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# Access to Cyano-Containing Isoxazolines via Copper-Catalyzed Domino Cyclization/Cyanation of Alkenyl Oximes

Fei Meng, Honglin Zhang, Kang Guo, Jiayue Dong, Ai-Min Lu, and Yingguang Zhu\*

Jiangsu Key Laboratory of Pesticide Science and Department of Chemistry, College

of Sciences, Nanjing Agricultural University, Nanjing 210095, P. R. China

E-mail: ygzhu@njau.edu.cn

#### ABSTRACT



A highly efficient copper-catalyzed cyclization/cyanation cascade of unactivated olefins bearing oximes is described. A variety of cyano-containing isoxazolines have been obtained in high yields with cheap  $Cu(NO_3)_2$  3H<sub>2</sub>O as the catalyst and TMSCN as the non-metallic cyanide source. The present method provides a mild, simple, and practical access to cyano-substituted isoxazolines and is amenable to gram scale. The simultaneous construction of  $C(sp^3)$ –CN and C–O bonds can be achieved in one step.

Difunctionalization of olefins represents a powerful synthetic strategy for the efficient introduction of two functional groups across a double bond and thus for the rapid construction of diverse molecules.<sup>1-3</sup> Radical-mediated alkene difunctionalization has recently received considerable attention due to its high efficency and generally mild conditions.<sup>2,3</sup> Despite significant advances over the last decade, the olefin substrates employed in radical difuctionalization reactions are mainly restricted to activated olefins.<sup>3</sup>

Isoxazolines are an important class of heterocycles found in some bioactive molecules, pharmaceuticals, and agrochemicals (Figure 1).<sup>4,5</sup> In addition, isoxazolines can serve as versatile precursors in organic synthesis.<sup>6</sup> Recently, the synthesis of isoxazolines from  $\beta$ , $\gamma$ -unsaturated oximes has been achieved via a novel C–O bond-forming cyclization strategy.<sup>7-11</sup> Such a synthetic method could construct the isoxazoline skeleton with simultaneous incorporation of one functional group onto the

Figure 1. Isoxazoline-containing biologically active molecules.



glycoprotein IIb/IIIa antagonist





estrogen receptor  $\alpha$  and  $\beta$  agonist

DNA methyltransferase 1 inhibitor

Methiozolin herbicide

 C–C double bond. However, studies in this area are far from being exhaustive. Mild and efficient synthetic approaches to isoxazolines bearing important functionalities remain to be further developed.

The cyano group as a key structural motif is ubiquitous in many medicines, agrochemicals, and organic materials.<sup>12</sup> Also, it is versatile building block that can be readily transformed into diverse derivatives including nitrogen-containing heterocycles, amines, amides, and acids, etc.<sup>13</sup> The methods for the synthesis of nitriles mainly include Sandmeyer reaction,<sup>14</sup> Rosenmund–von Braun reaction,<sup>15</sup> transition-metal-catalyzed cyanation,<sup>16</sup> direct cyanation of C–H bonds,<sup>17-19</sup> and other recently reported transformations.<sup>20</sup> However, difunctionalization of olefins with the simultaneous introduction of a cyano group has been less reported.<sup>21-23</sup> Herein, we report a copper-catalyzed domino cyclization/cyanation of oxime-tethered unactivated olefins with TMSCN as the non-metallic cyanide source and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as the oxidant, thus leading to a wide variety of cyano-containing isoxazolines in good to excellent yields under mild conditions.

Our initial studies were carried out with  $\beta$ , $\gamma$ -unsaturated ketoxime **1a** as a model substrate. To our delight, the desired isoxazoline product **2a** was obtained in 68% yield when **1a** was treated with TMSCN, Cu(OAc)<sub>2</sub> (20 mol %), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and NaHCO<sub>3</sub> in DMSO at rt for 24 h (Table 1, entry 1). Other cyanide sources were also examined, and TMSCN gave the highest yield (Table 1, entries 1–4). The catalytic efficiency of catalysts was next investigated. No product was formed when Fe(acac)<sub>2</sub> or CoCl<sub>2</sub> was used as the catalyst (Table 1, entries 5 and 6). Among the copper

		NOH + [CN] catalyst (20 mol%) oxidant, base solvent, rt, 24 h				
entry	[CN]	catalyst	oxidant	base	2a solvent	yield $(\%)^b$
1	TMSCN	Cu(OAc) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	68
2	Zn(CN) <sub>2</sub>	Cu(OAc) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	54
3	CuCN	Cu(OAc) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	49
4	K <sub>3</sub> Fe(CN) <sub>6</sub>	Cu(OAc) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	0
5	TMSCN	Fe(acac) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	0
6	TMSCN	CoCl <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	0
7	TMSCN	CuCl <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	55
8	TMSCN	Cu(acac) <sub>2</sub>	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	67
9	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	83
10	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$(NH_4)_2S_2O_8$	NaHCO <sub>3</sub>	DMSO	62
11	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	CAN	NaHCO <sub>3</sub>	DMSO	32
12	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	PhI(OAc) <sub>2</sub>	NaHCO <sub>3</sub>	DMSO	trace
13	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	NaOAc	DMSO	53
14	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	29
15	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	КОН	DMSO	57
16	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	NaHCO <sub>3</sub>	DMF	trace
17	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	NaHCO <sub>3</sub>	CH <sub>3</sub> CN	8
18	TMSCN	Cu(NO <sub>3</sub> ) <sub>2</sub> 3H <sub>2</sub> O	$K_2S_2O_8$	NaHCO <sub>3</sub>	dioxane	trace

#### Table 1. Optimization of the Reaction Conditions<sup>a</sup>

<sup>*a*</sup>All reactions were carried out with **1a** (0.40 mmol), cyanide source (0.80 mmol), catalyst (0.080 mmol), oxidant (1.0 mmol), and base (0.60 mmol) in solvent (3.2 mL) at room temperature for 24 h. <sup>*b*</sup>Yield based on **1a**. TMSCN = trimethylsilyl cyanide, CAN = ceric ammonium nitrate.

catalysts tested,  $Cu(NO_3)_2 \ 3H_2O$  was found to be the best catalyst because it afforded the highest product yield (83%) (Table 1, entry 9). Other oxidants such as  $(NH_4)_2S_2O_8$ , CAN, and PhI(OAc)<sub>2</sub> provided lower yield than  $K_2S_2O_8$  (Table 1, entries 9–12). The

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use of other bases gave inferior results for this transformation (Table 1, entry 9 and entries 13–15). Solvent had a remarkable effect on the reaction because DMF,  $CH_3CN$ , and 1,4-dioxane resulted in negligible product yield (Table 1, entries 16–18).

With the optimal reaction conditions in hand, we subsequently turned our attention to investigate the generality of this domino cyclization/cyanation reaction. As shown in Table 2, the current reaction can be extended to a broad range of alkenyl oximes, thus giving the corresponding cyano-substituted isoxazoline products in 59–92% yield. The aryl-substituted substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring proceeded smoothly and afforded the desired products (2a-2m) in good yields. It was noted that the position of substituents on the phenyl ring had little effect on this reaction. Naphthyl and thienyl were also tolerated, leading to the corresponding isoxazoline products (2n and 2o) in 77% and 61% yields, respectively. Pleasingly, primary, secondary, and tertiary alkyl-substituted  $\beta$ , y-unsaturated ketoximes were also effective substrates, affording the desired products 2p-2s in 69-90% yield. Aryl-substituted substrates with substitution at the alkyl chain moieties could also be converted into the corresponding products (2t and 2u) in good yields. The structure of product 2a was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).

To demonstrate the synthetic utility of the present protocol, gram-scale syntheses of isoxazolines **2a** and **2p** were carried out open to air under standard reaction conditions (Scheme 1). This transformation proceeded smoothly to give the products **2a** (1.48 g,

79% yield) and **2p** (1.58 g, 88% yield). Notably, no substantial drop in the yield was observed during the gram-scale synthesis.

# Table 2. Substrate Scope<sup>a,b</sup>



<sup>*a*</sup>All reactions were carried out with  $\beta$ , $\gamma$ -unsaturated ketoxime **1** (0.40 mmol), TMSCN (0.80 mmol), Cu(NO<sub>3</sub>)<sub>2</sub> 3H<sub>2</sub>O (0.080 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (1.0 mmol), and NaHCO<sub>3</sub> (0.60 mmol) in DMSO (3.2 mL) at room temperature for 24 h. <sup>*b*</sup>Yield based on **1**.







To gain some insight into the possible reaction mechanism, several control experiments were carried out using substrate **1a** (Scheme 2). No reaction occurred in the absence of  $Cu(NO_3)_2$  3H<sub>2</sub>O or K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, indicating that both of them are essential for this transformation (Scheme 2, eq 1). Moreover, the addition of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the model reaction resulted in the clean formation of TEMPO-trapped isoxazoline **3** in 81% yield, while the desired product **2a** was not formed (Scheme 2, eq 2). The results suggested that this reaction might proceed via a radical pathway.

#### **Scheme 2. Control Experiments**



Based on the above experimental results and literature reports,  $^{9-11,21b,22c}$  a plausible reaction mechanism is proposed in Scheme 3. Alkenyl oxime **1a** is first oxidized by Cu(II)/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> system to generate O-centered radical **A**, which undergoes an

intramolecular 5-*exo*-trig cyclization to form radical species **B**. The combination of Cu(II) catalyst with intermediate **B** gives Cu(III) species **C**, followed by the reaction with TMSCN to afford Cu(III) intermediate **D**. Subsequent reductive elimination of **D** delivers the desired product **2a** and Cu(I), which is oxidized by  $K_2S_2O_8$  to regenerate the Cu(II) catalyst.



**Scheme 3. Proposed Reaction Mechanism** 

In summary, we have developed a novel, robust, and efficient catalytic system that enables domino cyclization/cyanation of unactivated olefins bearing oximes. A wide range of cyano-substituted isoxazolines can be rapid accessed in high yields with Cu(NO<sub>3</sub>)<sub>2</sub> 3H<sub>2</sub>O as the catalyst and TMSCN as the cyanating agent. This synthetic protocol is characterized by very cheap catalyst, non-metallic cyanide source, high efficiency, mild conditions, broad substrate scope, and gram-scale synthesis, which makes it particularly attractive.

#### **EXPERIMENTAL SECTION**

General Information. All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200-300

mesh). <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz) spectra were recorded on a 400 MHz spectrometer. Chemical shifts ( $\delta$ ) were reported in ppm and coupling constants (*J*) were given in Hertz (Hz). Data were reported as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF ESI mass spectrometer. Melting points were uncorrected. Substrates **1a-1t** were prepared via the allylation<sup>24</sup> of the corresponding aldehyde, oxidation,<sup>25</sup> and oximation.<sup>11b</sup> Alkenyl oxime **1u** was obtained following the reported methods.<sup>26,25,11b</sup>

General Procedure for the Domino Cyclization/Cyanation of Alkenyl Oximes. To a reaction tube equipped with a magnetic stir bar were added oxime 1 (0.40 mmol), TMSCN (79.4 mg, 0.80 mmol), Cu(NO<sub>3</sub>)<sub>2</sub> 3H<sub>2</sub>O (19.3 mg, 0.080 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (270.3 mg, 1.0 mmol), NaHCO<sub>3</sub> (50.4 mg, 0.60 mmol), and DMSO (3.2 mL). The reaction mixture was vigorously stirred at room temperature for 24 h, diluted with water (25 mL), and extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 5:1 or 3:1) to afford product **2**.

2-(3-phenyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2a**). White solid (61.7 mg, 83%); mp 65-67 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 – 7.64 (m, 2H), 7.45 – 7.39 (m, 3H), 5.06 – 4.98 (m, 1H), 3.61 (dd, J = 17.0, 10.3 Hz, 1H), 3.26 (dd, J = 17.0, 6.3 Hz, 1H), 2.79 (dd, J = 16.8, 5.3 Hz, 1H), 2.72 (dd, J = 16.8, 6.6 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.3, 130.6, 128.8, 128.5, 126.8, 116.0, 75.5, 40.0, 23.6; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>NaO 209.0685, found 209.0689.

2-(3-(2-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2b**). Yellow oil (60.8 mg, 70%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (dd, J = 7.7, 1.6 Hz, 1H), 7.43 – 7.37 (m, 1H), 6.96 (dd, J = 17.4, 8.0 Hz, 2H), 4.99 – 4.91 (m, 1H), 3.86 (s, 3H), 3.70 (dd, J = 17.7, 10.2 Hz, 1H), 3.37 (dd, J = 17.7, 6.0 Hz, 1H), 2.74 (dd, J = 16.8, 5.4 Hz, 1H), 2.68 (dd, J = 16.8, 6.6 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.5, 155.9, 131.8, 129.3, 120.8, 117.6, 116.3, 111.3, 75.4, 55.4, 42.6, 23.4; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> 217.0972, found 217.0970.

2-(3-(o-tolyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2c**). Yellow oil (47.5 mg, 59%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.35 – 7.31 (m, 2H), 7.30 – 7.23 (m, 2H), 5.01 – 4.93 (m, 1H), 3.68 (dd, J = 16.9, 10.3 Hz, 1H), 3.30 (dd, J = 16.9, 6.1 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.56 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.1, 138.1, 131.7, 129.8, 128.9, 127.5, 125.9, 116.1, 74.5, 42.5, 23.5, 22.9; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO 223.0842, found 223.0853.

2-(3-(2-chlorophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (2d). Colorless oil (73.1 mg, 83%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.61 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.39 – 7.28 (m, 2H), 5.08 – 5.00 (m, 1H), 3.76 (dd, J = 17.4, 10.2 Hz, 1H), 3.37 (dd, J = 17.4, 5.9 Hz, 1H), 2.76 (d, J = 5.7 Hz, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.3, 132.7, 131.3, 130.5, 130.5, 127.9, 127.1, 116.1, 76.0, 42.2, 23.3; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>ClN<sub>2</sub>NaO 243.0296, found 243.0306.

2-(3-(3-bromophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2e**). Yellow viscous oil (97.4 mg, 92%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (s, 1H), 7.62 – 7.52 (m, 2H), 7.33 – 7.26 (m, 1H), 5.09 – 5.00 (m, 1H), 3.58 (dd, *J* = 17.0, 10.5 Hz, 1H), 3.22 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.84 – 2.72 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.3, 133.4, 130.4, 130.3, 129.6, 125.3, 122.8, 116.0, 75.8, 39.6, 23.5; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>BrN<sub>2</sub>O 264.9971, found 264.9984.

2-(3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2***f*). Light yellow solid (65.6 mg, 76%); mp 96-98 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.58 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.00 – 4.91 (m, 1H), 3.82 (s, 3H), 3.55 (dd, *J* = 16.9, 10.2 Hz, 1H), 3.20 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.79 – 2.65 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.3, 155.8, 128.3, 120.9, 116.2, 114.1, 75.2, 55.3, 40.1, 23.4; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO<sub>2</sub> 239.0791, found 239.0786.

2-(3-(*p*-tolyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2g**). White solid (64.7 mg, 81%); mp 69-71 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.02 – 4.94 (m, 1H), 3.57 (dd, *J* = 16.9, 10.3 Hz, 1H), 3.22 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.37 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.3, 140.9, 129.4, 126.7, 125.6, 116.1, 75.3, 40.0, 23.5, 21.4; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO 223.0842, found 223.0850.

2-(3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2h**). White solid (70.8 mg, 80%); mp 117-119 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.57 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 5.06 – 4.97 (m, 1H), 3.57 (dd, J = 17.0, 10.4 Hz, 1H), 3.21 (dd, J = 17.0, 6.4 Hz, 1H), 2.82 – 2.69 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 

155.4, 136.5, 129.0, 128.0, 126.9, 116.0, 75.7, 39.7, 23.5; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>ClN<sub>2</sub>NaO 243.0296, found 243.0295.

2-(3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (2i). Light yellow solid (64.7 mg, 79%); mp 89-91 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 – 7.61 (m, 2H), 7.13 - 7.06 (m, 2H), 5.05 – 4.97 (m, 1H), 3.58 (dd, *J* = 16.9, 10.3 Hz, 1H), 3.23 (dd, *J* = 16.9, 6.4 Hz, 1H), 2.82 – 2.69 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  163.9 (d, *J* = 250.0 Hz), 155.3, 128.8 (d, *J* = 8.5 Hz), 124.3 (d, *J* = 3.4 Hz), 116.01, 115.95 (d, *J* = 21.9 Hz), 75.6, 39.9, 23.5; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>FN<sub>2</sub>O 205.0772, found 205.0786.

2-(3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2***j*). White solid (78.4 mg, 77%); mp 96-98 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 5.12 – 5.03 (m, 1H), 3.63 (dd, *J* = 17.0, 10.5 Hz, 1H), 3.28 (dd, *J* = 17.0, 6.5 Hz, 1H), 2.85 – 2.73 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.3, 132.1 (q, *J* = 32.5 Hz), 131.90, 131.89, 127.1, 125.8 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 270.6 Hz), 115.8, 76.1, 39.5, 23.6; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O 255.0740, found 255.0745.

2-(3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2k**). Light yellow solid (57.2 mg, 62%); mp 151-153 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.27 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 5.17 – 5.07 (m, 1H), 3.66 (dd, J = 17.0, 10.6 Hz, 1H), 3.31 (dd, J = 17.0, 6.4 Hz, 1H), 2.90 – 2.76 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.8, 148.7, 134.5, 127.6, 124.1, 115.7, 76.5, 39.3, 23.6. HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>NaO<sub>3</sub> 254.0536; found 254.0541.

2-(3-(2,3-dimethoxyphenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2l**). Colorless oil (73.1 mg, 74%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.29 (dd, J = 7.9, 1.2 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 8.1, 1.3 Hz, 1H), 5.01 – 4.92 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.69 (dd, J = 17.7, 10.3 Hz, 1H), 3.35 (dd, J = 17.7, 6.1 Hz, 1H), 2.77 – 2.66 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  155.4, 153.0, 147.5, 124.3, 122.9, 120.5, 116.1, 114.2, 75.5, 61.1, 55.8, 42.1, 23.4; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> 247.1077, found 247.1073.

2-(3-(3,4-dichlorophenyl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2m**). White solid (71.7 mg, 70%); mp 95-97 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (d, J = 0.8 Hz, 1H), 7.50 – 7.45 (m, 2H), 5.08 – 5.00 (m, 1H), 3.56 (dd, J = 17.0, 10.4 Hz, 1H), 3.21 (dd, J = 17.0, 6.5 Hz, 1H), 2.83 – 2.72 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.6, 134.6, 133.1, 130.8, 128.4, 125.8, 115.8, 76.0, 39.5, 23.5; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>C<sub>12</sub>N<sub>2</sub>O 255.0086, found 255.0100.

2-(3-(naphthalen-2-yl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2n**). Light yellow solid (72.6 mg, 77%); mp 123-124 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (dd, J =8.7, 1.6 Hz, 1H), 7.88 (s, 1H), 7.86 – 7.81 (m, 3H), 7.57 – 7.49 (m, 2H), 5.09 – 5.00 (m, 1H), 3.68 (dd, J = 16.8, 10.3 Hz, 1H), 3.35 (dd, J = 16.8, 6.3 Hz, 1H), 2.81 (dd, J =16.9, 5.4 Hz, 1H), 2.74 (dd, J = 16.9, 6.6 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.4, 134.1, 132.8, 128.6, 128.3, 127.8, 127.4, 127.3, 126.8, 126.0, 123.2, 116.1, 75.7, 39.9, 23.5; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O 237.1022, found 237.1029. 2-(3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)acetonitrile (**2o**). White solid (47.1 mg, 61%); mp 72-74 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.42 (d, J = 5.1 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.07 (dd, J = 5.0, 3.7 Hz, 1H), 5.04 – 4.96 (m, 1H), 3.61 (dd, J = 16.8, 10.2 Hz, 1H), 3.26 (dd, J = 16.8, 6.4 Hz, 1H), 2.78 (dd, J = 16.9, 5.4 Hz, 1H), 2.72 (dd, J = 16.9, 6.5 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.1, 130.7, 129.2, 128.9, 127.4, 115.0, 75.7, 40.6, 23.4; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>9</sub>N<sub>2</sub>OS 193.0430, found 193.0441.

2-(3-pentyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2***p*). Light yellow oil (64.7 mg, 90%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.85 – 4.76 (m, 1H), 3.18 (dd, *J* = 17.3, 10.2 Hz, 1H), 2.81 (dd, *J* = 17.3, 6.1 Hz, 1H), 2.70 – 2.57 (m, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), 1.61 – 1.51 (m, 2H), 1.36 – 1.28 (m, 4H), 0.88 (t, *J* = 6.6 Hz, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 116.2, 74.2, 42.0, 31.2, 27.3, 25.8, 23.5, 22.2, 13.8; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>17</sub>N<sub>2</sub>O 181.1335, found 181.1333.

2-(3-benzyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2***q*). Yellow oil (68.2 mg, 85%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 – 7.27 (m, 3H), 7.26 – 7.20 (m, 2H), 4.83 – 4.74 (m, 1H), 3.70 (s, 2H), 3.08 (dd, *J* = 17.5, 10.3 Hz, 1H), 2.69 (dd, *J* = 17.5, 6.3 Hz, 1H), 2.65 – 2.54 (m, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  157.8, 134.9, 128.8, 128.7, 127.2, 116.1, 74.7, 41.2, 33.7, 23.4; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO 223.0842, found 223.0847.

2-(3-cyclohexyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2r**). Light yellow oil (52.9 mg, 69%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.83 – 4.74 (m, 1H), 3.18 (dd, J = 17.2, 10.2 Hz, 1H), 2.81 (dd, J = 17.2, 5.8 Hz, 1H), 2.67 – 2.56 (m, 2H), 2.46 – 2.38 (m,

 1H), 1.90 – 1.66 (m, 5H), 1.40 – 1.20 (m, 5H);  $^{13}C\{^{1}H\}$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 162.4, 116.2, 73.9, 40.3, 37.0, 30.24, 30.15, 25.7, 25.5, 23.5; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>NaO 215.1155, found 215.1163.

2-(3-(*tert-butyl*)-4,5-*dihydroisoxazol*-5-*yl*)*acetonitrile* (**2***s*). Colorless oil (49.1 mg, 74%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.85 – 4.77 (m, 1H), 3.22 (dd, *J* = 17.2, 10.2 Hz, 1H), 2.86 (dd, *J* = 17.2, 5.8 Hz, 1H), 2.68 – 2.57 (m, 2H), 1.21 (s, 9H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 116.2, 74.5, 39.3, 33.0, 27.9, 23.5; HRMS (ESI-TOF) m/z: [M+H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>15</sub>N<sub>2</sub>O 167.1179, found 167.1179.

2-(5-methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2t**). Colorless oil (57.1 mg, 71%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 – 7.61 (m, 2H), 7.45 – 7.37 (m, 3H), 3.39 (d, *J* = 17.0 Hz, 1H), 3.25 (d, *J* = 17.0 Hz, 1H), 2.77 (d, *J* = 17.2 Hz, 1H), 2.73 (d, *J* = 17.2 Hz, 1H), 1.67 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.6, 130.4, 128.9, 128.7, 126.6, 116.4, 83.6, 45.3, 28.9, 25.0; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>NaO 223.0842, found 223.0845.

2-(4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)acetonitrile (**2u**). Colorless oil (68.4 mg, 80%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 – 7.57 (m, 2H), 7.46 – 7.37 (m, 3H), 4.44 (t, *J* = 6.6 Hz, 1H), 2.77 (dd, *J* = 16.9, 6.4 Hz, 1H), 2.68 (dd, *J* = 16.9, 6.8 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.7, 130.0, 128.6, 128.2, 127.4, 116.3, 85.0, 51.7, 25.1, 18.9, 17.9; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>NaO 237.0998, found 237.1005.

**Procedure for the Radical Trapping Experiment (Scheme 2, eq 2).** To a reaction tube equipped with a magnetic stir bar were added oxime **1a** (64.5 mg, 0.40

mmol), TMSCN (79.4 mg, 0.80 mmol), Cu(NO<sub>3</sub>)<sub>2</sub> 3H<sub>2</sub>O (19.3 mg, 0.080 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (270.3 mg, 1.0 mmol), NaHCO<sub>3</sub> (50.4 mg, 0.60 mmol), TEMPO (250.0 mg, 1.60 mmol), and DMSO (3.2 mL). The mixture was stirred at room temperature for 24 h, diluted with water (25 mL), and extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give TEMPO-trapped isoxazoline **3** (102.4 mg, 81%) as a white solid. mp 76-78 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 – 7.66 (m, 2H), 7.43 – 7.37 (m, 3H), 4.92 – 4.82 (m, 1H), 4.02 – 3.93 (m, 2H), 3.38 (dd, *J* = 16.4, 10.9 Hz, 1H), 3.25 (dd, *J* = 16.4, 7.5 Hz, 1H), 1.58 – 1.28 (m, 6H), 1.19 (s, 6H), 1.07 (d, *J* = 2.1 Hz, 6H); <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  156.1, 129.9, 129.7, 128.6, 126.6, 79.1, 77.6, 60.0, 39.6, 37.0, 33.0, 32.9, 20.1, 17.0; HRMS (ESI-TOF) m/z: [M+Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>NaO<sub>2</sub> 339.2043, found 339.2045.

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: ygzhu@njau.edu.cn

#### ORCID

 Yingguang Zhu: 0000-0002-0429-6369

#### Notes

The authors declare no competing financial interest.

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#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI:

<sup>1</sup>H and <sup>13</sup>C $\{^{1}H\}$  NMR spectra of the synthesized compounds (PDF)

Crystallographic information for product 2a (CIF)

## REFERENCES

(1) For selected reviews, see: (a) Minatti, A.; Muñiz, K. Chem. Soc. Rev. 2007, 36, 1142. (b) Chemler, S. R.; Bovino, M. T. ACS Catal. 2013, 3, 1076. (c) Merino, E.; Nevado, C. Chem. Soc. Rev. 2014, 43, 6598. (d) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. Chem. Rev. 2014, 114, 8199. (e) Beccalli, E. M.; Broggini, G.; Gazzola, S.; Mazza, A. Org. Biomol. Chem. 2014, 12, 6767. (f) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. Acc. Chem. Res. 2014, 47, 3665. (g) Koike, T.; Akita, M. Acc. Chem. Res. 2016, 49, 1937. (h) Yin, G.; Mu, X.; Liu, G. Acc. Chem. Res. 2016, 49, 2413.

(2) For selected reviews, see: (a) Pintauer, T.; Matyjaszewski, K. Chem. Soc. Rev.

2008, *37*, 1087. (b) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* 2011, *40*, 114. (c)
Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* 2014, *53*, 8294. (d) Chen, Z.-M.;
Zhang, X.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* 2015, *44*, 5220. (e) Cao, M.-Y.; Ren, X.; Lu,
Z. *Tetrahedron Lett.* 2015, *56*, 3732. (f) Kindt, S.; Heinrich, M. R. *Synthesis* 2016, *48*, 1597. (g) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* 2016, *55*, 58.

(3) For selected reviews, see: (a) Chen, J.-R.; Yu, X.-Y.; Xiao, W.-J. Synthesis 2015, 47, 604. (b) Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H. Synthesis 2015, 47, 1195. (c) Li, C.-C.; Yang, S.-D. Org. Biomol. Chem. 2016, 14, 4365.

(4) (a) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang,
S.; Jiang, B.; Emmett, G.; Ma, P.; Mousa, S. A.; Ma, P.; Olson, R. E.; Wexler, R. R. J. *Med. Chem.* 1997, 40, 50. (b) Poutiainen, P. K.; Ven ä änen, T. A.; Per äkyl ä, M.;
Matilainen, J. M.; V äs änen, S.; Honkakoski, P.; Laatikainen, R.; Pulkkinen, J. T. *Bioorg. Med. Chem.* 2010, 18, 3437. (c) Cheng, J.-F.; Huang, Y.; Penuliar, R.;
Nishimoto, M.; Liu, L.; Arrhenius, T.; Yang, G.; O'Leary, E.; Barbosa, M.; Barr, R.;
Dyck, J. R. B.; Lopaschuk, G. D.; Nadzan, A. M. J. Med. Chem. 2006, 49, 4055. (d)
Castellano, S.; Kuck, D.; Viviano, M.; Yoo, J.; López-Vallejo, F.; Conti, P.; Tamborini,
L.; Pinto, A.; Medina-Franco, J. L.; Sbardella, G. J. Med. Chem. 2011, 54, 7663.

(5) (a) Grossmann, K.; Ehrhardt, T. *Pest Manag. Sci.* 2007, *63*, 429. (b) Hwang, I.
T.; Kim, H. R.; Jeon, D. J.; Hong, K. S.; Song, J. H.; Cho, K. Y. *J. Agric. Food Chem.*2005, *53*, 8639. (c) Hwang, K.-H.; Lim, J.-S.; Kim, S.-H.; Jeon, M.-S.; Lee, D.-G.;
Chung, K.-H.; Koo, S.-J.; Kim, J.-H. *J. Agric. Food Chem.* 2013, *61*, 9285.

#### The Journal of Organic Chemistry

(6) (a) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. Angew. Chem., Int. Ed.
2001, 40, 2082. (b) Minter, A. R.; Fuller, A. A.; Mapp, A. K. J. Am. Chem. Soc. 2003,
125, 6846. (c) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. J. Am. Chem. Soc.

, *127*, 5376.

(7) For selected examples, see: (a) Jiang, D.; Peng, J.; Chen, Y. Org. Lett. 2008, 10, 1695. (b) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. J. Am. Chem. Soc. 2010, 132, 6284; (c) Triandafillidi, I.; Kokotos, C. G. Org. Lett. 2017, 19, 106.

(8) Tripathi, C. B.; Mukherjee, S. Angew. Chem., Int. Ed. 2013, 52, 8450.

(9) (a) Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* 2012, *51*, 8816. (b) Zhu, L.; Yu, H.; Xu, Z.; Jiang, X.; Lin, L.; Wang, R. *Org. Lett.* 2014, *16*, 1562. (c) Peng, X.-X.; Deng, Y.-J.; Yang, X.-L.; Zhang, L.; Yu, W.; Han, B. *Org. Lett.* 2014, *16*, 4650. (d) Zhang, X.-W.; Xiao, Z.-F.; Zhuang, Y.-J.; Wang, M.-M.; Kang, Y.-B. *Adv. Synth. Catal.* 2016, *358*, 1942. (e) Liu, R.-H.; Wei, D.; Han, B.; Yu, W. *ACS Catal.* 2016, *6*, 6525. (f) Hu, X.-Q.; Chen, J.; Chen, J.-R.; Yan, D.-M.; Xiao, W.-J. *Chem. - Eur. J.* 2016, *22*, 14141.

(10) (a) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang,
Y.-M.; *Chem. Commun.* 2013, 49, 5687. (b) Zhu, L.; Wang, G.; Guo, Q.; Xu, Z.;
Zhang, D.; Wang, R. *Org. Lett.* 2014, 16, 5390. (c) Wei, Q.; Chen, J.-R.; Hu, X.-Q.;
Yang, X.-C.; Lu, B.; Xiao, W.-J. *Org. Lett.* 2015, 17, 4464.

(11) (a) Liu, Y.-Y.; Yang, J.; Song, R.-J.; Li, J.-H. Adv. Synth. Catal. 2014, 356, 2913. (b) Kong, W.; Guo, Q.; Xu, Z.; Wang, G.; Jiang, X.; Wang, R. Org. Lett. 2015, 17, 3686. (c) Zhao, J.; Jiang, M.; Liu, J.-T. Adv. Synth. Catal. 2017, 359, 1626.

(12) (a) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983. (b) Miller, J. S.;
Manson, J. L. Acc. Chem. Res. 2001, 34, 563.

(13) (a) Larock, R. C. Comprehensive Organic Transformations; Wiley-VCH: New York, 1989; p 819. (b) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. J. Am. Chem. Soc. 2005, 127, 9260. (c) Liskey, C. W.; Liao, X.; Hartwig, J. F. J. Am. Chem. Soc. 2010, 132, 11389.

(14) (a) Sandmeyer, T. Ber. Dtsch. Chem. Ges. 1884, 17, 1633. (b) Galli, C. Chem. Rev. 1988, 88, 765.

(15) (a) Rosenmund, K. W.; Struck, E. Chem. Ber. 1919, 52, 1749. (b) Ellis, G. P.;
Romney-Alexander, T. M. Chem. Rev. 1987, 87, 779.

(16) For selected recent publications, see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* 2011, *40*, 5049. (b) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* 2011, *50*, 519. (c) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* 2015, *137*, 13902. (d) Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* 2017, *8*, 1790.

(17) For selected publications on the direct cyanation of C(sp<sup>3</sup>)–H bonds, see: (a)
Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. J. Am. Chem. Soc. 2003, 125,
15312. (b) North, M. Angew. Chem., Int. Ed. 2004, 43, 4126. (c) Tajima, T.; Nakajima,
A. J. Am. Chem. Soc. 2008, 130, 10496. (d) Ma, L.; Chen, W.; Seidel, D. J. Am. Chem.
Soc. 2012, 134, 15305. (e) Ping, Y.; Ding, Q.; Peng, Y. ACS Catal. 2016, 6, 5989. (f)
Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Science

, *353*, 1014.

(18) For selected publications on the direct cyanation of C(sp<sup>2</sup>)–H bonds, see: (a)
Kim, J.; Chang, S. J. Am. Chem. Soc. 2010, 132, 10272. (b) Ren, X.; Chen, J.; Chen,
F.; Cheng, J. Chem. Commun. 2011, 47, 6725. (c) Kim, J.; Kim, H. J.; Chang, S.
Angew. Chem., Int. Ed. 2012, 51, 11948. (d) Gong, T.-J.; Xiao, B.; Cheng, W.-M.; Su,
W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. J. Am. Chem. Soc. 2013, 135, 10630. (e) Yu,
D.-G.; Gensch, T.; Azambuja, F. D.; V ásquez-C éspedes, S.; Glorius, F. J. Am. Chem.
Soc. 2014, 136, 17722. (f) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J.
Angew. Chem., Int. Ed. 2014, 53, 2186. (g) Yang, Y.; Buchwald, S. L. Angew. Chem.,
Int. Ed. 2014, 53, 8677. (h) Li, J.; Ackermann, L. Angew. Chem., Int. Ed. 2015, 54,
3635. (i) McManus, J. B.; Nicewicz, D. A. J. Am. Chem. Soc. 2017, 139, 2880.

(19) For a recent example on the direct cyanation of C(sp)–H bonds, see: Rong, G.;Mao, J.; Zheng, Y.; Yao, R.; Xu, X. *Chem. Commun.* 2015, *51*, 13822.

(20) For selected publications, see: (a) Wang, T.; Jiao, N. J. Am. Chem. Soc. 2013, 135, 11692. (b) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. Angew. Chem., Int. Ed. 2013, 52, 10573. (c) Wang, T.; Jiao, N. Acc. Chem. Res. 2014, 47, 1137. (d) Wu, Q.; Luo, Y.; Lei, A.; You, J. J. Am. Chem. Soc. 2016, 138, 2885.

(21) (a) Yamasaki, S.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2001, 123, 1256.
(b) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang Q. Angew.
Chem., Int. Ed. 2013, 52, 2529. (c) Quinn, R. K.; Schmidt, V. A.; Alexanian, E. J.
Chem. Sci. 2013, 4, 4030. (d) Wang, D.; Wang, F.; Chen, P.; Lin, Z.; Liu, G. Angew.
Chem., Int. Ed. 2017, 56, 2054. During the preparation of this manuscript, a novel

oxycyanation of olefins using stoichiometric CuCN as the cyanide source in the presence of a triamine ligand (2.5 equiv) was reported by Han and co-workers, see: (e) Chen, F.; Zhu, F.-F.; Zhang, M.; Liu, R.-H.; Yu, W.; Han, B. *Org. Lett.* **2017**, *19*, 3255.

(22) (a) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. Chem. - Eur. J. 2007, 13, 961. (b) He,

Y.-T.; Li, L.-H.; Yang, Y.-F.; Zhou, Z.-Z.; Hua, H.-L.; Liu, X.-Y.; Liang, Y.-M. Org.

Lett. 2014, 16, 270. (c) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. J. Am.

Chem. Soc. 2016, 138, 15547.

(23) Fang, X.; Yu, P.; Morandi, B. Science 2016, 351, 832.

(24) Imai, T.; Nishida, S. Synthesis 1993, 395.

(25) Rajam, S.; Jadhav, A.V.; Li, Q.; Sarkar, S. K.; Singh, P. N. D.; Rohr, A.; Pace,

T. C. S.; Li, R.; Krause, J. A.; Bohne, C.; Ault, B. S.; Gudmundsdottir, A. D. J. Org. *Chem.* **2014**, *79*, 9325.

(26) Kobayashi, S.; Nishio, K. Chem. Lett. 1994, 23, 1773.