^+$) found *m*/*z* 168.1388

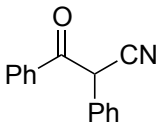
2-cyanocycloheptanone (2aj)



According to the procedure C, the reaction using cycloheptanone (57.1 mg, 0.509 mmol), *i*Pr_2NEt (71.3 mg, 0.552 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and NCTS (163.2 mg, 0.599 mmol) in DME (2 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 8:2) gave the product as a colorless liquid (49.1 mg, 70% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 7.8, 3.9 Hz, 1H), 2.74–2.59 (m, 2H), 2.18–1.98 (m, 2H), 1.98–1.82 (m, 2H), 1.82–1.55 (m, 4H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 203.3, 117.4, 44.7, 42.3, 29.2, 28.7, 27.8, 23.3

The analytical data for this compound were in excellent agreement with the reported data.[48]

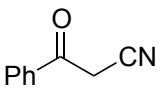
3-oxo-2,3-diphenylpropanenitrile (2ak)



According to the typical procedure C, the reaction using benzyl phenyl ketone (98.5 mg, 0.502 mmol), *i*Pr_2NEt (71.5 mg, 0.553 mmol), *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol), and TsCN (109.2 mg, 0.603 mmol) in Et_2O (1 mL) was carried out at 0 °C. Purification by flash column chromatography on silica gel (hexane/EtOAc = 8:2) gave the product as a white solid (84.3 mg, 76% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.56–7.34 (m, 7H), 5.60 (s, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 188.8, 134.4, 133.6, 130.3, 129.6, 129.2, 129.1, 129.0, 128.2, 116.5, 46.6

The analytical data for this compound were in excellent agreement with the reported data.[7e]

3-oxo-3-phenylpropanenitrile (2al)

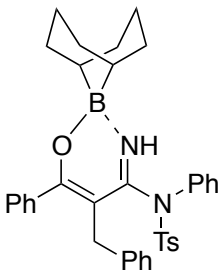


A flame-dried reaction flask containing a magnetic stir bar was charged with acetophenone (60.3 mg, 0.502 mmol), *i*Pr_2NEt (71.3 mg, 0.552 mmol), and Et_2O (1 mL) under nitrogen. To the solution, *B*-I-9-BBN (1 M in hexane, 0.55 mL, 0.55 mmol) was added slowly at -78 °C, and

the mixture was stirred for 1 h at same temperature. Then, TsCN (108.8 mg, 0.600 mmol) was added to the solution at -78 °C, and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:2) to give the product as a pale yellow solid (50.8 mg, 70% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.09 (s, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 187.1, 134.7, 134.2, 129.1, 128.4, 113.8, 29.4

The analytical data for this compound were in excellent agreement with the reported data.[7e]

boron complex 2a'



^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.68 (brs, 1H), 7.55–7.39 (m, 3H), 7.39–7.07 (m, 14H), 6.98–6.85 (m, 2H), 3.08 (s, 2H), 2.40 (s, 3H), 2.07–1.79 (m, 4H), 1.78–1.30 (m, 8H), 1.00–0.85 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 179.8, 161.2, 145.5, 140.9, 136.7, 136.5, 134.5, 130.3, 130.2, 129.7, 129.2, 128.6, 128.3, 127.94, 127.85, 127.8, 125.8, 102.0, 33.1, 31.2, 30.8, 24.9, 24.4, 22.6, 21.6 (one sp^2 signal was not observed because of overlapping); ^{11}B NMR: (128 MHz, $CDCl_3$) δ 4.7; HRMS: (EI) calcd for ($C_{37}H_{39}BN_2O_3S$) 602.2774 (M^+) found *m*/*z* 602.2782

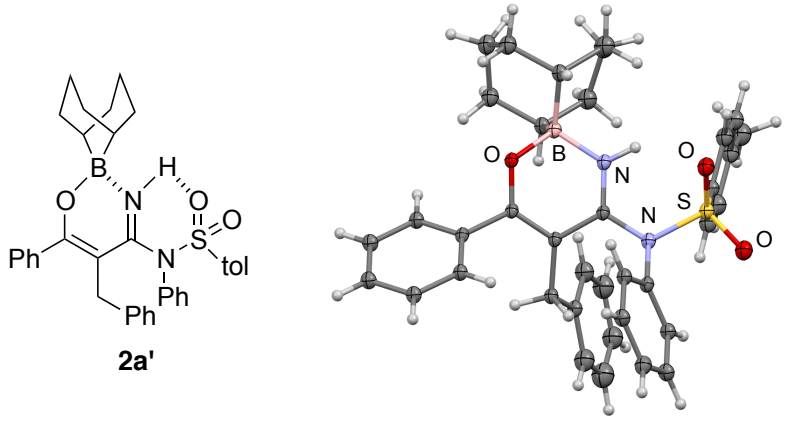
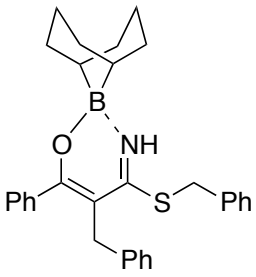


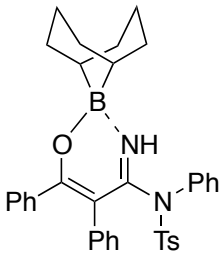
Figure 2. Crystal structure of **2a'**. CCDC 1481827 contains the supplementary crystallographic data. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

boron complex 2a'-SBn



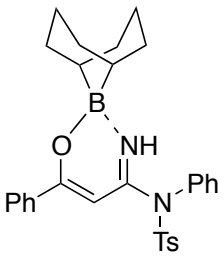
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55–7.40 (m, 2H), 7.39–7.07 (m, 13H), 6.76 (brs, 1H), 4.08 (s, 2H), 3.81 (s, 2H), 2.00–1.68 (m, 4H), 1.67–1.38 (m, 5H), 1.31–1.20 (m, 1H), 1.19–1.05 (m, 2H), 0.85–0.70 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 172.3, 140.7, 136.9, 133.4, 129.8, 129.4, 128.8, 128.5, 128.3, 128.2, 128.0, 127.9, 125.9, 103.6, 34.9, 33.5, 31.3, 30.7, 24.8, 24.4, 23.2; ^{11}B NMR: (128 MHz, $CDCl_3$) δ -16.2; HRMS: (FAB) calcd for ($C_{31}H_{34}BNOS$) 479.2454 (M^+) found *m*/*z* 479.2463

boron complex 2ak'



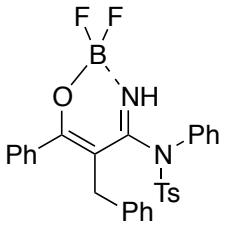
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.80 (brs, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.19–6.90 (m, 9H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 6.26 (d, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 2.00–1.35 (m, 12H), 1.08–0.92 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 178.3, 161.0, 145.7, 136.6, 136.0, 134.3, 131.9, 130.3, 130.0, 129.4, 128.5, 128.3, 127.9, 127.8, 127.6, 127.2, 126.4, 107.1, 31.2, 30.4, 24.8, 24.6, 23.1, 21.7 (one sp^2 signal was not observed because of overlapping); ^{11}B NMR: (128 MHz, $CDCl_3$) δ -16.5; HRMS: (MALDI–TOF) calcd for ($C_{36}H_{37}BN_2O_3S$) 588.2618 (M^+) found *m*/*z* 588.2626

boron complex 2al'



^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.86 (brs, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.60–7.40 (m, 5H), 7.40–7.32 (m, 3H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.15 (d, *J* = 7.3 H, 2H), 5.06 (d, *J* = 2.4 H, 1H), 2.47 (s, 3H), 2.06–1.48 (m, 12H), 0.93–0.80 (m, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 174.5, 158.2, 146.0, 135.6, 135.4, 135.0, 131.3, 130.6, 130.3, 130.2, 129.7, 128.3, 127.9, 127.0, 85.5, 31.5, 30.7, 25.0, 24.6, 23.3, 21.7; ^{11}B NMR: (128 MHz, $CDCl_3$) δ -16.2; HRMS: (EI) calcd for ($C_{30}H_{33}BN_2O_3S$) 512.2305 (M^+) found *m*/*z* 512.2305

boron complex A



^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.77 (brs, 1H), 7.55–7.47 (m, 3H), 7.40 (d, J = 8.3 Hz, 2H), 7.39–7.20 (m, 7H), 7.16 (d, J = 8.3 Hz, 2H), 7.13–7.08 (m, 1H), 7.03 (t, J = 7.2 Hz, 2H), 6.64 (d, J = 7.2 Hz, 2H), 3.09 (s, 2H), 2.45 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 177.9, 164.0, 146.0, 139.8, 135.8, 134.9, 133.0, 131.1, 130.3, 129.8, 129.6, 129.4, 128.9, 128.5, 128.4, 128.1, 127.1, 125.9, 102.2, 32.3, 21.7; ^{11}B NMR: (128 MHz, $CDCl_3$) δ 0.27 (t, J_{BF} = 14.7 Hz); ^{19}F NMR: (377 MHz, $CDCl_3$) δ -145.2 (d, J_{BF} = 14.7 Hz); HRMS: (EI) calcd for ($C_{29}H_{25}BF_2N_2O_3S$) 530.1647 (M^+) found m/z 530.1647

2-5. References and Notes

1. For selected examples, see: (a) Pask, C. M.; Camm, K. D.; Kilner, C. A.; Halcrow, M. A. *Tetrahedron Lett.* **2006**, *47*, 2531. (b) Suryakiran, N.; Srikanth Reddy, T.; Asha Latha, K.; Prabhakar, P.; Yadagiri, K.; Venkateswarlu, Y. *J. Mol. Catal. A: Chem.* **2006**, *258*, 371. (c) Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett.* **2010**, *12*, 4648. (d) Kim, B. R.; Sung, G. H.; Ryu, K. E.; Lee, S.-G.; Yoon, H. J.; Shin, D.-S.; Yoon, Y.-J. *Chem. Commun.* **2015**, *51*, 9201.

2. For selected examples, see: (a) Gudmundsson, K. S.; Johns, B. A.; Weatherhead, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5689. (b) Zhu, X.; Zhang, M.; Liu, J.; Ge, J.; Yang, G. *J. Agric. Food Chem.* **2015**, *63*, 3377.

3. For selected examples, see: (a) Gewald, K. *Chem. Ber.* **1965**, *98*, 3571. (b) Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94. (c) Baraldi, P. G.; Zaid, A. N.; Lampronti, I.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Shryock, J. C.; Leung, E.; Romagnoli, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1953. (d) Puterová, Z.; Andicsová, A.; Végh, D. *Tetrahedron* **2008**, *64*, 11262.

4. For selected examples, see: (a) Hauser, C. R.; Eby, C. J. *J. Am. Chem. Soc.* **1957**, *79*, 728.

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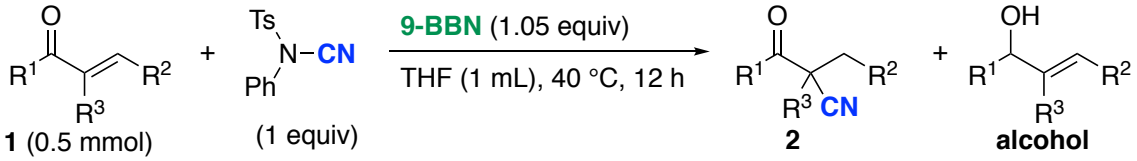
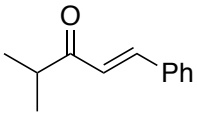
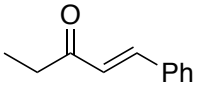
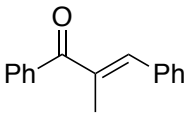
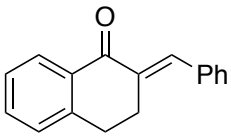
20. The details of reactions using enones **1s**, **1t**, **1y**, and **1z** are summarized in Table 5. The steric hindrance of aliphatic substituents at the 2-positions is crucial for the selectivity between 1,2- and 1,4-hydroboration. The reaction using enone **1s** bearing an isoprpyl group at the 2-position afforded the cyanated product in 78% yield along with the allylic

alcohol that was produced by competitive 1,2-hydroboration in 17% yield (entry 1). Enone **1t** bearing a smaller ethyl group resulted in a lower yield of the cyanated product because of lower selectivity of hydroboration step (entry 2). In reactions using α-substituted enones, competitive 1,2-hydroboration occurred to give allylic alcohols (entries 3 and 4).

Table 5. Details of Reactions Using Enones **1s**, **1t**, **1y**, and **1z**



entry	1		yield (%)[a]	
			2	**alcohol**
1		**1s**	78 (70)	17
2		**1t**	65 (58)	25
3		**1y**	(52)	(41)
4		**1z**	70 (61)	18

[a] ^{1}H NMR yields. Values in parentheses are isolated yields.

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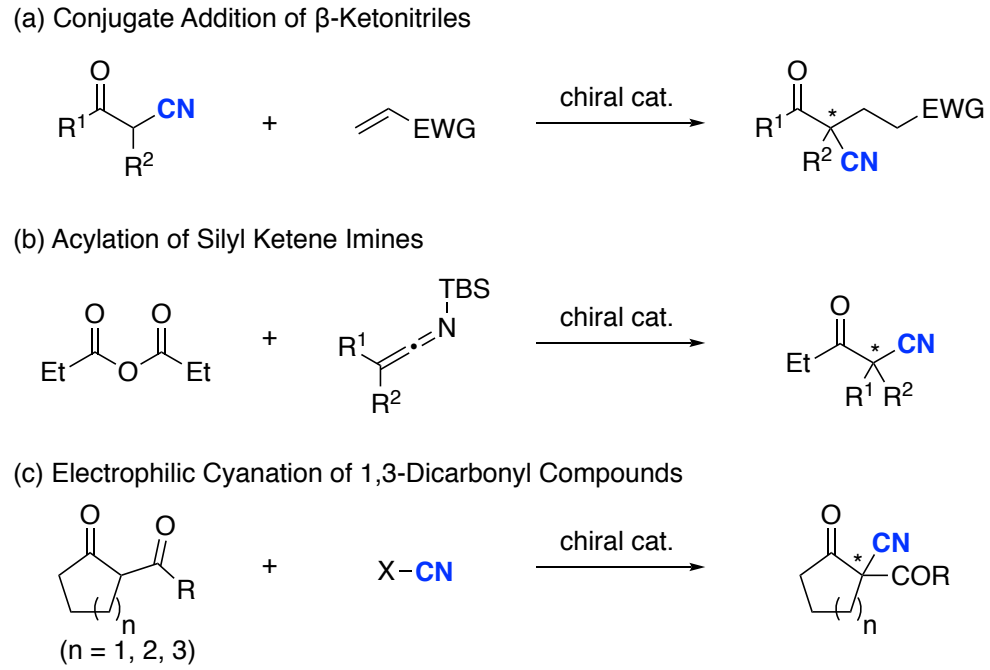
Chapter 3

Enantioselective Electrophilic Cyanation of Boron Enolates

3-1. Introduction

Chiral β-ketonitriles bearing a stereogenic carbon center at the α-position are useful precursors of chiral 1,3-aminoalcohols and β-hydroxy nitriles, which are ubiquitous building blocks for a variety of biologically active compounds.[1] Accordingly, the development of efficient methods for the synthesis of chiral β-ketonitriles represents an important research topic in organic chemistry. Among the methods for preparing chiral β-ketonitriles, the catalytic enantioselective α-alkylation of β-ketonitriles, which includes the conjugate addition of β-ketonitriles, is the most widely used approaches (Scheme 1a).[2-4] Meanwhile, the enantioselective acylation of silyl ketene imines has also been reported (Scheme 1b).[5,6] In addition to these transformations using β-ketonitriles or alkyl nitrile equivalents as a starting material, enantioselective cyanation, the direct introduction of a cyano group into the α-position of a ketone, is also a promising strategy for preparing a variety of chiral β-ketonitriles. To achieve such reactions, the enantioselective electrophilic cyanation of ketone enolate equivalents has been developed in recent years. However, the methods reported to date are limited to the cyanation of cyclic 1,3-dicarbonyl compounds (Scheme 1c)[7] with the only one

exception, in which the reaction of tetralone-derived lithium enolates proceeded with moderate enantioselectivity.[8]



Scheme 1. Synthetic Models for Preparing β-Ketonitriles

This limitation is due to the difficulties both of the stereoselective preparation of the essential α,α-disubstituted enolates needed for the reaction as well as the subsequent enantioselective cyanation. Therefore, the enantioselective electrophilic cyanation of ketone-derived enolates remains largely undeveloped and continues to be a challenging task.

As described in Chapter 2, the author achieved the highly efficient electrophilic cyanation of 9-BBN-based boron enolates with NCTS to provide β-ketonitriles. It was assumed that the cyanation would proceed via an activation process analogous to the formation of 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. This finding encouraged the author to investigate the use of boron enolates with a chiral ligand in enantioselective electrophilic cyanation reactions, which might proceed via the formation of a conformationally rigid transition state.[9] In Chapter 3, the author examined the cyanation of a series of boron enolates, prepared by the

hydroboration of α,β-unsaturated ketones with diisopinocampheylborane (Ipc_2BH), a commonly used chiral reagent that is readily prepared from the inexpensive α-pinene,[10] and found that, when TsCN was employed as a cyanating reagent, the desired β-ketonitrile derivatives were formed with a high degree of enantioselectivity.

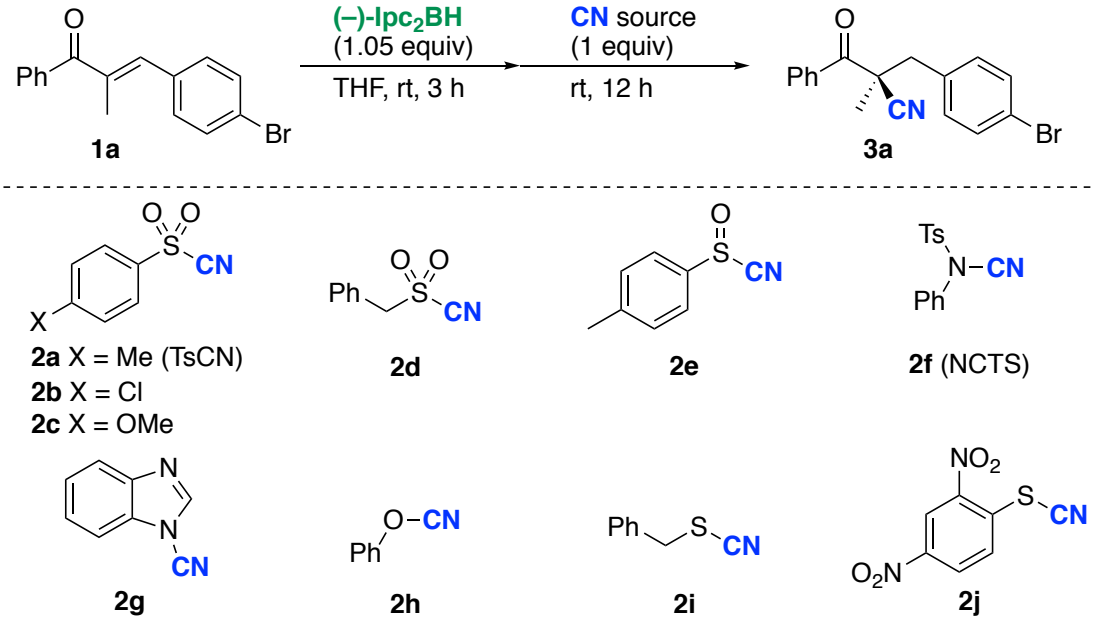
3-2. Results and Discussion

3-2-1. Optimization of Reaction Conditions

The electrophilic cyanation of a boron enolate prepared by the hydroboration of α,β-unsaturated ketone **1a** with (–)-Ipc_2BH was investigated (Table 1). The β-ketonitrile **3a** was produced with a high enantioselectivity albeit in low yield when TsCN was used as a cyanating reagent (entry 1). In this reaction, several by-products, probably derived from the decomposition of the unreacted boron enolate, were observed. Various cyanating reagents were then screened in order to improve the efficiency of the cyanation. Although the sulfonyl cyanide **2b** bearing a chloro moiety on the phenyl ring, which would be expected to increase the electrophilicity of the cyano carbon, was tested, the desired **3a** was obtained in low yield, but the enantioselectivity remained high (entry 2). The use of the electron-rich aromatic sulfonyl cyanide **2c** failed to improve the yield of **3a** (entry 3). Only a trace amount of **3a** was obsereved when alkyl substituted sulfonyl cyanide **2d** and sulfinyl cyanide **2e** were employed (entries 4 and 5). Other commonly used electrophilic cyanating reagents, such as cyanamides (**2f** and **2g**), a cyanate (**2h**), and thiocyanates (**2i** and **2j**) were also found to be not effective for this cyanation (entries 6–10). These results revealed that only aromatic sulfonyl cyanides are capable of inducing the desired cyanation. Hence, using TsCN as a cyanating reagent, the reaction of other chiral boron enolates, which were prepared from commercially available chiral sources such as [1*S*]-di-2-isocaranylborane (2-$^{d}Icr_2BH$) and [1*S*]-di-4-

isocaranylborane (4-^{d}Icr$_2$BH), was investigated. However, neither of these reagents were effective and gave only trace amounts of **3a** were formed (entries 11 and 12). Further screening of reaction parameters employing (–)-Ipc$_2$BH and TsCN revealed that

Table 1. Optimization of Reaction Conditions[a]



entry	CN source	yield (%)[b]	ee (%)[c]
1	**2a**	17	94
2	**2b**	18	95
3	**2c**	18	94
4	**2d**	<5[d]	-
5	**2e**	<5[d]	-
6	**2f**	<5[d]	-
7	**2g**	<5[d]	-
8	**2h**	<5[d]	-
9	**2i**	<5[d]	-
10	**2j**	<5[d]	-
11[e]	**2a**	<5[d]	-
12[f]	**2a**	<5[d]	-
13[g]	**2a**	26	94
14[g,h]	**2a**	44	94
15[g,i]	**2a**	63	94

[a] Reaction conditions: **1a** (0.2 mmol), borane (0.21 mmol), THF (1 mL), **2** (0.2 mmol), rt. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR analysis of the crude product. [e] 2-^{d}Icr$_2$BH was used instead of (–)-Ipc$_2$BH. [f] 4-^{d}Icr$_2$BH was used instead of (–)-Ipc$_2$BH. [g] Cyanation was conducted for 24 h. [h] **2a** (2 equiv) was used. [i] **2a** (3 equiv) was used.

increasing the amount of TsCN used and extending the time resulted in improved yields of **3a** (entries 13–15), and the use of three equivalents of TsCN resulted in the formation of **3a** in 63% yield with 94% ee (entry 15). Fortunately, recrystallization of the product (94% ee) from hexane/CH_2Cl_2 provided a small amount of racemic crystalline **3a**, and it was possible to isolate the enantiomerically pure product (>99% ee) from the mother liquor. The absolute configuration of **3a** was determined to be (*S*) by X-ray crystallographic analysis (Figure 1).

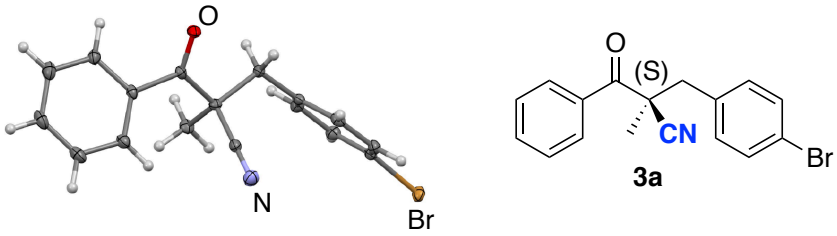


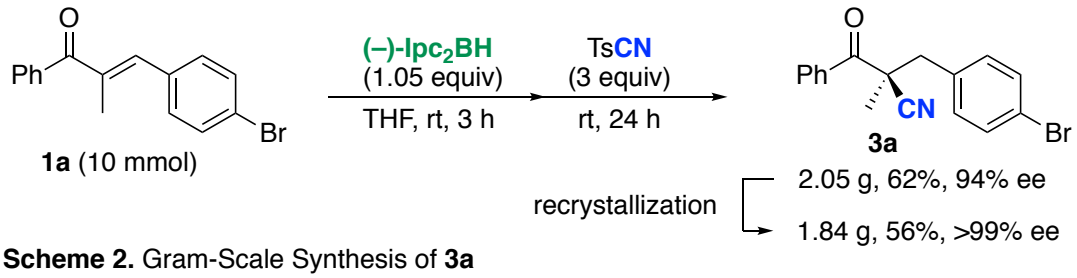
Figure 1. X-ray Structure of **3a**

3-2-2. Scope of Enones

With the optimized reaction conditions identified (Table 1, entry 15), the substrate scope of the reaction was investigated (Table 2). It should be noted here that, when (+)-Ipc_2BH was used instead of (–)-Ipc_2BH, the cyanation proceeded with the same efficiency with inverse of enantioselectivity (entry 2). This result demonstrates that the present method provides facile access to both enantiomers of β-ketonitriles with a high enantiomeric excess. Substrates bearing a phenyl group and an electron-donating *para*-methoxy phenyl group as the R^2 substituent were converted into the corresponding β-ketonitriles in good yields with high enantioselectivities (entries 3 and 4). However, the reaction of **1d**, which contain an electron-withdrawing NO_2 group, resulted in a low yield of **3d**, albeit with a high enantioselectivity, along with several unidentified by-products and the recovered starting material (19%) (entry 5). The presence of an ethyl group at the β-position caused a substantial decrease in enantioselectivity, with **3e** being

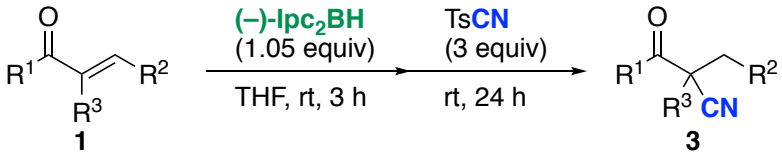
formed in 77% ee (entry 6). Substrates bearing electron-donating and -withdrawing groups at the para positions on the phenyl ring as the R^1 substituent afforded the corresponding cyanated products in good yields and high enantioselectivities (entries 7–10). Substituents at *meta*- or *ortho*-positions had a small effect on the reaction efficiency (entries 11 and 12). Although enones with small alkyl groups such as methyl (**1l**) and ethyl (**1m**) groups as the R^1 substituent were transformed into the corresponding β-ketonitriles with high enantioselectivities albeit in somewhat low yields (entries 13 and 14), a bulkier isopropyl group led to a decreased enantioselectivity (entry 15). Replacement of methyl group at the α-position with an *n*-butyl group resulted in a decreased yield of the product (entry 16), while the desired product was not obtained when a substrate with a phenyl substituent was used in the reaction (entry 17). A cyclic boron enolate derived from **1q** was also applicable to this cyanation, providing **3q** in high enantioselectivity (entry 18).

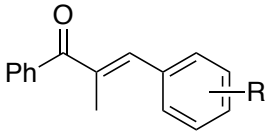
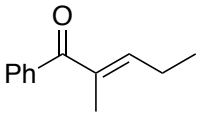
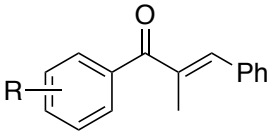
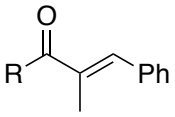
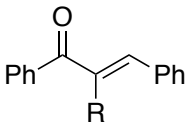
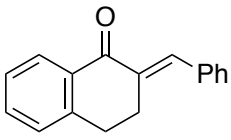
To establish the synthetic utility of this cyanation, a gram-scale synthesis of the β-ketonitrile **3a** was carried out (Scheme 2). On a 10 mmol scale, the reaction proceeded smoothly, furnishing **3a** in 62% isolated yield with 94% ee. After a simple recrystalization process to remove a small amount of racemic **3a**, the enantiomerically pure product was obtained in 56% yield (1.84 g).



Scheme 2. Gram-Scale Synthesis of **3a**

Table 2. Substrate Scope for the Enantioselective Electrophilic Cyanation[a]



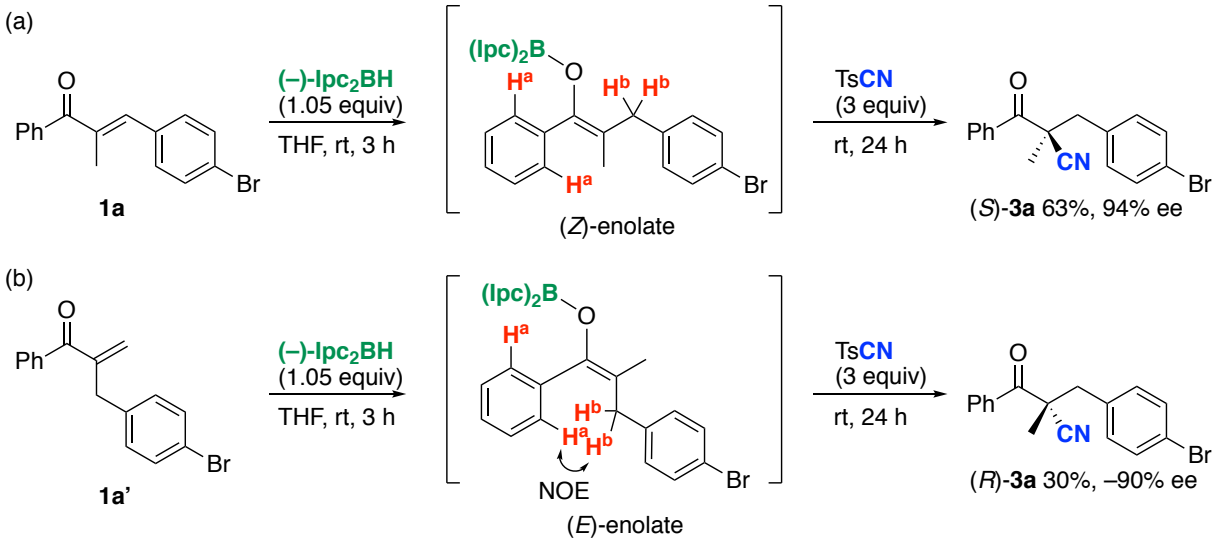
entry	1		3, yield (%)[b]	ee (%)[c]
1		**1a**, R = 4-Br	(*S*)-**3a**, 63	94
2[d]		**1a**, R = 4-Br	(*R*)-**3a**, 64	–95
3		**1b**, R = H	**3b**, 58	91
4		**1c**, R = 4-MeO	**3c**, 71	95
5		**1d**, R = 4-NO_2	**3d**, 22	94
6		**1e**	**3e**, 46	77
7[e]		**1f**, R = 4-MeO	**3f**, 65	95
8		**1g**, R = 4-Me	**3g**, 70	94
9		**1h**, R = 4-Cl	**3h**, 64	95
10		**1i**, R = 4-CF_3	**3i**, 53	93
11		**1j**, R = 2-Cl	**3j**, 58	90
12		**1k**, R = 3-Cl	**3k**, 65	92
13		**1l**, R = Me	**3l**, 45	93
14		**1m**, R = Et	**3m**, 33	93
15		**1n**, R = *i*Pr	**3n**, 31	77
16		**1o**, R = *n*Bu	**3o**, 15	92
17		**1p**, R = Ph	**3p**, 0	-
18		**1q**	**3q**, 23	92

[a] Reaction was conducted on a 0.2 mmol scale. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] (+)-Ipc_2BH was used instead of (–)-Ipc_2BH. [e] Hydroboration was conducted at rt for 12 h.

3-2-3. Determination of *E*/*Z* of Boron Enolates and Their Use in Electrophilic Cyanation

The hydroboration of α,β-unsaturated ketones is known to proceed via a six-membered ring transition state, in which a carbonyl group of the ketone coordinates to the boron center, with stereochemically defined α-monosubstituted boron enolates being formed from β-monosubstituted α,β-unsaturated ketones.[11] However, there is only one report of the preparation of stereochemically defined acyclic α,α-disubstituted boron enolates derived from α,β-unsaturated morpholine carboxamides.[11f] Although α,α-disubstituted boron enolates would be expected to be formed in a stereospecific manner by the hydroboration of α,β-unsaturated ketones **1**, in order to confirm their stereochemistry, the hydroboration of **1a** with (–)-Ipc_2BH in THF was examined, and the reaction mixture was monitored by ^1H NMR analysis (Scheme 3a). The ^1H NMR spectrum revealed that a boron enolate was produced as a single stereoisomer, which was then identified as the *Z*-form due to the absence of a nuclear Overhauser effect (NOE) between the *ortho*-protons (H^a) of the phenyl ring and benzylic protons (H^b). Based on this result, the author next examined the reaction of **1a'** with (–)-Ipc_2BH with the expectation that the *E*-enolate would be formed (Scheme 3b). Indeed, a single boron enolate, but different from that observed in the reaction of **1a**, was generated and was clearly confirmed as the *E*-form by NOE correlation between *ortho*-protons (H^a) and benzylic protons (H^b). These results strongly support the conclusion that the hydroboration proceeds via a six-membered ring transition state to afford α,α-disubstituted boron enolates in a stereospecific manner, which is a crucial factor in achieving the following enantioselective cyanation. Given the fact that the use of **1a** and (–)-Ipc_2BH in a cyanation reaction provided the (*S*)-enantiomer exclusively, the *Z*-enolate would lead to the (*S*)-enantiomer. Furthermore, when the cyanation was conducted using **1a'** as a substrate under optimized reaction conditions (Table 1, entry 15), the (*R*)-enantiomer of **3a** was obtained with a high enantiomeric excess (90% ee) (Scheme 4b). The facial selectivity of the enolates appears to be precisely controlled

by the chiral isopinocampheyl (Ipc) moieties.



Scheme 3. Determination of *E*/*Z* configuration of boron enolates prepared by the hydroboration of α,β-unsaturated ketones with (–)-Ipc_2BH and their use in electrophilic cyanation.

3-2-4. DFT Calculation

Given the fact that aldol-type reactions employing boron enolates generally proceeds via a six-membered ring transition state, known as the Zimmerman-Traxler model,[9] the present cyanation would also be expected to procced through a similar six-membered ring transition state **TS_6,** in which the nitrogen atom of the cyano group of TsCN coordinates to the boron center (Figure 2). However, an alternate possibility is that the reaction could proceed via a seven-membered ring transition state **TS_7** or an acyclic transition state **TS_{acyc}** (Figure 2). To identify the actual transition state, DFT calculations were conducted using the small model system at the B97D/6-31G* level.[12,13] The reaction was found to proceed preferentially through the **TS_6** because it is much more stable than the **TS_7** and **TS_{acyc}** due to the presence of a highly strained N−C−S moiety. Based on the energetically most favored **TS_6**, a realistic model system was developed to clarify the origin of the high enantioselectivity. To gain deeper insights into the factors that control the enantioselectivity of the reaction, DFT calculations on diastereomeric six-membered ring transition states [**TS-*S*** and **TS-*R*** leading to (*S*)- and (*R*)-products, respectively] for the reaction of (*Z*)- and (*E*)-boron enolates (**TS-*Z*** and **TS-*E***) derived

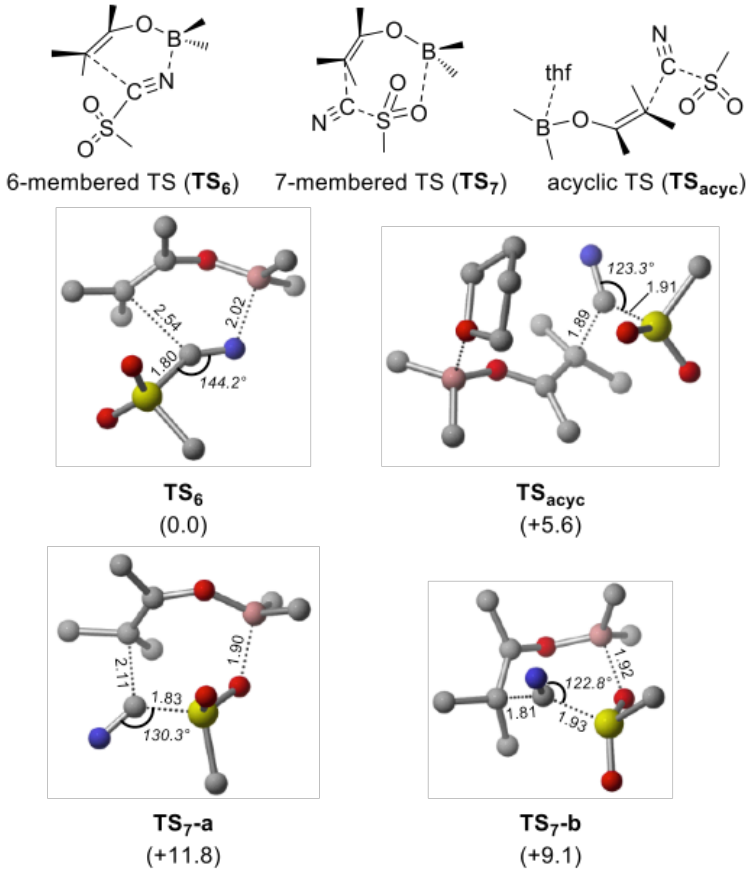


Figure 2. The 3D structures and the relative Gibbs energies (kcal mol^{-1} in parentheses) of six-membered (**TS$_6$**), seven-membered (**TS$_7$**), and acyclic (**TS$_{acyc}$**) transition states that could be formed during the cyanation of a boron enolate using model substrates. Bond lengths are in Å. The N–C–S angles are shown in *italics*.

from (–)-Ipc$_2$BH with TsCN was conducted (Figure 3). As for the (*Z*)-boron enolate, **TS-*ZS*** leading to the major (*S*)-enantiomer is 5.6-kcal mol^{-1} more stable than **TS-*ZR*** leading to the minor (*R*)-enantiomer. This computational result is qualitatively consistent with the experimental results showing that the (*Z*)-boron enolate afforded the (*S*)-enantiomer exclusively. In the case of **TS-*ZR***, steric repulsion between the Ipc moiety and the phenyl group in the boron enolate induces some structural distortion, resulting in **TS-*ZR*** located at the higher energy level than **TS-*ZS***.[14] **TS-*ZS*** can form a relatively strong hydrogen bond between the benzylic hydrogen of the (*Z*)-boron enolate and the oxygen atom of the Ts group in addition to a strong Lewis acid (boron)-Lewis base (nitrogen) interaction. The notable substituent

effects (R^1 = *i*Pr, R^2 = Et) observed in some experiments (Table 2, entries 6 and 15) can be readily explained by the destabilization of **TS-*ZS***. The steric repulsion between the sterically demanding *i*Pr group and the Ipc moiety (i.e., R^1 = *i*Pr) and the loss of the additional hydrogen bond with the Ts group (i.e., R^2 = Et) would also destabilize **TS-*ZS***, resulting in a decrease in the energy difference between **TS-*ZS*** and **TS-*ZR***. Regarding the (*E*)-boron enolate, in contrast, **TS-*ER*** is 2.4-kcal mol^{-1} more stable than **TS-*ES***, in good agreement with the experimental results. In a manner similar to **TS-*ZS*/*ZR***, a larger structural distortion caused by the steric repulsion between the Ipc moiety and the phenyl group in the boron enolate destabilizes **TS-*ES***. These computational studies on transition states provided a reasonable explanation for the formation of the (*S*)- and (*R*)-enriched products in the reaction of the (*Z*)- and (*E*)-enolates derived from (–)-Ipc_2BH, respectively.

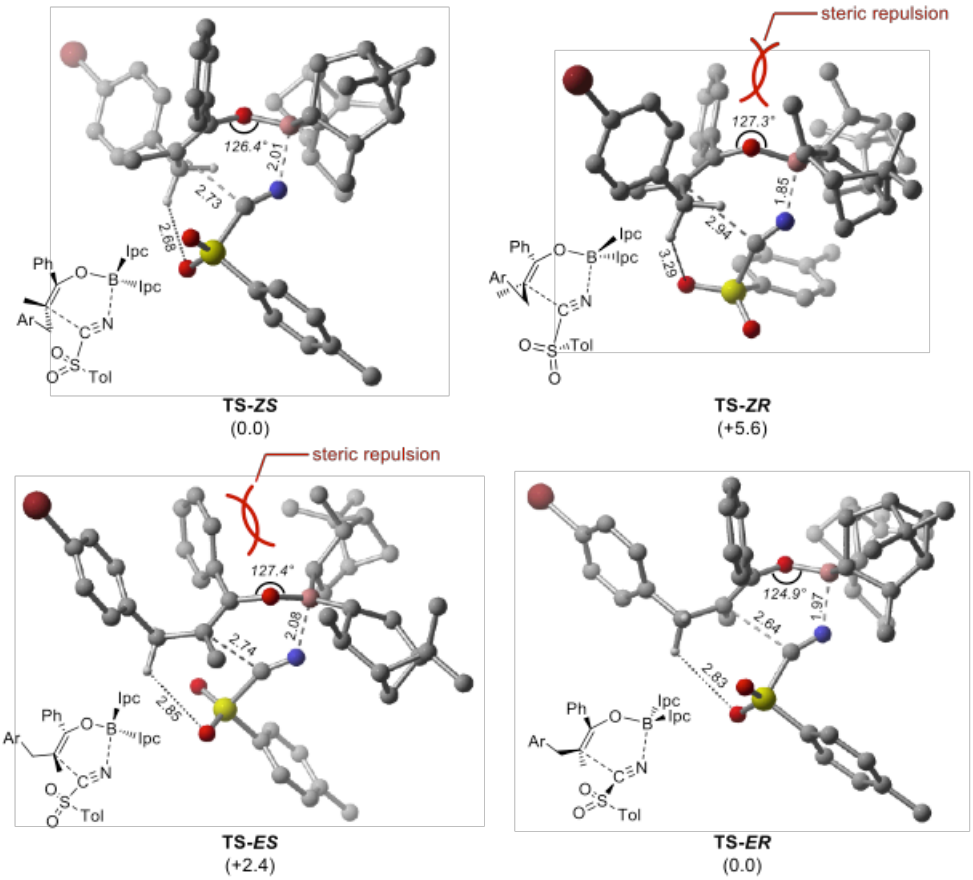


Figure 3. The 3D structures of **TS-*ZS***, **TS-*ZR***, **TS-*ES***, and **TS-*ER***. The relative Gibbs energies (kcal mol-1) for **TS-*Z*** and **TS-*E*** are shown in parentheses. Bond lengths are in Å. The C–O–B angles are shown in *italics*.

3-3. Conclusion

In conclusion, the highly enantioselective electrophilic cyanation of boron enolates prepared from α,β-unsaturated ketones and (–)-Ipc_2BH was developed. Using this protocol, acyclic chiral β-ketonitriles that are difficult to access by existing methods could be synthesized with a high degree of enantioselectivity. NMR studies revealed that acyclic α,α-disubstituted boron enolates are formed stereospecifically by the hydroboration of α,β-unsaturated ketones **1** with (–)-Ipc_2BH. Furthermore, computational studies on the transition states indicates that an unprecedented six-membered ring transition state is formed in the cyanation step and this provides a reasonable explanation for the high enantioselectivity observed for these reactions. Finally, the present study provides a new type of reaction that allows the construction of a chiral quaternary carbon center at the α-position of a ketone.[15]

3-4. Experimental Section

General Remarks

New compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, MS, and HRMS. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL JMTC-400/54/SS spectrometer (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz; ^{19}F NMR, 377 MHz). ^{1}H NMR chemical shifts were determined relative to Me_4Si (0.00 ppm) as an internal standard. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ (77.0 ppm). ^{19}F NMR chemical shifts were determined relative to C_6F_6 (−164.9 ppm) as an external standard. Infrared spectra were recorded on a SHIMADZU IRAffinity-1 FT-IR spectrometer. Mass spectra were obtained on a SHIMADZU GCMS-QP2010 and a JEOL JMS-700 mass spectrometer. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer (magnetic sector type mass spectrometer). Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The X-ray diffraction data of the single crystal were collected on a two-dimensional X-ray detector (PILATUS 200K/R) equipped in Rigaku XtaLAB PRO diffractometer using thin multi-layer mirror monochromated Cu-Kα radiation (λ =1.54187 Å). Chiral-phase high-performance liquid chromatography (HPLC) was performed on a SHIMADZU prominence series instruments and a Waters Alliance 2695 Separations Module equipped with chiral columns. Optical rotations were measured in a thermostated conventional 10 cm cell on a JASCO DIP-1000 polarimeter using the sodium-D line (589 nm). All reactions were carried out under nitrogen. Products were purified by chromatography on silica gel BW-300 (Fuji Silysia Chemical Ltd.) or Chromatorex NH (Fuji Silysia Chemical Ltd.). Analytical thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (Merck silica gel 60 F_{254} and Fuji Silysia Chromatorex NH, 0.25 mm thickness). Compounds were visualized with UV lamp or treatment with an ethanolic solution of phosphomolybdic acid followed by heating. Recycle gel permeation chromatography (GPC) was performed with $CHCl_3$ as the eluent.

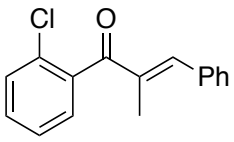
Materials

α,β-Unsaturated ketones **1a**,[16] **1b**,[16] **1c**,[16] **1d**,[16] **1e**,[17,18] **1f**,[19] **1g**,[19] **1h**,[19] **1i**,[20] **1l**,[18] **1m**,[21] **1n**,[22] **1o**,[23] **1p**,[18] and **1q**[24] were prepared according to literature procedures. Analytical data for **1a**,[19] **1c**,[19] **1d**,[23] and **1m**[25] were in excellent agreement with reported data. Cyanating reagents **2f**[26] and **2h**[27] were prepared according to literature procedures. (–)-Ipc_2BH,[10a] (+)-Ipc_2BH,[10a] 2-$^{d}Icr_2BH$,[28] and 4-$^{d}Icr_2BH$[29] were prepared according to literature procedures. Dehydrated THF

was used from a solvent purification system. All other solvents and reagents were purchased and used as obtained.

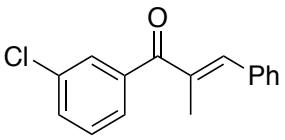
Preparation of α,β-unsaturated ketones

(*E*)-1-(2-chlorophenyl)-2-methyl-3-phenylprop-2-en-1-one (1j)



According to a literature procedure,[19] the reaction using 1-(2-chlorophenyl)propan-1-one (0.73 mL, 5 mmol, 1 equiv), *tert*-amyl-OH (10 mL), dibenzylamine (4.8 mL, 25 mmol, 5 equiv), and $(NH_4)_2S_2O_8$ (3.42 g, 15 mmol, 3 equiv) was conducted. Purification by flash column chromatography on silica gel (hexane/EtOAc = 95:5) gave a yellow liquid. Hexane was added to the liquid, and the resulting solution was cooled to −78 °C to give a precipitate, which was washed with hexane at −78 °C to give the product as a pale yellow solid (1.02 g, 79% yield). mp: 52.8–53.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.30 (m, 9H), 7.11 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 145.1, 139.2, 137.2, 135.5, 131.0, 130.5, 129.8, 129.0, 128.8, 128.4, 126.5, 12.8; IR: (ATR) 1651 cm^{-1}; MS: (EI) *m*/*z* 258 ([M+2]$^+$, 5), 256 (M$^+$, 12), 139 (40), 116 (23), 115 (100), 113 (20), 111 (56), 91 (41), 75 (50), 51 (30), 50 (22); HRMS: (EI) calcd for ($C_{16}H_{13}ClO$) 256.0655 (M$^+$) found *m*/*z* 256.0656

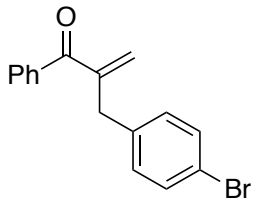
(*E*)-1-(3-chlorophenyl)-2-methyl-3-phenylprop-2-en-1-one (1k)



According to a literature procedure,[19] the reaction using 1-(3-chlorophenyl)propan-1-one (2.53 g, 15 mmol, 1 equiv), *tert*-amyl-OH (30 mL), dibenzylamine (14.4 mL, 75 mmol, 5 equiv), and $(NH_4)_2S_2O_8$ (10.26 g, 45 mmol, 3 equiv) was conducted. Purification by flash column chromatography on silica gel (hexane/EtOAc = 95:5) gave a yellow liquid. Hexane was added to the liquid, and the resulting solution was cooled to −78 °C to give a precipitate, which was washed with hexane at −78 °C to give the product as a white solid (2.63 g, 68% yield). mp:

48.9–49.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.49–7.32 (m, 6H), 7.17 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 143.0, 140.3, 136.5, 135.5, 134.4, 131.6, 129.8, 129.5, 129.4, 128.9, 128.5, 127.5, 14.3; IR: (ATR) 1641 cm^{-1}; MS: (EI) *m*/*z* 258 ([M+2]$^{+}$, 10), 256 (M^{+}, 28), 255 (26), 221 (24), 139 (33), 117 (28), 116 (23), 115 (100), 113 (21), 111 (62), 91 (46), 75 (44), 51 (25), 50 (20); HRMS: (EI) calcd for ($C_{16}H_{13}ClO$) 256.0655 (M^{+}) found *m*/*z* 256.0659

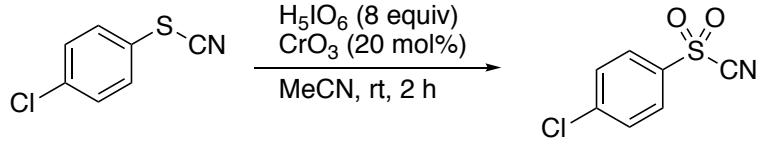
2-(4-bromophenylmethyl)-1-phenylprop-2-en-1-one (1a')



According to a literature procedure,[30] the reaction using 3-(4-bromophenyl)-1-pheynlpropan-1-one (2.89 g, 10 mmol, 1 equiv), morpholine (0.48 g, 5 mmol, 0.5 equiv), glacial acetic acid (20 mL), 37% aqueous formaldehyde solution (5 mL, 62 mmol, 6.2 equiv) was conducted. Purification by flash column chromatography on silica gel (hexane/EtOAc = 95:5) gave the product as a colorless liquid (1.74 g, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.53 (t, J = 8.3 Hz, 1H), 7.47–7.38 (m, 4H), 7.14 (d, J = 8.8 Hz, 2H), 5.79 (s, 1H), 5.71 (s, 1H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 147.0, 137.7, 137.5, 132.3, 131.6, 130.9, 129.4, 128.2, 127.3, 120.2, 37.8; IR: (ATR) 1653 cm^{-1}; MS: (EI) *m*/*z* 302 ([M+2]$^{+}$, 17), 300 (M^{+}, 18), 221 (24), 131 (26), 116 (20), 115 (57), 105 (100), 77 (93), 51 (32); HRMS: (EI) calcd for ($C_{16}H_{13}BrO$) 300.0150 (M^{+}) found *m*/*z* 300.0150

Preparation of cyanating reagents

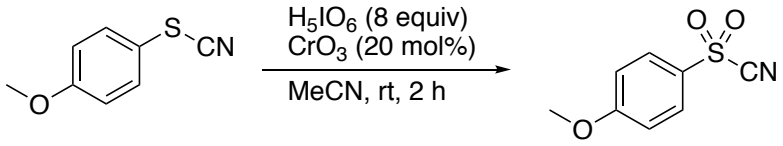
***p*-chlorobenzenesulfonyl cyanide (2b)**



The compound was prepared following the reported procedure with modification.[17] H_5IO_6 (10.9 g, 48 mmol, 8 equiv) was dissolved in acetonitrile (95 mL) by vigorous stirring at room

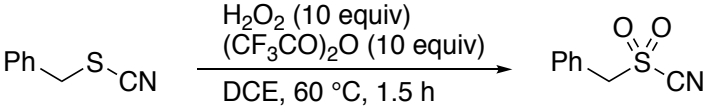
temperature for 30 min, and then CrO_3 (123 mg, 1.2 mmol, 20 mol%) was added to the solution. The mixture was stirred at room temperature for 5 min. To this solution was added *p*-chlorophenyl thiocyanate (1.02 g, 6 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h, then the mixture was filtered through a celite and washed with ethyl acetate (60 mL). The filtrate was washed with iced water (3 x 60 mL) and iced brine (60 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Recrystallization from hexane/CH_2Cl_2 gave the product as a white solid (277 mg, 23%). mp: 54.9–55.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 135.5, 130.8, 130.4, 113.7; IR: (ATR) 2189 cm^{-1}; MS: (EI) *m/z* 203 ([M+2]$^+$, 35), 201 (M$^+$, 94), 177 (25), 175 (63), 127 (28), 113 (31), 111 (100), 75 (41), 58 (22); HRMS: (EI) calcd for ($C_7H_4ClNO_2S$) 200.9651 (M$^+$). found 200.9651

_p_-methoxybenzenesulfonyl cyanide (2c)



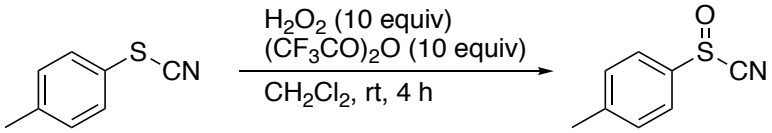
The compound was prepared following the reported procedure with modification.[31] H_5IO_6 (18.2 g, 80 mmol, 8 equiv) was dissolved in acetonitrile (160 mL) by vigorous stirring at room temperature for 30 min, and then CrO_3 (199 mg, 2 mmol, 20 mol%) was added to the solution. The mixture was stirred at room temperature for 5 min. To this solution was added *p*-methoxyphenyl thiocyanate (1.66 g, 10 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h, then the mixture was filtered through a celite and washed with ethyl acetate (100 mL). The filtrate was washed with iced water (3 x 100 mL) and iced brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Recrystallization from hexane/CH_2Cl_2 gave the product as a yellow solid (1.50 g, 76%). mp: 63.3–64.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 131.8, 128.1, 115.6, 114.5, 56.2; IR: (ATR) 2181 cm^{-1}; MS: (EI) *m/z* 197 (M$^+$, 100), 171 (65), 123 (21), 107 (36), 92 (23), 77 (26); HRMS: (EI) calcd for ($C_8H_7NO_3S$) 197.0147 (M$^+$). found 197.0149

benzylsulfonyl cyanide (2d)



The compound was prepared following the reported procedure with modification.[32] Hydrogen peroxide (30 wt% solution in water, 5.9 mL, 57.5 mmol, 10 equiv) was added dropwise at 0 °C to a mixture of trifluoroacetic anhydride (8.0 mL, 57.5 mmol, 10 equiv) in dry 1,2-dichloroethane (15 mL). After being stirred for 40 min at 0 °C, benzyl thiocyanate (858 mg, 5.75 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred at 60 °C for 1.5 h, then quenched with water at 0 °C. The aqueous layer was extracted with dichloromethane (100 mL) and the combined organic layers were washed with water (3 x 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude mixture was purified by recrystallization from hexane/CH_2Cl_2 to give the product as a white solid (376 mg, 36%). mp: 85.0–85.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.42 (m, 5H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 130.8, 129.6, 123.3, 111.7, 64.6; IR: (ATR) 2189 cm^{-1}; HRMS: (EI) calcd for ($C_8H_7NO_2S$) 181.0197 (M^+). found 181.0198

***p*-toluenesulfinyl cyanide (2e)**



The compound was prepared following the reported procedure with modification.[32] Hydrogen peroxide (30 wt% solution in water, 5.9 mL, 57.5 mmol, 10 equiv) was added dropwise at 0 °C to a mixture of trifluoroacetic anhydride (8.0 mL, 57.5 mmol, 10 equiv) in dry dichloromethane (15 mL). After being stirred for 40 min at 0 °C, *p*-toluene thiocyanate (877 mg, 5.75 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred at room temperature for 4 h, then quenched with water at 0 °C. The aqueous layer was extracted with dichloromethane (100 mL) and the combined organic layers were washed with water (3 x 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude mixture was

purified by recrystallization from hexane/CH_2Cl_2 to give the product as a white solid (570 mg, 60%). mp: 47.5–48.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 135.9, 131.0, 125.9, 116.0, 21.7; IR: (ATR) 2166 cm^{-1}; HRMS: (EI) calcd for (C_8H_7NOS) 165.0248 (M^+). found 165.0248

Experimental procedure for NMR analysis of the reaction mixture of α,β-unsaturated ketones and (−)-Ipc$_2$BH

Reaction of α,β-unsaturated ketone 1a with (−)-Ipc$_2$BH

In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with (–)-Ipc$_2$BH (0.21 mmol), THF-d_8 (1 mL), and **1a** (0.2 mmol). The resulting solution was stirred at room temperature for 3 h, transferred to NMR tube, and analyzed by ^{1}H NMR. The resulting ^{1}H NMR spectrum shown in Figure S1 revealed that a boron enolate was produced as a single stereoisomer, which was identified as the *Z*-form due to the absence of a nuclear Overhauser effect (NOE) between the *ortho*-protons (H^a) of the phenyl ring and benzylic protons (H^b).

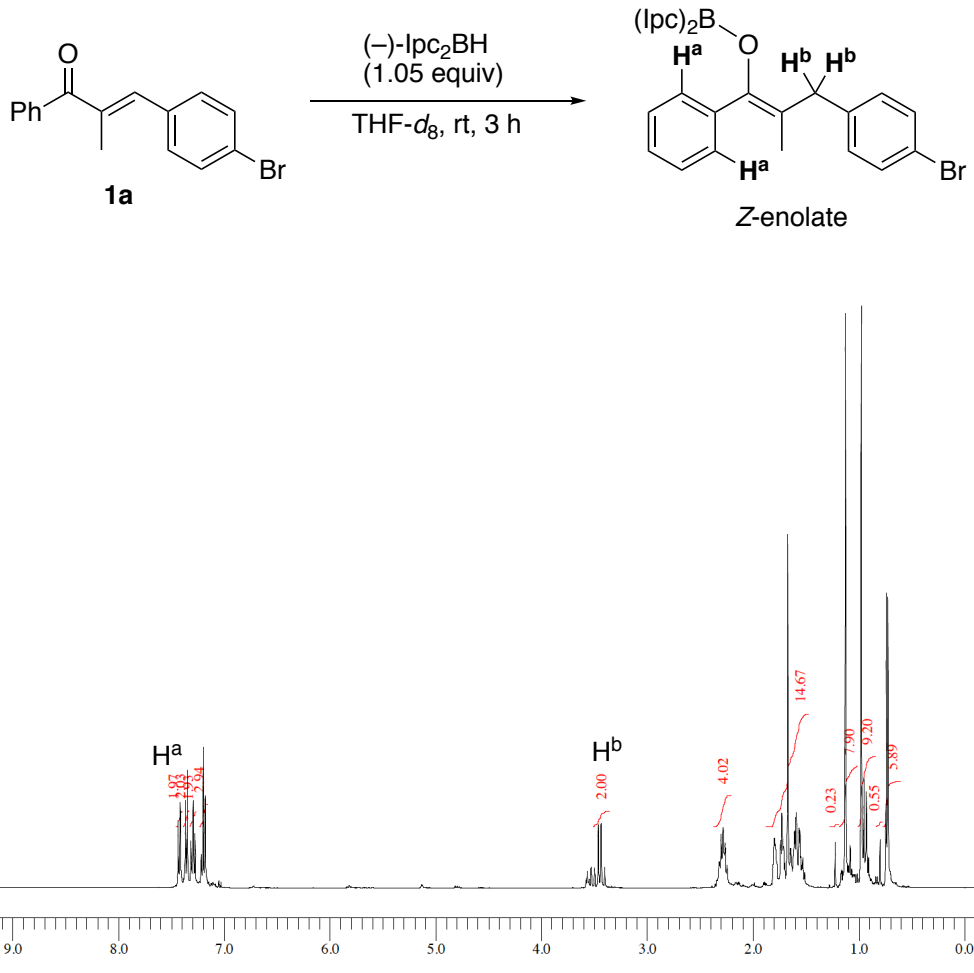


Figure S1. ^{1}H NMR spectrum of the mixture of **1a** and (–)-Ipc$_2$BH in THF-d_8 after stirring at room temperature for 3 h.

Reaction of α,β-unsaturated ketone 1a' with (−)-Ipc$_2$BH

In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with (–)-Ipc$_2$BH (0.21 mmol), THF-d_8 (1 mL), and **1a'** (0.2 mmol). The resulting solution was stirred at room temperature for 3 h, transferred to NMR tube, and analyzed by ^{1}H NMR. The resulting ^{1}H NMR spectrum is shown in Figure S2. The resulting ^{1}H NMR spectrum shown in Figure S2 revealed that a boron enolate was produced as a single stereoisomer, which was clearly confirmed as the *E*-form by NOE correlation between *ortho*-protons (H^a) and benzylic protons (H^b).

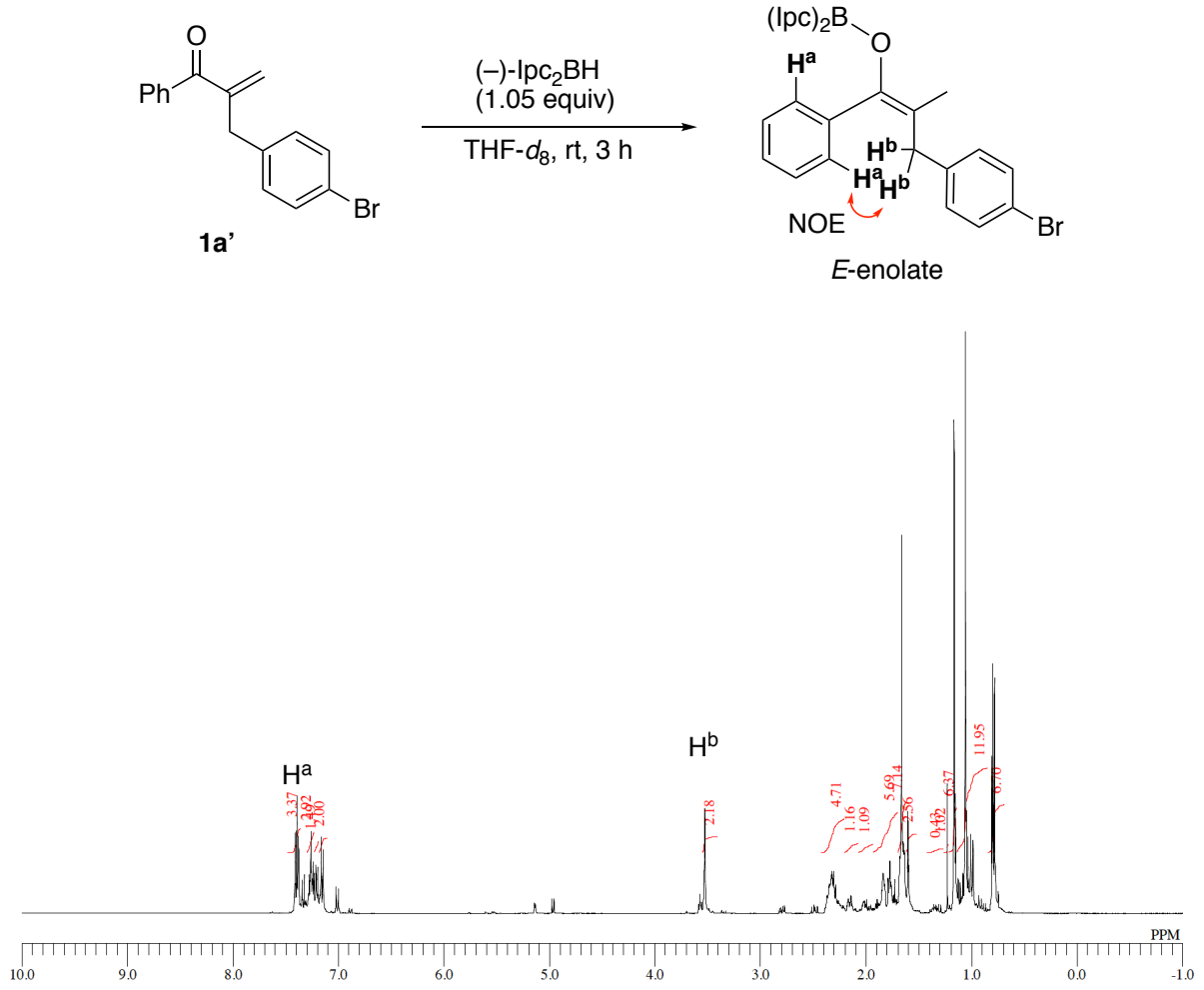


Figure S2. ^{1}H NMR spectrum of the mixture of **1a'** and (–)-Ipc$_2$BH in THF-d_8 after stirring at room temperature for 3 h.

Experimental procedures

Typical procedure for the preparation of racemic products

Racemic β-ketonitriles **3a**–**3o** were prepared according to a literature procedure.[33] In a glove box, an oven dried reaction flask containing a magnetic stir bar was charged with 9-BBN dimer (0.263 mmol). The reaction flask was capped, removed from the glove box, and put under nitrogen. Then, THF (1 mL) and α,β-unsaturated ketone (0.500 mmol) was added to the flask. The mixture was stirred for 3 h at room temperature before NCTS (0.500 mmol) was added. The mixture was stirred at 40 °C for 12 h, and the reaction was then quenched by passing the solution through a short column (silica gel) using CH_2Cl_2 as the eluent. The solution was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (hexane/EtOAc) gave the products.

Racemic β-ketonitrile **3q** was prepared according to a literature procedure.[33]

Typical procedure for the enantioselective electrophilic cyanation of boron enolates

In a glove box, an oven dried schlenk flask containing a magnetic stir bar was charged with (–)-Ipc_2BH (0.21 mmol) and THF (1 mL). The reaction flask was capped, removed from the glove box, and put under nitrogen. α,β-Unsaturated ketone (0.20 mmol) was added to the flask, which was then shielded. The mixture was stirred for 3 h at room temperature, then TsCN (0.60 mmol) was added under a stream of nitrogen, and the flask was shielded again. The mixture was stirred for 24 h at room temperature before the reaction was quenched by sat. $NaHCO_3$ aq (10 mL) and extracted by diethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc), followed by flash column chromatography on silica gel (hexane/EtOAc) or GPC ($CHCl_3$) gave the product.

Experimental procedure of gram-scale synthesis of 3a

In a glove box, an oven dried 200 mL schlenk flask containing a magnetic stir bar was charged with (–)-Ipc_2BH (3.01 g, 10.5 mmol) and THF (50 mL). The reaction flask was capped,

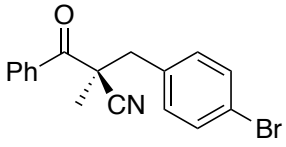
removed from the glove box, and put under nitrogen. α,β-Unsaturated ketone **1a** (3.01 g, 10.0 mmol) was added to the flask, which was then shielded. The mixture was stirred for 3 h at room temperature, then TsCN (5.43 mg, 30.0 mmol) was added under a stream of nitrogen, and the flask was shielded again. The mixture was stirred for 24 h at room temperature before the reaction was quenched by sat. $NaHCO_3$ aq (50 mL) and extracted by diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 93:7), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product **3a** as a white solid (2.05 g, 62% yield, 94% ee). Recrystallization of the product from hexane/CH_2Cl_2 provided racemic, crystalline **3a**, and an enantimerically pure **3a** (white solid, 1.84g, 56%, >99% ee) was isolated from the mother liquor.

Experimental procedure for the enantioselective electrophilic cyanation of 1a'

In a glove box, an oven dried schlenk flask containing a magnetic stir bar was charged with (–)-Ipc_2BH (60.3 mg, 0.211 mmol) and THF (1 mL). The reaction flask was capped, removed from the glove box, and put under nitrogen. α,β-Unsaturated ketone **1a'** (60.2 mg, 0.200 mmol) was added to the flask, which was then shielded. The mixture was stirred for 3 h at room temperature, then TsCN (108.6 mg, 0.599 mmol) was added under a stream of nitrogen and the flask was shielded again. The mixture was stirred for 24 h at room temperature before the reaction was quenched by sat. $NaHCO_3$ aq (10 mL) and extracted by diethyl ether (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a white solid (19.7 mg, 30% yield, −90% ee).

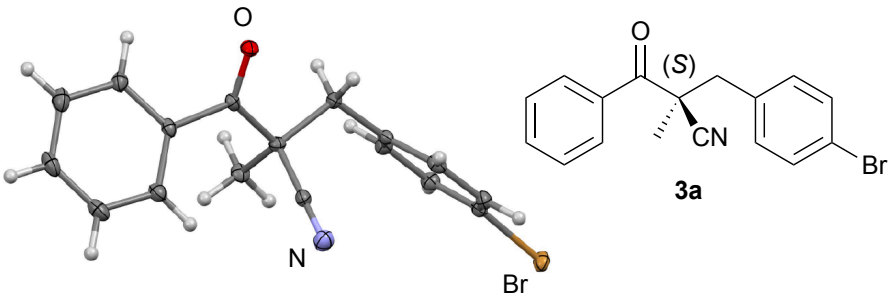
Product data

(*S*)-2-(4-bromophenylmethyl)-2-methyl-3-oxo-3-phenylpropanenitrile (3a)

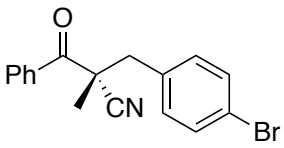


According to the typical procedure, the reaction using α,β-unsaturated ketone **1a** (60.1 mg, 0.200 mmol), (–)-Ipc$_2$BH (60.2 mg, 0.210 mmol), and TsCN (109.4 mg, 0.604 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a white solid (41.3 mg, 63% yield, 94% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 8.16 min; Specific rotation $[\alpha]_D^{20}$ = +35.6 (c = 0.98, $CHCl_3$); mp: 82.7–83.5 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.51–7.43 (m, 4H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.46 (d, *J* = 13.7 Hz, 1H), 3.04 (d, *J* = 13.7 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.3, 134.4, 133.7, 133.4, 132.1, 131.7, 129.1, 128.6, 122.0, 121.4, 47.3, 42.9, 24.2; IR: (ATR) 2237, 1695 cm^{-1}; MS: (EI) *m*/*z* 329 ([M+2]$^+$, 4), 327 (M$^+$, 4), 105 (100); HRMS: (EI) calcd for ($C_{17}H_{14}BrNO$) 327.0259 (M$^+$) found *m*/*z* 327.0257

Recrystallization of the product (94% ee) from hexane/CH_2Cl_2 provided racemic, crystalline **3a**, and an enantimerically pure **3a** (>99% ee) was isolated from the mother liquor. The absolute configuration of **3a** was determined to be (*S*) by X-ray crystallographic analysis. CCDC 1856484 contains the supplementary crystallographic data for this paper.

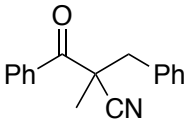


(*R*)-2-(4-bromophenylmethyl)-2-methyl-3-oxo-3-phenylpropanenitrile (3a)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1a** (60.2 mg, 0.200 mmol), (+)-Ipc_2BH (60.3 mg, 0.211 mmol), and TsCN (108.4 mg, 0.598 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a white solid (42.2 mg, 64% yield, −95% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 8.51 min; Specific rotation $[\alpha]_D^{20} = -34.6$ (c = 0.58, $CHCl_3$)

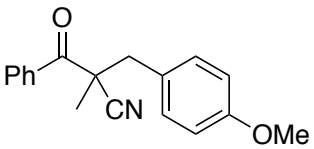
2-benzyl-2-methyl-3-oxo-3-phenylpropanenitrile (3b)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1b** (44.3 mg, 0.199 mmol), (–)-Ipc_2BH (60.3 mg, 0.211 mmol), and TsCN (109.7 mg, 0.605 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 9:1), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a colorless liquid (29.0 mg, 58% yield, 91% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 6.69 min.

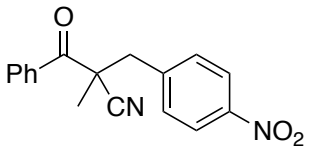
The analytical data for this compound were in excellent agreement with the reported data.[33]

2-(4-methoxyphenylmethyl)-2-methyl-3-oxo-3-phenylpropanenitrile (3c)



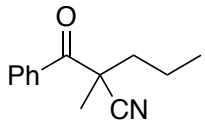
According to the typical procedure, the reaction using α,β-unsaturated ketone **1c** (50.8 mg, 0.201 mmol), (–)-Ipc_2BH (60.5 mg, 0.211 mmol), and TsCN (109.5 mg, 0.604 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a white solid (40.0 mg, 71% yield, 95% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 1:99; λ = 254 nm): t_R 10.5 min; Specific rotation $[\alpha]_D^{20}$ = +53.3 (c = 0.61, $CHCl_3$); mp: 102.9–103.6 °C; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 195.0, 159.2, 134.7, 133.5, 131.5, 129.1, 128.5, 126.3, 121.8, 113.9, 55.2, 47.7, 43.1, 23.9; IR: (ATR) 2236, 1680 cm^{-1}; MS: (EI) *m*/*z* 279 (M^+, 9), 121 (100), 105 (29); HRMS: (EI) calcd for ($C_{18}H_{17}NO_2$) 279.1259 (M^+) found *m*/*z* 279.1258

2-methyl-2-(4-nitrophenylmethyl)-3-oxo-3-phenylpropanenitrile (3d)



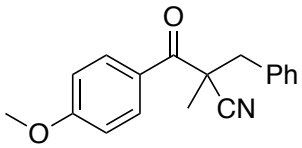
According to the typical procedure, the reaction using α,β-unsaturated ketone **1d** (53.7 mg, 0.201 mmol), (–)-Ipc_2BH (60.3 mg, 0.211 mmol), and TsCN (108.7 mg, 0.600 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 85:15) gave the product as a colorless liquid (13.1 mg, 22% yield, 94% ee). HPLC analysis (Chiralcel OD-H; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 26.7 min; Specific rotation $[\alpha]_D^{20}$ = +20.5 (c = 0.28, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.53–7.44 (m, 4H), 3.63 (d, *J* = 13.7 Hz, 1H), 3.18 (d, *J* = 13.7 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 193.7, 147.6, 142.0, 134.1, 131.5, 129.1, 128.8, 123.6, 121.0, 47.1, 42.9, 24.7 (one sp^2 signal was not observed because of overlapping); IR: (ATR) 2234, 1694 cm^{-1}; MS: (EI) *m*/*z* 294 (M^+, 1), 105 (100), 77 (64); HRMS: (EI) calcd for ($C_{17}H_{14}N_2O_3$) 294.1004 (M^+) found *m*/*z* 294.1008

2-methyl-3-oxo-3-phenyl-2-propylpropanenitrile (3e)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1e** (35.2 mg, 0.202 mmol), (–)-Ipc_2BH (60.1 mg, 0.210 mmol), and TsCN (108.1 mg, 0.597 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 97:3), followed by flash column chromatography on silica gel (hexane/EtOAc = 95:5) gave the product as a colorless liquid (18.7 mg, 46% yield, 77% ee). HPLC analysis (Chiralcel OJ-H; 1.0 mL/min; *i*-PrOH/*n*-hexane 3:97; λ = 242 nm): t_R 8.76 min; Specific rotation $[\alpha]_D^{20}$ = +2.2 (c = 0.21, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 2.23–2.10 (m, 1H), 1.89–1.75 (m, 1H), 1.70 (s, 3H), 1.60–1.45 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.5, 134.3, 133.6, 129.1, 128.6, 122.0, 46.0, 40.3, 23.8, 18.4, 13.9; IR: (ATR) 2234, 1690 cm^{-1} HRMS: (CI) calcd for ($C_{13}H_{16}NO$) 202.1232 ($[M+H]^+$) found *m*/*z* 202.1228

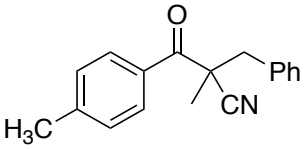
2-benzyl-3-(4-methoxyphenyl)-2-methyl-3-oxopropanenitrile (3f)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1f** (50.7 mg, 0.201 mmol), (–)-Ipc_2BH (60.5 mg, 0.211 mmol), and TsCN (108.3 mg, 0.598 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (36.3 mg, 65% yield, 95% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 9.42 min; Specific rotation $[\alpha]_D^{20}$ = +62.8 (c = 0.95, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.37–7.25 (m, 5H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.47 (d, *J* = 13.7 Hz, 1H), 3.09 (d, *J* = 13.7 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 192.5, 163.8, 134.5, 131.9, 130.4, 128.5, 127.7, 127.1, 122.0, 113.8, 55.5, 46.8, 43.8, 23.9; IR: (ATR) 2234,

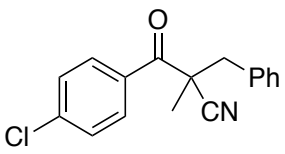
1678 cm^{-1}; MS: (EI) *m*/*z* 279 (M^+, 3), 135 (100), 77 (21); HRMS: (CI) calcd for ($C_{18}H_{18}NO_2$) 280.1338 ($[M+H]^+$) found *m*/*z* 280.1339

2-benzyl-2-methyl-3-(4-methylphenyl)-3-oxopropanenitrile (3g)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1g** (47.6 mg, 0.201 mmol), (–)-Ipc_2BH (60.2 mg, 0.210 mmol), and TsCN (109.0 mg, 0.602 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a colorless liquid (36.7 mg, 70% yield, 94% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 6.26 min; Specific rotation $[\alpha]_D^{20}$ = +53.0 (c = 0.85, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.39–7.20 (m, 7H), 3.47 (d, *J* = 13.7 Hz, 1H), 3.09 (d, *J* = 13.7 Hz, 1H), 2.41 (s, 3H), 1.67 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.1, 144.6, 134.4, 131.9, 130.4, 129.4, 129.2, 128.5, 127.7, 121.8, 47.2, 43.8, 23.9, 21.6; IR: (ATR) 2236, 1684 cm^{-1}; MS: (EI) *m*/*z* 263 (M^+, 4), 119 (100), 91 (45); HRMS: (CI) calcd for ($C_{18}H_{18}NO$) 264.1388 ($[M+H]^+$) found *m*/*z* 264.1390

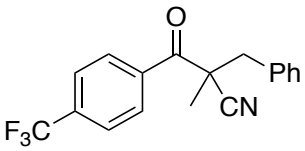
2-benzyl-3-(4-chlorophenyl)-2-methyl-3-oxopropanenitrile (3h)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1h** (51.1 mg, 0.199 mmol), (–)-Ipc_2BH (60.2 mg, 0.210 mmol), and TsCN (108.3 mg, 0.598 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel

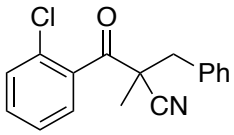
(hexane/EtOAc = 93:7) gave the product as a colorless liquid (36.0 mg, 64% yield, 95% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 6.95 min; Specific rotation $[\alpha]_D^{20}$ = +55.6 (c = 0.81, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.38–7.22 (m, 5H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 193.8, 140.1, 134.1, 132.9, 130.5, 130.3, 128.8, 128.6, 127.9, 121.5, 47.5, 43.9, 24.0; IR: (ATR) 2236, 1688 cm^{-1}; MS: (EI) *m*/*z* 285 ($[M+2]^+$, 3), 283 (M^+, 9), 141 (40), 139 (100), 111 (55), 91 (63), 75 (31), 65 (20); HRMS: (EI) calcd for ($C_{17}H_{14}ClNO$) 283.0764 (M^+) found *m*/*z* 283.0763

2-benzyl-2-methyl-3-oxo-3-(4-(trifluoromethyl)phenyl)propanenitrile (3i)



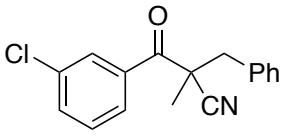
According to the typical procedure, the reaction using α,β-unsaturated ketone **1i** (57.8 mg, 0.199 mmol), (–)-Ipc_2BH (60.3 mg, 0.211 mmol), and TsCN (108.9 mg, 0.601 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a colorless liquid (33.7 mg, 53% yield, 93% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 6.57 min; Specific rotation $[\alpha]_D^{20}$ = +39.7 (c = 0.36, $CHCl_3$); ^1H NMR: (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.40–7.21 (m, 5H), 3.46 (d, *J* = 13.7 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.9, 137.8, 134.5 (q, J_{CF} = 33.7 Hz), 134.0, 130.3, 129.3, 128.7, 128.0, 125.5 (q, J_{CF} = 3.9 Hz), 123.3 (q, J_{CF} = 272.8 Hz), 121.3, 48.1, 44.0, 24.2; ^{19}F NMR: (377 MHz, $CDCl_3$) δ −56.8; IR: (ATR) 2237, 1697 cm^{-1}; MS: (EI) *m*/*z* 317 (M^+, 10), 173 (100), 145 (54), 91 (67); HRMS: (EI) calcd for ($C_{18}H_{14}F_3NO$) 317.1027 (M^+) found *m*/*z* 317.1030

2-benzyl-3-(2-chlorophenyl)-2-methyl-3-oxopropanenitrile (3j)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1j** (51.5 mg, 0.201 mmol), (–)-Ipc$_2$BH (60.3 mg, 0.211 mmol), and TsCN (109.0 mg, 0.602 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a colorless liquid (33.3 mg, 58% yield, 90% ee). HPLC analysis (Chiralcel IC-3; 0.5 mL/min; *i*-PrOH/*n*-hexane 1:99; λ = 215 nm): t_R 22.9 min; Specific rotation $[\alpha]_D^{20}$ = +5.7 (c = 0.48, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 7H), 7.18 (td, *J* = 7.4, 1.1 Hz, 1H), 6.65 (dd, *J* = 7.4, 1.7 Hz, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 199.1, 137.7, 134.2, 131.6, 130.5, 129.93, 129.88, 128.7, 127.9, 126.9, 126.5, 120.5, 51.3, 43.6, 24.0; IR: (ATR) 2239, 1713 cm^{-1}; MS: (EI) *m*/*z* 285 ([M+2]$^+$, 0.4), 283 (M$^+$, 1), 141 (33), 139 (100), 111 (44), 91 (54), 75 (33), 65 (20); HRMS: (EI) calcd for ($C_{17}H_{14}ClNO$) 283.0764 (M$^+$) found *m*/*z* 283.0766

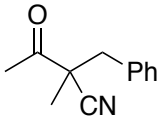
2-benzyl-3-(3-chlorophenyl)-2-methyl-3-oxopropanenitrile (3k)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1k** (51.5 mg, 0.201 mmol), (–)-Ipc$_2$BH (60.2 mg, 0.210 mmol), and TsCN (108.9 mg, 0.601 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel (hexane/EtOAc = 93:7) gave the product as a colorless liquid (37.0 mg, 65% yield, 92% ee). HPLC analysis (Chiralcel IB; 1.0 mL/min; *i*-PrOH/*n*-hexane 2:98; λ = 254 nm): t_R 6.81 min; Specific rotation $[\alpha]_D^{20}$ = +52.5 (c = 0.42, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87–7.78 (m, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.41–7.22 (m, 6H), 3.45 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* =

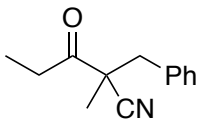
13.7 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 194.0, 136.2, 134.9, 134.1, 133.4, 130.3, 129.7, 129.1, 128.6, 127.9, 127.0, 121.3, 47.8, 43.9, 24.1; IR: (ATR) 2236, 1692 cm^{-1}; MS: (EI) *m*/*z* 285 ($[M+2]^+$, 2), 283 (M^+, 7), 141 (33), 139 (100), 111 (55), 91 (64), 75 (30), 65 (20); HRMS: (EI) calcd for ($C_{17}H_{14}ClNO$) 283.0764 (M^+) found *m*/*z* 283.0761

2-benzyl-2-methyl-3-oxobutanenitrile (3l)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1l** (32.6 mg, 0.203 mmol), (–)-Ipc_2BH (60.3 mg, 0.211 mmol), and TsCN (109.7 mg, 0.605 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 9:1), followed by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (17.0 mg, 45% yield, 93% ee). HPLC analysis (Chiralcel OD-H; 0.5 mL/min; *i*-PrOH/*n*-hexane 1:99; λ = 215 nm): t_R 25.5 min; Specific rotation $[\alpha]_D^{20}$ = +34.1 (c = 0.12, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 3.17 (d, *J* = 13.2 Hz, 1H), 2.91 (d, *J* = 13.2 Hz, 1H), 2.28 (s, 3H), 1.50 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 202.6, 134.2, 130.0, 128.7, 127.8, 121.2, 50.2, 42.9, 28.3, 22.4; IR: (ATR) 2237, 1724 cm^{-1}; MS: (EI) *m*/*z* 187 (M^+, 8), 145 (21), 144 (24), 91 (100), 78 (50), 65 (25), 51 (20); HRMS: (EI) calcd for ($C_{12}H_{13}NO$) 187.0997 (M^+) found *m*/*z* 187.0999

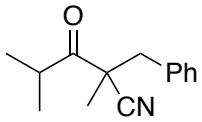
2-benzyl-2-methyl-3-oxopentanenitrile (3m)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1m** (34.7 mg, 0.199 mmol), (–)-Ipc_2BH (60.4 mg, 0.211 mmol), and TsCN (108.9 mg, 0.601 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 8:2), followed by flash column chromatography on silica gel

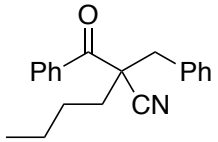
(hexane/EtOAc = 9:1) gave the product as a colorless liquid (13.4 mg, 33% yield, 93% ee). HPLC analysis (Chiralcel AD-H; 1.0 mL/min; EtOH/*n*-hexane 1:100; λ = 215 nm): t_R 9.81 min; Specific rotation $[\alpha]_D^{20}$ = +42.0 (c = 0.34, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 3.16 (d, *J* = 13.7 Hz, 1H), 2.91 (d, *J* = 13.7 Hz, 1H), 2.74 (dq, *J* = 20.2, 6.3 Hz, 1H), 2.39 (dq, *J* = 20.2, 6.3 Hz, 1H), 1.52 (s, 3H), 0.99 (dd, *J* = 6.3, 6.3 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 205.5, 134.4, 129.9, 128.6, 127.8, 121.3, 49.9, 43.5, 34.7, 22.9, 7.3; IR: (ATR) 2236, 1726 cm^{-1}; MS: (EI) *m*/*z* 201 (M^+, 5), 91 (46), 57 (100); HRMS: (EI) calcd for ($C_{13}H_{15}NO$) 201.1154 (M^+) found *m*/*z* 201.1155

2-benzyl-2,4-dimethyl-3-oxopentanenitrile (3n)



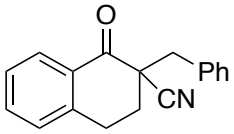
According to the typical procedure, the reaction using α,β-unsaturated ketone **1n** (37.5 mg, 0.199 mmol), (–)-Ipc_2BH (60.2 mg, 0.210 mmol), and TsCN (109.7 mg, 0.605 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 97:3), followed by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (13.3 mg, 31% yield, 77% ee). HPLC analysis (Chiralcel OJ-H; 0.5 mL/min; *i*-PrOH/*n*-hexane 1:99; λ = 212 nm): t_R 18.7 min; Specific rotation $[\alpha]_D^{20}$ = +41.4 (c = 0.10, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 3.21 (d, *J* = 13.2 Hz, 1H), 2.98 (qq, *J* = 6.8, 6.8 Hz, 1H), 2.88 (d, *J* = 13.2 Hz, 1H), 1.53 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 208.7, 134.5, 130.1, 128.5, 127.7, 121.4, 49.9, 43.3, 39.1, 23.7, 18.9, 17.8; IR: (ATR) 2236, 1721 cm^{-1}; MS: (EI) *m*/*z* 215 (M^+, 4), 91 (60), 78 (33), 71 (100); HRMS: (EI) calcd for ($C_{14}H_{17}NO$) 215.1310 (M^+) found *m*/*z* 215.1311

2-benzyl-2-butyl-3-oxo-3-phenylpropanenitrile (3o)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1o** (52.5 mg, 0.199 mmol), (–)-Ipc$_2$BH (60.5 mg, 0.211 mmol), and TsCN (109.9 mg, 0.606 mmol) in THF (1 mL) was carried out. Purification by flash column chromatography on silica gel (hexane/EtOAc = 97:3) and GPC ($CHCl_3$) gave the product as a colorless liquid (8.5 mg, 15% yield, 92% ee). HPLC analysis (Chiralcel IB; 0.5 mL/min; *i*-PrOH/*n*-hexane 1:99; λ = 254 nm): t_R 11.9 min; Specific rotation $[\alpha]_D^{20}$ = +48.0 (c = 0.20, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42–7.21 (m, 7H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.15 (d, *J* = 13.7 Hz, 1H), 2.32–2.20 (m, 1H), 1.97–1.85 (m, 1H), 1.60–1.28 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 196.8, 136.5, 134.5, 133.0, 130.3, 128.6, 128.6, 128.2, 127.8, 121.4, 54.1, 44.0, 38.4, 27.4, 22.6, 13.7; IR: (ATR) 2234, 1686 cm^{-1}; MS: (EI) *m*/*z* 291 (M^+, 3), 105 (100), 91 (25), 77 (36); HRMS: (CI) calcd for ($C_{20}H_{22}NO$) 292.1701 ($[M+H]^+$) found *m*/*z* 292.1704

2-benzyl-2-cyano-3,4-dihydro-1(*2H*)-naphthalenone (3q)



According to the typical procedure, the reaction using α,β-unsaturated ketone **1q** (46.5 mg, 0.198 mmol), (–)-Ipc$_2$BH (60.3 mg, 0.211 mmol), and TsCN (108.8 mg, 0.600 mmol) in THF (1 mL) was carried out. Purification by passing the crude product through a short column of NH silica gel (hexane/EtOAc = 9:1), followed by flash column chromatography on silica gel (hexane/EtOAc = 9:1) gave the product as a colorless liquid (11.8 mg, 23% yield, 92% ee). HPLC analysis (Chiralcel IC-3; 1.0 mL/min; *i*-PrOH/*n*-hexane 5:95; λ = 254 nm): t_R 20.1 min; Specific rotation $[\alpha]_D^{20}$ = +15.6 (c = 0.26, $CHCl_3$)

The analytical data for this compound were in excellent agreement with the reported data.[34]

Computational details

All calculations were performed with the Gaussian 09 package.[35] Frequency analyses were also carried out to identify the transition state (one imaginary frequency) and to estimate thermodynamic properties at 298.15 K and 1atm and Gibbs free energies. The molecular

structures were depicted by using the CYLview v1.0.561 β.[36] We identified the promising TS structure using the small model system, which was expanded to the realistic model system and reoptimized at the B97D/6-31G* level. After screening of the orientation of two Ipc moieties (16 diastereomeric transition states in total) for (*Z*)- and (*E*)-boron enolates, respectively, the origin of the enantioselectivity was investigated by comparison with the most stable diastereomeric transition states, **TS-*S*_1** and **TS-*R*_1** (Tables S1 and S2).

Table S1. The relative energies for the diastereomeric transition states **TS-*ZS*** and **TS-*ZR***.

TS	Δ E (kcal/mol)	Δ G (kcal/mol)	TS	Δ E (kcal/mol)	Δ G (kcal/mol)
TS-*ZS*_1	0.0	0.0	**TS-*ZR*_1**	2.1	5.6
TS-*ZS*_2	4.6	8.4	**TS-*ZR*_2**	7.7	8.9
TS-*ZS*_3	4.7	11.3	**TS-*ZR*_3**	5.2	6.6
TS-*ZS*_4	5.9	7.4	**TS-*ZR*_4**	6.6	7.4
TS-*ZS*_5	8.3	9.0	**TS-*ZR*_5**	5.1	7.1
TS-*ZS*_6	10.0	14.9	**TS-*ZR*_6**	7.7	11.0
TS-*ZS*_7	7.1	9.5	**TS-*ZR*_7**	2.8	5.9
TS-*ZS*_8	4.5	8.5	**TS-*ZR*_8**	3.2	6.3

Table S2. The relative energies for the diastereomeric transition states **TS-*ES*** and **TS-*ER***.

TS	Δ E (kcal/mol)	Δ G (kcal/mol)	TS	Δ E (kcal/mol)	Δ G (kcal/mol)
TS-*ER*_1	0.0	0.0	**TS-*ES*_1**	3.6	2.4
TS-*ER*_2	6.9	6.0	**TS-*ES*_2**	7.4	7.4
TS-*ER*_3	6.1	7.1	**TS-*ES*_3**	5.1	6.1
TS-*ER*_4	5.5	4.7	**TS-*ES*_4**	8.2	8.4
TS-*ER*_5	8.4	6.7	**TS-*ES*_5**	6.7	4.2
TS-*ER*_6	10.8	11.6	**TS-*ES*_6**	6.3	7.0
TS-*ER*_7	12.0	12.2	**TS-*ES*_7**	5.0	4.8
TS-*ER*_8	8.9	9.6	**TS-*ES*_8**	4.6	4.9

3-5. References and Notes

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Conclusion

The present thesis deals with electrophilic cyanation of enolate equivalents utilizing Lewis acidity of boron. The results obtained through the studies are summarized as follows:

Chapter 1 described $B(C_6F_5)_3$-catalyzed electrophilic cyanation of silyl enol ethers with 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (CDBX). The Lewis acidic activation of CDBX through the coordination of the cyano group to the boron center, which was confirmed by IR and NMR studies, was the key for the electrophilic cyanation.

Chapter 2 described electrophilic cyanation of 9-BBN-based boron enolates with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS). Boron enolates derived from various types of ketones including α,β-unsaturated ketones could be applied to this cyanation. Various β-ketonitriles were synthesized by this protocol, which has a remarkably broad substrate scope compared to conventional methods.

Chapter 3 described enantioselective electrophilic cyanation of Ipc_2B-based boron

enolates with TsCN. Acyclic chiral β-ketonitriles that are difficult to access by existing methods could be synthesized with a high degree of enantioselectivity. NMR studies revealed that acyclic α,α-disubstituted boron enolates are formed stereospecifically by the hydroboration of α,β-unsaturated ketones with (–)-Ipc_2BH. Furthermore, computational studies on the transition states indicates that the six-membered ring transition state is formed in the cyanation step and this provides a reasonable explanation for the high enantioselectivity observed for this reaction.

A wide variety of achiral and chiral β-ketonitriles are synthesized by using these methods. As β-ketonitriles are an important synthetic intermediate, the mothods contribute to the synthesis of pharmaceuticals and agricultural chemicals. Furthermore, the findings that Lewis acidic boron compounds can activate a cyano group to promote electrophilic cyanation provide novel synthetic strategies for nitriles.

List of Publications

The content of this thesis has been published in the following papers.

1) Electrophilic Cyanation of Boron Enolates: Efficient Access to Various β-Ketonitrile Derivatives
Kensuke Kiyokawa, Takaya Nagata, Satoshi Minakata
Angew. Chem., Int. Ed. **2016**, *55*, 10458–10462.

2) Catalytic Activation of 1-Cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole with $B(C_6F_5)_3$ Enabling the Electrophilic Cyanation of Silyl Enol Ethers
Takaya Nagata, Hiroki Matsubara, Kensuke Kiyokawa, Satoshi Minakata
Org. Lett. **2017**, *19,* 4672–4675.

3) Enantioselective Electrophilic Cyanation of Boron Enolates: Scope and Mechanistic Studies
Takaya Nagata, Atsuko Tamaki, Kensuke Kiyokawa, Ryosuke Tsutsumi, Masahiro Yamanaka, Satoshi Minakata
Chem. Eur. J. **2018**, *24*, 17027–17032.

List of Supplementary Publication

1) Straightforward Synthesis of 1,2-Dicyanoalkanes from Nitroalkenes and Silyl Cyanide Mediated by Tetrabutylammonium Fluoride
Kensuke Kiyokawa, Takaya Nagata, Junpei Hayakawa, Satoshi Minakata
Chem. Eur. J. **2015**, *21*, 1280–1285.

2) Recent Advances in the Synthesis of β-Ketonitriles
Kensuke Kiyokawa, Takaya Nagata, Satoshi Minakata
Synthesis **2018**, *50*, 485–498.

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