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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 11 Jun 2015

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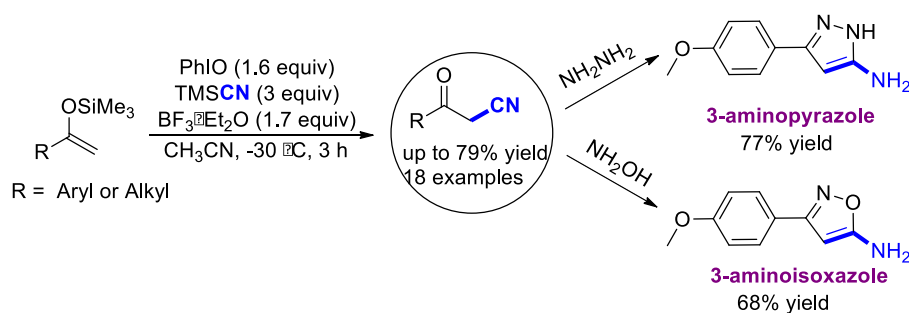
An Umpolung Strategy for Synthesis of β -Ketonitriles through Hypervalent Iodine-Promoted Cyanation of Silyl Enol Ethers

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ABSTRACT: An efficient method to synthesize β -ketonitriles from silyl enol ethers by an umpolung hypervalent iodine(III)-CN species generated *in situ* from PhIO/BF₃·Et₂O/TMSCN has been developed for the first time. This method can be applied to structurally diverse aromatic and aliphatic substrates and further extended to preparation of bioactive compounds like 3-aminopyrazole and 3-aminoisoxazole.

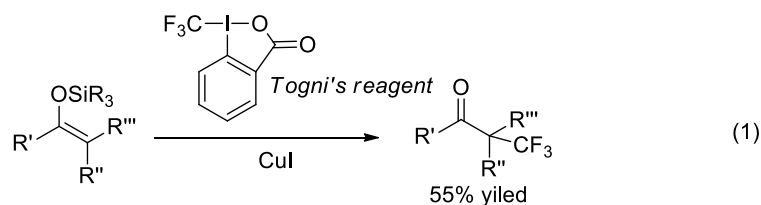
INTRODUCTION

β -Ketonitriles are important intermediates to synthesize different biologically and pharmacologically active heterocycles including aminopyrazoles,¹ aminoisoxazoles,² imidazoles,³ furans,⁴ thiophenes,⁵ 2-pyridones⁶ and triazoles.⁷ Owing to their importance, a variety of methods have been developed to access β -ketonitriles, such as coupling of acetonitriles

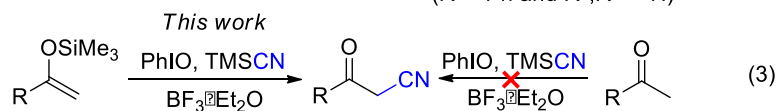
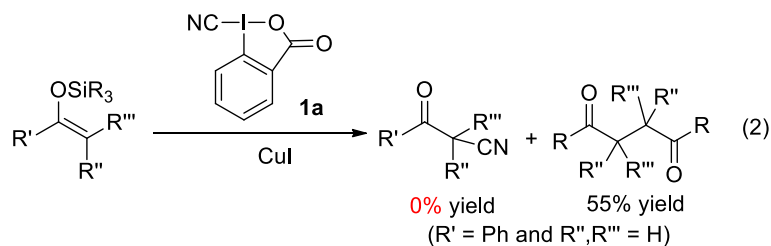
with esters,⁸ cyanide displacement reaction with α -bromo ketones,⁹ C-arylation of resin-bound cyanoacetates,¹⁰ indium-mediated coupling of bromoacetonitriles with aromatic acyl cyanides,¹¹ Pd-catalyzed carbonylation of aryl iodides with trimethylsilylacetonitrile,¹² transformation of enaminones via isoxazoles¹³ and kinetic cyanations of ketone enolates using p-toluenesulfonyl cyanide (TsCN).¹⁴ Regardless of these progress, the development of direct α -cyanation of ketones and their reactive enolates is still highly expected.^{15,16}

Scheme 1. Design of Cyanation for Synthesis of β -Ketonitriles

Chen and Guo's work:



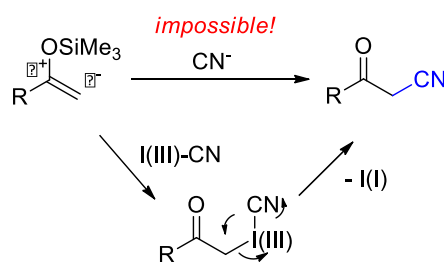
Our design of direct cyanation:



Tautomerism of carbonyl compounds to more reactive enolates and their derivatives such as silyl enol ethers made them preferable to serve as versatile nucleophiles to react with different electrophiles.¹⁷ Recently, hypervalent iodine reagents have been paid much attentions owing to their low toxicity, commercial availability as well as environmental friendliness.¹⁸ Chen and Guo et. al. reported trifluoromethylation of silyl enol ethers using Togni's reagent through a free radical addition in 2014 (Eq. 1, Scheme 1).¹⁹ This inspired us to design cyanobenziodoxole (**1a**)-promoted cyanation to synthesize β -ketonitriles from silyl enol ethers. However, **1a** resulted in the failure of direct cyanation accompanied with generation of 1,4-diketone (55% yield, R' = Ph and R'', R''' = H)

through oxidative α -C self-coupling of ketone (Eq. 2). After much literature review, we found that hypervalent iodine reagents have been already used to achieve umpolung of silyl enol ethers, on the basis of their high electrophilicity.²⁰ Umpolung or polarity inversion of silyl enol ethers exactly provides an alternative way to get target molecules that are hardly synthesized using routine methods (Figure 1).²¹ The combination of trimethylsilyl cyanide (TMSCN) with bis(trifluoroacetoxy)iodobenzene (PIFA) or iodosobenzene (PhIO) have been reported about *in situ* prepared hypervalent iodine(III)-CN intermediates, which were already utilized to accomplish cyanation of heteroaromatics.²² So we further attempted PIFA/TMSCN and PhIO/TMSCN systems to (β -styryloxy)trimethylsilane, and fortunately as envisioned, 3-oxo-3-phenylpropanenitrile was assembled. It was also observed that direct α -cyanation of acetophenone failed in our studies (Eq. 3).

Figure 1. Pathways of Cyanation to β -Ketonitrile.

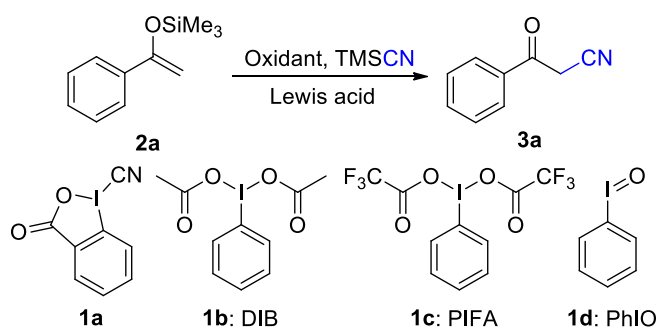


RESULTS AND DISCUSSION

The optimization studies for cyanation were initiated by using (β -styryloxy)trimethylsilane as model substrate, which was prepared freshly from corresponding ketone in the presence of trimethylsilyl chloride, sodium iodide and triethylamine, and trimethylsilyl cyanide (TMSCN) as cyanide source along with hypervalent iodine reagents **1a-d** as oxidants in CHCl_3 . As shown in Table 1, the efficiencies of various hypervalent iodine reagents were firstly examined, cyanobenziodoxole **1a** and (diacetoxyiodo)benzene **1b** did not furnish the desired product (entries 1 and 2), while iodosobenzene **1d** was proved to be most effective and bis(trifluoroacetoxy)iodobenzene **1c** only gave a trace of

desired product (entries 3 and 4), where hypervalent iodines (except **1a**) were premixed with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and TMSCN for preactivation of 40 min before adding (β -styryloxy)trimethylsilane. Without $\text{BF}_3 \cdot \text{Et}_2\text{O}$, **1d** was disabled to this transformation (entry 5). Different amounts of **1d** were then investigated and as a result, 1.6 equivalents was found to be the most suitable (entries 6-7). The reaction was also found to be sensitive to the solvent, and CH_3CN afforded the best result than others, including CHCl_3 , CH_2Cl_2 , DCE, THF as well as DMF (entries 8-12).

Table 1. Screening Oxidants and Solvents^a



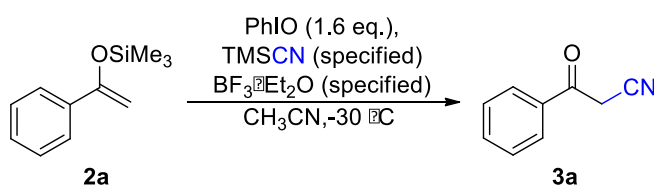
Entry	Solvent	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (eq.)	Oxidant (eq.)	TMSCN (eq.)	Yield (%) ^b
1	DMF	0	1a /1.2	-	0 ^c
2	CHCl_3	2	1b /1.2	3	0
3	CHCl_3	2	1c /1.2	3	trace
4	CHCl_3	2	1d /1.2	3	43
5	CHCl_3	0	1d /1.2	3	0
6	CHCl_3	2	1d /1.6	3	60
7	CHCl_3	2	1d /2.0	3	50
8	CH_2Cl_2	2	1d /1.6	3	48
9	DCE	2	1d /1.6	3	56
10	THF	2	1d /1.6	3	19
11	CH_3CN	2	1d /1.6	3	78
12	DMF	2	1d /1.6	3	48

^a Reaction conditions: (β -styryloxy)trimethylsilane (0.5 mmol), oxidant (specified), TMSCN

(specified), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (specified), and solvent (3.0 mL) at -30°C for 3 h. ^b Isolated yields. ^c $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was replaced by CuI at rt for 3 h, the same conditions for trifluoromethylation referred to lit. 19. DCE = 1,2-dichloroethane.

Other influencing factors of the reaction such as amounts of TMSCN and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, preactivation time and reaction concentration were then examined, with results depicted in Table 2. Fixing 2.0 equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, different amount of TMSCN was screened and as a result, 3.0 equivalents of TMSCN was proved to be most beneficial (Table 2, entries 1-3). With 3.0 equivalents of TMSCN , further decreasing the amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to 1.7 equivalents provided the best yield of 79% (Table 2, entries 4-5). Preactivation time of **1d** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and TMSCN , and reaction time were also investigated, the results showed that either prolonging or shortening preactivation and reaction time was unbeneficial to this reaction (entries 6-9). Increase or decrease of the concentration through adjusting amount of CH_3CN was found to be detrimental to this cyanation (entries 10-11). Moreover, a coupling product 1,4-diketone **4** was generated when using CuCN as cyanide source, where the yield is higher than the reported (Scheme 2).^{20a}

Table 2. Optimization of Reaction Conditions^a



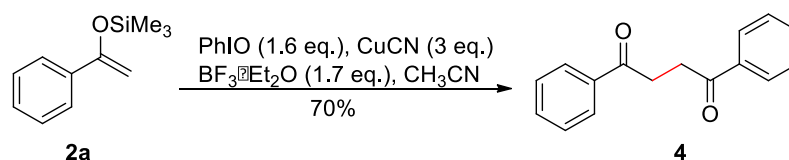
Entry	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (eq.)	TMSCN (eq.)	Yield (%) ^b
1	2	3	78
2	2	2.5	56
3	2	3.5	78
4	1.7	3	79
5	1.5	3	65
6	1.7	3	56 ^c
7	1.7	3	77 ^d

8	1.7	3	60 ^e
9	1.7	3	70 ^f
10	1.7	3	69 ^g
11	1.7	3	77 ^h

^a Reaction conditions: (β-styryloxy)trimethylsilane (0.5 mmol), PhIO (0.8 mmol), TMSCN (specified), BF₃•Et₂O (specified) and CH₃CN (3.0 mL) at -30 °C for 3 h. ^b Isolated yields.

^cPreactivation for 0 hour. ^d Preactivation for 1 hour. ^e 4 h of reaction time. ^f 2 h of reaction time. ^g 4 mL of CH₃CN. ^h 2mL of CH₃CN.

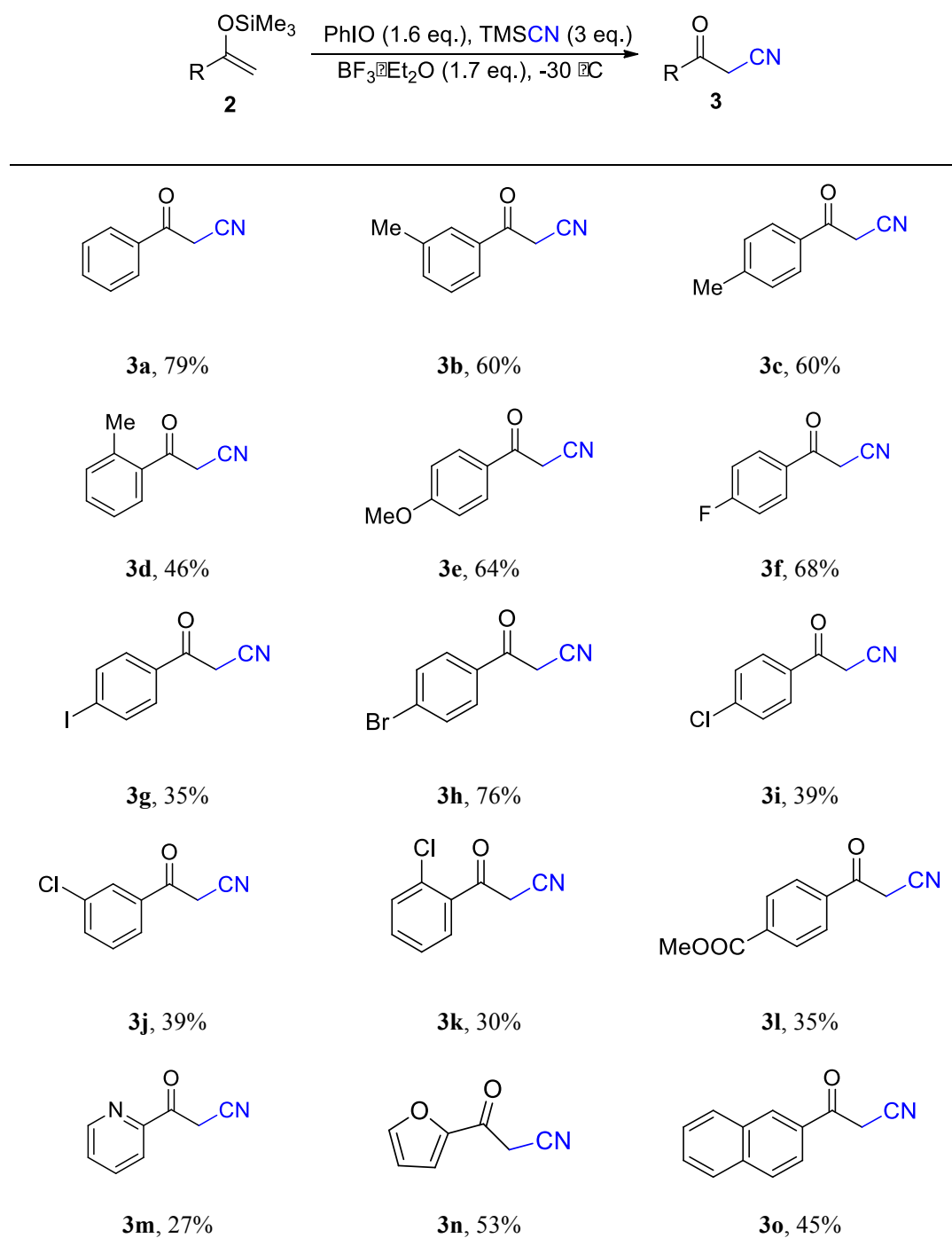
Scheme 2. An Approach to 1,4-Diketone

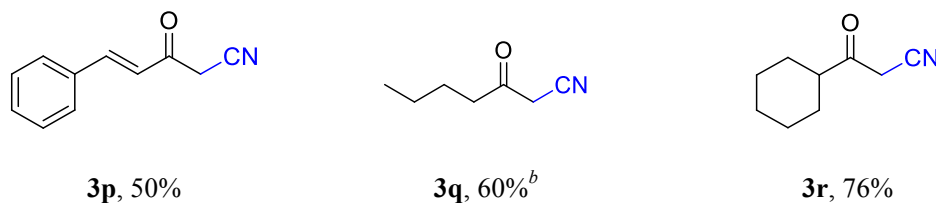


With the optimal conditions in hand, we then generalized the protocol developed for the oxidative cyanation. As described in Table 3, the reactions of different silyl enol ethers bearing either electron-donating substituents, such as methyl and methoxyl, or electron-withdrawing substituents, like halogen and ester, on aromatic ring gave the corresponding cyanated products in moderate to good isolated yields (**3a-l**). *Meta*-substituents and *para*-substituents were found to be more favorable than *ortho*-substituents (**3b-c** vs **3d**, **3i-j** vs **3k**) and the ability of withdrawing electron of groups didn't influence the reaction with regularity (**3f-i**). In addition, heteroaryl-containing compounds were converted into the corresponding β-ketonitriles in moderate yields (**3m-n**) and naphthalene-containing substrate also led to 45% yield (**3o**). It is worthy to note that cinnamyl-containing and aliphatic substrates smoothly afforded the cyanation products with up to 76% yield (**3p-r**), and only terminal cyano products were detected (also see Scheme 3). Likewise, silyl enol ether of propiophenone **2s** did not give the desired cyanation product using this method, whereas a highly substituted oxazole was produced when switching the feeding order, namely adding TMSCN immediately after the mixture of PhIO, BF₃•Et₂O and silyl enol ether in sequence, where the solvent CH₃CN was involved into the

reaction.²³ However, the same procedure to **2a** generated **3a** in 60% yield as a major product with relatively small amounts of oxazole **6** in 22%, which suggested the early interaction of hypervalent iodine and solvent CH₃CN before TMSCN (Scheme 4).

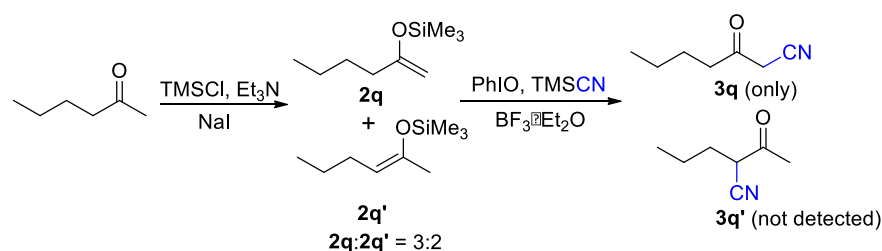
Table 3. Substrate Scope^a



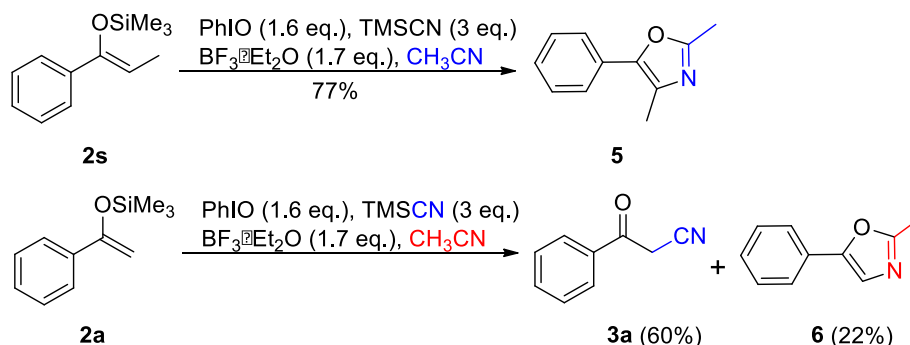


^a Reaction conditions: silyl enol ether (0.5 mmol), PhIO (0.8 mmol), TMSCN (1.5 mmol), BF₃•Et₂O (0.85 mmol), and CH₃CN (3.0 mL) at -30 °C for 3 h; Isolated yields. ^b The yield was based on portion of terminal ene.

Scheme 3. Regioselectivity of the Method

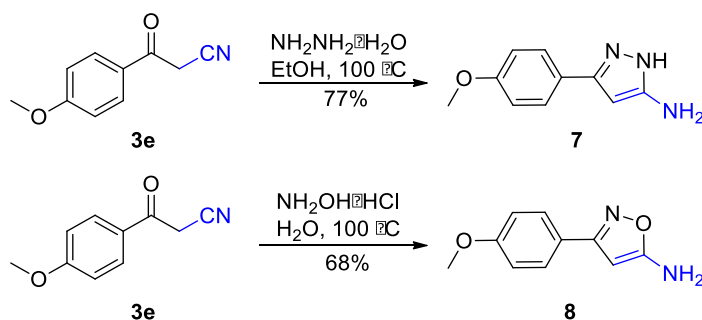


Scheme 4. Approach to Synthesis of Oxazoles



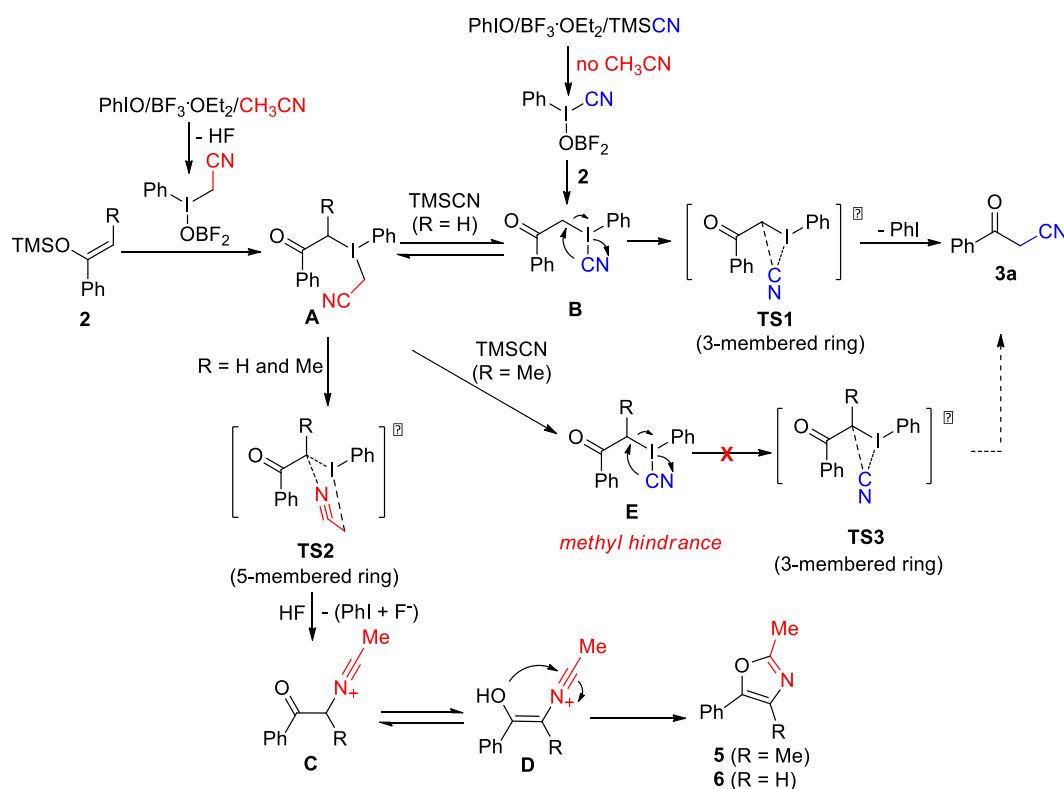
We next moved toward the applications of β -Ketonitrile to the preparation of two important intermediates, viz. 3-aminopyrazole and 3-aminoisoxazole, which can be further converted into a variety of biologically active products.^{1,2} As shown in Scheme 4, the reactions of 4-methoxybenzoylacetone with hydrazine hydrate¹ and hydroxylamine hydrochloride^{2b} can easily give 3-aminopyrazole and 3-aminoisoxazole with the good yields of 77% and 68%, respectively (Scheme 5).

Scheme 5. Applications of β -Ketonitrile



Based on our experimental results, a plausible mechanistic pathway for the synthesis of β -ketonitriles was proposed to interpret the observed reactivities (Figure 2). Active hypervalent iodine(III)- CH_2CN species is firstly formed *in situ* from the mixture of $\text{PhIO}/\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{CH}_3\text{CN}$. Then silyl enol ether **2** is oxidated by hypervalent iodine(III)- CH_2CN species to achieve umpolung and give intermediate **A**. The CH_2CN moiety in **A** is exchanged by CN^- in the presence of TMSCN to reach **B**. Through an intramolecular $\text{S}_{\text{N}}2$ reaction and an electron transfer in a three-membered ring transition state **TS1**, cyanation product **3a** is furnished, accompanied with the release of iodobenzene. Alternatively, intermediate **A** can be converted into a five-membered ring transition state **TS2** through nitrogen attack of cyano group and an oxazole **5** or **6** is formed eventually through a decomposition of **TS2**, tautomerism of ketone **C** to enol **D** and nucleophilic addition of hydroxyl. From our studies on cyanation of (Z)-trimethyl(1-phenylprop-1-enyloxy)silane **2s** where no cyanation product was generated, we speculated rationally that methyl hindered the attack of CN in intermediate **E** to form **TS3**.

Figure 2. Proposed Reaction Mechanisms.



In conclusion, we have developed a direct cyanation method of silyl enol ethers to synthesize β -ketonitriles through umpolung strategy by $\text{PhIO}/\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{TMSCN}$ system, in which diversely substituted aromatic, heteroaromatic and aliphatic substrates worked well. Further studies about synthetic utility of this versatile oxidative system and more mechanistic details are presently pursued in our laboratories.

EXPERIMENTAL SECTION

General Information. ^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 or DMSO-d_6 on a 500 spectrometer (500 MHz for ^1H , 125 MHz for ^{13}C) at 20~25 $^\circ\text{C}$. ^1H NMR spectra were reported in parts per million using tetramethylsilane TMS ($\delta = 0.00$ ppm) as an internal standard. The data of ^1H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (J , Hz), and integration. ^{13}C NMR spectra were reported in parts per million using solvent CDCl_3 ($\delta = 77.2$ ppm) or DMSO-d_6 ($\delta = 39.5$ ppm) as an internal standard, The

data of ^{13}C NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), and coupling constants (J , Hz). High-resolution mass spectra (HRMS) electrospray ionization (ESI) was carried out on a UPLC-Q-ToF MS spectrometer. Reactions were monitored by TLC and column chromatography was performed using silica gel. All solvents were purified by conventional methods, distilled before use. Commercially available reagents were used without further purification unless otherwise specified.

Procedure for Synthesis of cyanobenziodoxole (1a). **1a** was synthesized according to the reported method:²⁴ 1-acetoxy-1,2-benziodoxol-3(1H)-one (4.58 g, 15.0 mmol) were dissolved in dry CH_2Cl_2 (40 mL) under Ar atmosphere. After the addition of Me_3SiCN (4.3 mL, 30 mmol), the mixture was stirred for 24 h at room temperature. The crude product was filtered off, washed with CH_2Cl_2 , and dried at 40 °C under vacuum to give white solid cyanobenziodoxole **1a**; 70% yield, 2.82 g. NMR data were in complete agreement with the reported ones.²⁴

Procedure for Synthesis of Iodosylbenzene PhIO. PhIO was synthesized according to the reported method:²⁵ To (diacetoxyiodo)benzene (3.2 g, 10 mmol) in a 100 mL Erlenmeyer flask was added 54 ml of sodium hydroxide solution (1.88 M) dropwise at room temperature. The light yellow suspension appeared slowly and the resulting mixture was stirred for three hours at room temperature. The precipitate was filtered under high vacuum and washed with water until the washing water got neutral to afford the slightly yellow solid which was dried in the air and then mortared into fine powder for use.

General Procedure for Preparation of Silyl Enol Ether. Silyl enol ethers were synthesized according to the reported method:²⁶ The 100 mL-three-necked flask loaded with a mixture of ketone (25 mmol) and sodium iodide (4.5 g, 30 mmol) was evacuated and filled with argon three times, then dry acetonitrile (30 mL) was added. The resulting solution was stirred for 5 min at room temperature, and triethylamine (4.2 mL, 30 mmol) was added, followed by

chlorotrimethylsilane (3.82 mL, 30 mmol). The reaction mixture was then stirred at 40 °C for overnight. The reaction was quenched by cold pentane (50 mL) and ice water (50 mL). The organic phase was separated and the aqueous layer was extracted with pentane (30 mL×2). The combined organics were washed with brine, and then dried over anhydrous MgSO₄. The solvents was removed firstly in vacuo by rotatory evaporator, and the residue was distilled under reduced pressure to provide pure silyl enol ether **2**.

General Procedure for Preparation of β -Ketonitriles. For a sealed 50 mL two-necked bottle filled with PhIO (176 mg, 0.8 mmol), argon replacement was executed for three times in one hour and cooled to -30 °C. Dry solvent (3 mL), BF₃·Et₂O (0.11 mL, 0.85 mmol) and TMSCN (0.19 mL, 1.5 mmol) were then added successively under stirring conditions. After 40 min for preactivation, silyl enol ether **2** (0.5 mmol) was added to the mixture slowly and reacted at -30 °C for 3 h. The reaction was quenched by saturated sodium bicarbonate, sodium thiosulfate solution and ethyl acetate. The organic phase was separated and the aqueous layer was extracted with EtOAc (8 mL×3). The organic extract was combined, dried with MgSO₄ and filtered to get clear organic solution. The solvents were removed under reduced pressure. The resulting residue was purified by column chromatography using EtOAc-petroleum ether as eluent to give desired product **3**.

3-Oxo-3-phenylpropanenitrile (3a).^{12a} Pale yellow solid; 79% yield, 57.5 mg; mp 68-70 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, J = 8.0 Hz, 2H), 7.68 (tt, J = 7.5, 1.0 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 4.10 (s, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 187.2, 134.9, 134.4, 129.3, 128.7, 113.9, 29.6. HRMS (ESI) calcd for C₉H₇NO [M+H]⁺ 146.0599, found 146.0597.

3-Oxo-3-m-tolylpropanenitrile (3b).^{12a} Pale yellow solid; 60% yield, 47.6 mg; mp 65-67 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 7.0 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 4.09 (s, 2H), 2.43 (s, 3H). ¹³C NMR

(125 MHz, CDCl₃) δ 187.5, 139.3, 135.7, 134.4, 129.1, 129.0, 125.8, 114.1, 29.6, 21.4. HRMS (ESI) calcd for C₁₀H₉NO [M+H]⁺ 160.0757, found 160.0758.

3-Oxo-3-p-tolylpropanenitrile (3c).^{12a} Pale yellow solid; 60% yield, 47.4 mg; mp 94-96 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.05 (s, 2H), 2.44 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 186.8, 146.2, 132.0, 130.0, 128.8, 114.0, 29.4, 22.0. HRMS (ESI) calcd for C₁₀H₉NO [M+H]⁺ 160.0757, found 160.0759.

3-oxo-3-o-tolylpropanenitrile (3d).^{12a} Pale yellow solid; 46% yield, 36.5 mg; mp 68-70 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.62 (d, *J* = 8 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.33-7.31 (m, 2H), 4.05 (s, 2H), 2.57 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 189.5, 140.6, 134.0, 133.5, 130.0, 129.4, 126.3, 114.2, 31.6, 22.0. HRMS (ESI) calcd for C₁₀H₉NO [M+H]⁺ 160.0757, found 160.0761.

3-(4-Methoxyphenyl)-3-oxopropanenitrile (3e).^{12a} Pale yellow solid; 64% yield, 55.8 mg; mp 119-121 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 8 Hz, 2H), 4.03 (s, 2H), 3.90 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 185.6, 164.9, 131.1, 127.5, 114.5, 114.3, 55.9, 29.2. HRMS (ESI) calcd for C₁₀H₉NO₂ [M+H]⁺ 176.0706, found 176.0713.

3-(4-Fluorophenyl)-3-oxopropanenitrile (3f).^{12a} Pale yellow solid; 68% yield, 55.6 mg; mp 75-77 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.97 (t, *J* = 6.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 4.07 (s, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 185.6, 166.8 (d, *J* = 262.5 Hz), 131.5 (d, *J* = 10 Hz), 130.9 (d, *J* = 2.5 Hz), 116.6 (d, *J* = 22.5 Hz), 113.7, 29.5. HRMS (ESI) calcd for C₉H₆FNO [M+H]⁺ 164.0506, found 164.0506.

3-(4-Iodophenyl)-3-oxopropanenitrile (3g).^{1d} Yellow solid; 35% yield, 47 mg; mp 173-175 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 8 Hz, 2H), 4.04 (s, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 186.5, 138.8, 133.7, 129.8, 113.5, 103.5, 29.5. HRMS (ESI) calcd for C₉H₆INO [M+H]⁺ 271.9567, found 271.9563.

3-(4-Bromophenyl)-3-oxopropanenitrile (3h).^{12a} Pale yellow solid; 76% yield, 85.4 mg; mp 156-157 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.68

(d, $J = 8.5$ Hz, 2H), 4.05 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 186.3, 133.2, 132.8, 130.5, 130.1, 113.5, 29.5. HRMS (ESI) calcd for $\text{C}_9\text{H}_6\text{BrNO}$ $[\text{M}+\text{H}]^+$ 223.9706, found 223.9703.

3-(4-Chlorophenyl)-3-oxopropanenitrile (3i).^{12a} Pale yellow solid; 39% yield, 35.4 mg; mp 121-123 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.88 (d, $J = 9$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 4.06 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 186.1, 141.7, 132.7, 130.0, 129.8, 113.6, 29.6. HRMS (ESI) calcd for $\text{C}_9\text{H}_6\text{ClNO}$ $[\text{M}+\text{H}]^+$ 180.0211, found 180.0215.

3-(3-Chlorophenyl)-3-oxopropanenitrile (3j).²⁷ Pale yellow solid; 39% yield, 35.3 mg; mp 72-73 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.91 (s, 1H), 7.80 (d, $J = 8$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.49 (t, $J = 8$ Hz, 1H), 4.08 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 186.2, 135.9, 135.8, 134.9, 130.7, 128.7, 126.7, 113.5, 29.7. HRMS (ESI) calcd for $\text{C}_9\text{H}_6\text{ClNO}$ $[\text{M}+\text{H}]^+$ 180.0211, found 180.0208.

3-(2-Chlorophenyl)-3-oxopropanenitrile (3k).²⁷ Pale yellow solid; 30% yield, 27 mg; mp 95-97 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 7.5$ Hz, 1H), 7.51-7.47 (m, 2H), 7.41 (t, $J = 7.5$ Hz, 1H), 4.15 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.6, 135.9, 133.9, 131.9, 131.2, 130.6, 127.7, 113.5, 33.1. HRMS (ESI) calcd for $\text{C}_9\text{H}_6\text{ClNO}$ $[\text{M}+\text{H}]^+$ 180.0211, found 180.0215.

Methyl-4-(2-cyanoacetyl)benzoate (3l).^{12a} Pale yellow solid; 35% yield, 35.3 mg; mp 163-164 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.19 (d, $J = 8$ Hz, 2H), 7.99 (d, $J = 8$ Hz, 2H), 4.12 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 186.9, 165.9, 137.5, 135.6, 130.5, 128.6, 113.5, 52.9, 29.9. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_9\text{NO}_3$ $[\text{M}+\text{H}]^+$ 204.0655, found 204.0662.

3-(Pyridine-2-yl)-3-oxopropanenitrile (3m).^{1c} Pale yellow solid; 27% yield, 19.4 mg; mp 94-96 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.69 (d, $J = 4.5$ Hz, 1H), 8.11 (d, $J = 8$ Hz, 1H), 7.91 (td, $J = 7.5, 1.5$ Hz, 1H), 7.57 (ddd, $J = 7.5, 5.0, 1.0$ Hz, 1H), 4.40 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.6, 151.0, 149.5, 137.6, 128.7, 122.6, 114.6, 28.7. HRMS (ESI) calcd for $\text{C}_8\text{H}_6\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 147.0553, found 147.0553.

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4 *3-(Furan-2-yl)-3-oxopropanenitrile (3n)*.²⁷ Pale yellow solid; 53% yield, 35.9
5 mg; mp 63-65 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.67 (d, *J* = 0.5 Hz, 1H), 7.39 (dd, *J* =
6 3.5, 0.5 Hz, 1H), 6.65 (dd, *J* = 3.5, 1.5 Hz, 1H), 3.97 (s, 2H). ¹³C NMR (125 MHz,
7 CDCl₃) δ 175.9, 150.7, 147.9, 119.5, 113.6, 113.5, 29.0. HRMS (ESI) calcd for
8 C₇H₅NO₂ [M+H]⁺ 136.0393, found 136.0395.
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14 *3-(Naphthalen-2-yl)-3-oxopropanenitrile (3o)*.²⁷ Yellow solid; 45% yield, 43.5
15 mg; mp 107-108 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.42 (s, 1H), 7.99-7.90 (m, 4H),
16 7.67 (t, *J* = 7 Hz, 1H), 7.61 (t, *J* = 7 Hz, 1H), 4.22 (s, 2H). ¹³C NMR (125 MHz, CDCl₃)
17 δ 187.2, 136.4, 132.5, 131.8, 130.9, 129.9, 129.7, 129.4, 128.1, 127.6, 123.6,
18 114.0, 29.6. HRMS (ESI) calcd for C₁₃H₉NO [M+H]⁺ 196.0757, found 196.0758.
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24 *Cinnamoylacetonitrile (3p)*.²⁸ Yellow solid; 50% yield, 43 mg; mp 94-95 °C.
25 ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, *J* = 16 Hz, 1H), 7.59 (d, *J* = 7 Hz, 2H),
26 7.47-7.42 (m, 3H), 6.88 (d, *J* = 16 Hz, 1H), 3.72 (s, 2H). ¹³C NMR (125 MHz, CDCl₃)
27 δ 186.5, 146.8, 133.6, 131.9, 129.4, 129.0, 122.6, 114.2, 31.0. HRMS (ESI) calcd
28 for C₁₁H₉NO [M+H]⁺ 172.0757, found 172.0753.
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34 *3-Oxoheptanenitrile (3q)*.²⁹ White solid; 60% yield, 37.7 mg; decomposition
35 before melt. ¹H NMR (500 MHz, CDCl₃) δ 3.47 (s, 2H), 2.62 (t, *J* = 7 Hz, 2H),
36 1.63-1.59 (m, 2H), 1.37-1.33 (m, 2H), 0.93 (t, *J* = 7 Hz, 3H). ¹³C NMR (125 MHz,
37 CDCl₃) δ 197.8, 114.0, 42.1, 32.1, 25.5, 22.2, 13.9. HRMS (ESI) calcd for C₇H₁₁NO
38 [M+H]⁺ 126.0914, found 126.0919.
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45 *3-Cyclohexyl-3-oxopropionitrile (3r)*. Pale yellow oil; 76% yield, 57.7 mg. ¹H
46 NMR (500 MHz, CDCl₃) δ 3.51 (s, 2H), 2.55 (tt, *J* = 11.0, 3.5 Hz, 1H), 1.92-1.89 (m,
47 2H), 1.83-1.79 (m, 2H), 1.71-1.68 (m, 1H), 1.42-1.20 (m, 5H). ¹³C NMR (125 MHz,
48 CDCl₃) δ 200.6, 114.1, 50.2, 30.4, 28.3, 25.7, 25.4. HRMS (ESI) calcd for C₉H₁₃NO
49 [M+H]⁺ 152.1070, found 152.1066.
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55 **Typical Procedure for Synthesis of 1,4-Diketone 4.**^{20a} For a sealed 50 mL
56 two-necked bottle filled with PhIO (176 mg, 0.8 mmol), argon replacement was
57 executed for three times in one hour and cooled to -30 °C. Dry CH₃CN (3 mL),
58 BF₃·Et₂O (0.11 mL, 0.85 mmol) and CuCN (134 mg, 1.5 mmol) were then added
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successively under stirring condition. After 40 min for preactivation, silyl enol ether **2a** (98 mg, 0.5 mmol) and TMSCN (0.19 mL, 1.5 mmol) was added to the mixture slowly and reacted at -30 °C for 3 h. The reaction was quenched by saturated sodium bicarbonate, sodium thiosulfate solution and ethyl acetate. The organic phase was separated and the aqueous layer was extracted with EtOAc (8 mL×3). The organic extract was combined, dried with MgSO₄ and filtered to get clear organic solution. The solvents were removed under reduced pressure. The resulting residue was purified by column chromatography using EtOAc-petroleum ether as eluent to give white solid 1,4-Diphenyl-1,4-butadiene **4**; 70% yield, 42 mg; mp 142-143 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, *J* = 7.5 Hz, 4H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 8 Hz, 4H), 3.47 (s, 4H). ¹³C NMR (125 MHz, CDCl₃) δ 198.9, 136.9, 133.3, 128.8, 128.3, 32.7. HRMS (ESI) calcd for C₁₆H₁₄O₂ [M+H]⁺ 239.1067, found 239.1074.

Typical Procedure for Synthesis of Oxazole 5.^{23c} A dry 50 mL two-necked bottle was charged with PhIO (176 mg, 0.8 mmol) and then evacuated and backfilled with argon. After cooling to -30 °C, BF₃·Et₂O (0.11 mL, 0.85 mmol), silyl enol ether **2s** (103 mg, 0.5 mmol) and TMSCN (0.19 mL, 1.5 mmol) were added subsequently. The reaction mixture was stirred for 3 h at -30 °C. The reaction mixture was quenched with saturated sodium bicarbonate, sodium thiosulfate solution and ethyl acetate. The organic phase was separated and the aqueous layer was extracted with EtOAc (8 mL×3). The combined organic extract was then concentrated and the resulting residue was purified by column chromatography on silica gel to get white solid 2,4-dimethyl-5-phenyloxazole **5**; 77% yield, 67 mg; mp 45-47 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 8 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 159.5, 145.3, 131.8, 129.5, 128.9, 127.5, 125.2, 14.1, 13.4 HRMS (ESI) calcd for C₁₁H₁₁NO [M+H]⁺ 174.0914, found 174.0907.

The Similar Procedure for Synthesis of Oxazole 6.
2-Methyl-5-phenyloxazole (6).^{23c} Pale yellow solid; 22% yield, 17.6 mg; mp 55-58

°C. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (d, J = 7 Hz, 2H), 7.41 (t, J = 8 Hz, 2H), 7.31 (t, J = 7 Hz, 1H), 7.18 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.2, 151.3, 129.0, 128.3, 124.7, 124.1, 121.9, 14.3. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_9\text{NO}$ $[\text{M}+\text{H}]^+$ 160.0757, found 160.0750.

Procedure for Preparation of 3-Aminopyrazole 7. **7** was synthesized according to the reported method:³⁰ To a solution of **3e** (103 mg, 0.5 mmol) in 3 mL of ethanol in a 50 mL round-bottom flask was added hydrazine hydrate (0.08 mL, 2.5 mmol), and the resulting mixture was heated at 100 °C for 6 h. After cooling to rt, the solvents were removed under reduced pressure and the resulting residue was purified by column chromatography to give white solid 3-(4-methoxyphenyl)-5-amine-1H-pyrazol **7**; 77% yield, 72 mg; mp 136-137 °C. ^1H NMR (500 MHz, DMSO) δ 11.7 (br s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 5.71 (s, 1H), 4.75 (br s, 2H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 158.6, 126.1, 114.0, 55.1. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 190.0975, found 190.0969.

Procedure for Preparation of 3-Aminoisoxazole 8. **8** was synthesized according to the reported method:³¹ To a stirred solution of compound **3e** (103 mg, 0.5 mmol) and sodium hydroxide (40 mg, 1 mmol) in water (1.5 mL) was added hydroxylamine hydrochloride (34 mg, 0.5 mmol), and the resulting mixture was heated at 100 °C for 2.5 h. After cooling to rt, the mixture was diluted with CHCl_3 and the organic layer was separated. The aqueous layer was further extracted with CHCl_3 , and the combined organic layers were dried over MgSO_4 and then concentrated under reduced pressure to afford orange solid 3-(4-methoxyphenyl)-5-amine-isoxazol **8**; 68% yield, 64 mg; mp 110-113 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.66 (d, J = 9 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 5.38 (s, 1H), 4.55 (brs, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.8, 163.7, 161.0, 128.2, 122.4, 114.3, 78.2, 55.5. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 191.0815, found 191.0818.

ACKNOWLEDGMENT

We gratefully acknowledge funding from the National Natural Science Foundation of China (No. 21372265), the Natural Science Foundation Project of CQ CSTC (No. cstc2013jcyjA0217), and the Fundamental Research Funds for the Central Universities (No. CQDXWL-2013-Z012 and No. CDJZR14225502).

SUPPORTING INFORMATION

Copies of NMR spectra of compounds **3**, **4**, **5**, **6**, **7**, **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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