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An aerobic Cu-mediated practical approach to aromatic nitriles using cyanide anions as the nitrogen source†

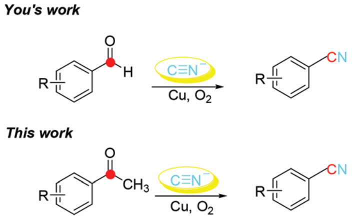
Lijun Gu,*[a] Cheng Jin,[b] Hongtao Zhang,[a] Jiyan Liu,[a] Ganpeng Li*[a] and Zhi Yang[c]

A Cu-mediated cyanation of aryl methyl ketones using cyanide anions as the nitrogen source was achieved to provide aromatic nitriles in moderate to good yields. The reaction tolerates a variety of synthetically important functional groups.

The nitrile group is a prevalent functional group in organic synthesis.[1] In particular, aromatic nitriles are a class of valuable compounds with numerous applications in various areas, including pharmaceuticals, dyes, pesticides, and materials.[2,3] In addition, aromatic nitriles are also potent intermediates in fine chemical synthesis because the nitrile group can be easily used for functional group transformations, including the formation of amines, amides, acids, aldehydes and heterocycles. As a result, the development of new methods used to prepare aromatic nitriles has been intensively studied in synthetic organic chemistry.

Traditional synthetic methods are the Sandmeyer reaction and the Rosenmund–von Braun reaction.[4] The nucleophilic cyanation of aryl halides under transition metal catalysis with cyanating agents has emerged as an alternative route to aryl nitriles.[5] Recently, transition-metal-catalyzed C–H bond functionalization has enabled the direct cyanation of aromatic C–H bonds.[6] The cleavage of C–C single bonds in a selective manner is a very important reaction in both academic research and industrial applications. The chemoselective C(CO)–C(α) bond cleavage of ketones is a fundamental reaction that has been extensively studied.[7] Very recently, the Guo group has reported the copper-catalyzed aerobic synthesis of aromatic nitriles from ketones *via* C(CO)–C(α) bond cleavage.[8] Ammonium salts are used as the nitrogen source in the conversion. However, in contrast to ammonium salts used as the nitrogen source in the synthesis of aromatic nitriles, using a coordinated cyanide anion (CN−) as the nitrogen source is more challenging because the negatively charged cyanide anion is usually regarded as a pseudohalide and exists as an integrated component in many chemical reactions. Very recently, Lei and You developed a copper-catalyzed aerobic conversion of the C═O bond of aldehydes to a C≡N bond using coordinated cyanide anions as the nitrogen source.[9] Given the importance of aromatic nitriles, we disclose herein our preliminary results on the copper-catalyzed conversion of aromatic ketones to aromatic nitriles using coordinated cyanide anions as the nitrogen source in the presence of molecular oxygen. The protocol involves the cleavage of the C(CO)–C(α) single bond of ketones and the C≡N triple bond of the cyanide anion (Scheme 1).

We started our investigation on ketone nitrogenation employing acetophenone **1a** as a model substrate. Specifically, treatment of acetophenone **1a** with CuCN at 150 °C for 14 hours under an oxygen atmosphere led to the formation of the desired benzonitrile **2a** in 76% yield (Table 1, entry 1). Solvent screening revealed that DMF gave a lower yield (49%) (Table 1, entry 2), while the other solvents studied such as DCE, NMP and $PhCF_3$ were all inferior in terms of the reaction yield (Table 1, entries 3–5). Replacement of CuCN with the $CuBr_2/K_3[Fe(CN)_6]$ system gave a comparable yield (61%) (Table 1, entry 6). Changing CuCN to $Cu(OAc)_2/K_3[Fe(CN)_6]$, $CuCl_2/K_3[Fe(CN)_6]$, $CuCl/K_3[Fe(CN)_6]$ or $CuBr/K_3[Fe(CN)_6]$ diminished the reactivity (Table 1, entries 7–10). No desired



Scheme 1 Synthetic route to aromatic nitriles using cyanide anions as the nitrogen source.

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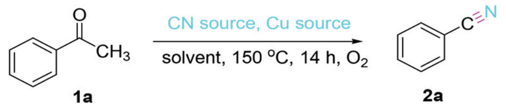
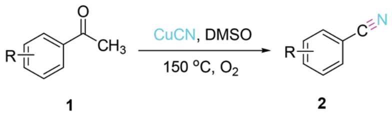
Table 1 Optimization of the reaction conditions[a]

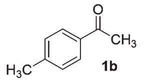
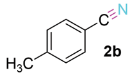
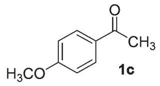
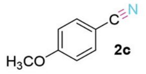
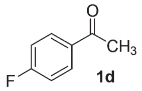
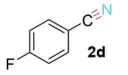
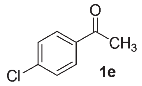
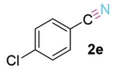
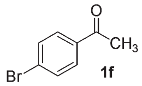
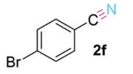
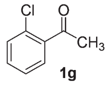
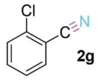
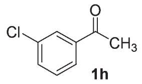
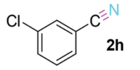
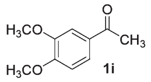
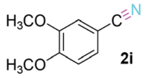
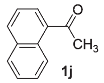
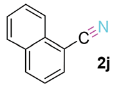
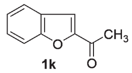
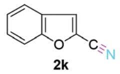
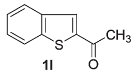
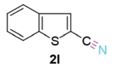
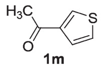
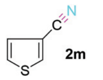
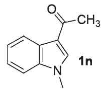
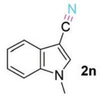


Entry	Cyanide	Cu source	Solvent	Yield[b] (%)
1	None	CuCN	DMSO	76
2	None	CuCN	DMF	49
3	None	CuCN	DCE	Trace
4	None	CuCN	NMP	11
5	None	CuCN	$PhCF_3$	Trace
6	$K_3[Fe(CN)_6]$	$CuBr_2$	DMSO	61
7	$K_3[Fe(CN)_6]$	$Cu(OAc)_2$	DMSO	33
8	$K_3[Fe(CN)_6]$	$CuCl_2$	DMSO	17
9	$K_3[Fe(CN)_6]$	CuCl	DMSO	25
10	$K_3[Fe(CN)_6]$	CuBr	DMSO	13
11[c]	None	CuCN	DMSO	0
12[d]	None	CuCN	DMSO	0

[a] Reaction conditions: **1a** (0.5 mmol), Cu source (0.7 mmol), $K_3[Fe(CN)_6]$ (0.2 mmol), solvent (2 mL), 150 °C in O_2 for 14 h. [b] Isolated yield. [c] $K_2S_2O_8$ was used as the oxidant, in Ar for 20 h. [d] Under an Ar atmosphere.

Table 2 Scope of aryl methyl ketones[a]



Entry	Ketone **1**	Product **3**	Yield[b] (%)
1	 **1b**	 **2b**	71
2	 **1c**	 **2c**	67
3	 **1d**	 **2d**	76
4	 **1e**	 **2e**	70
5	 **1f**	 **2f**	62
6	 **1g**	 **2g**	69
7	 **1h**	 **2h**	78
8	 **1i**	 **2i**	65
9	 **1j**	 **2j**	57
10	 **1k**	 **2k**	66
11	 **1l**	 **2l**	72
12	 **1m**	 **2m**	63
13	 **1n**	 **2n**	74

[a] Reaction conditions: **1a** (0.5 mmol), CuCN (0.7 mmol), DMSO (2 mL), 150 °C in O_2 for 14–16 h. [b] Isolated yield.

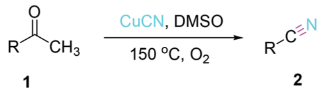
benzonitrile **2a** was obtained when $K_2S_2O_8$ was used as the oxidant (Table 1, entry 11). Reactions in the absence of an oxygen atmosphere did not generate a detectable amount of product **2a** (Table 1, entry 12). The results imply that O_2 is crucial to the cyanation reaction.

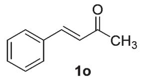
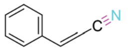
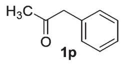
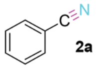
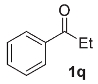
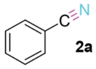
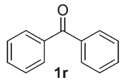
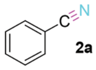
With the optimized reaction conditions in hand, we went on to explore the scope of the copper-promoted cyanation reaction and found that the transformation was compatible with a wide range of functional groups. Several substituted acetophenones reacted smoothly with the CuCN/O_2 system to generate the corresponding aryl nitriles in moderate to good yields under the optimized conditions (Table 2). Electron-donating and electron-withdrawing groups on the aryl ring of the aryl methyl ketone moiety were compatible with the reaction conditions and halide substituents, such as F, Cl and Br, did not affect the reactivity of the substrates. Substituents in the *para*-, *meta*- or *ortho*-position of the phenyl ring were well tolerated. For example, substrates **1e**, **1g**, and **1h** with a Cl group were transformed into products **2e**, **2g**, and **2h**, respectively, in good yield. Importantly, the polysubstituted derivative **1i** gave the desired product **2i** in good yield. Aromatic methyl ketone **1j** with a naphthyl group also participated in this Cu-mediated cyanation reaction, affording the desired product in 57% yield (Table 2, entry 9). It is worth noting that the heteroaryl groups worked well to afford the corresponding products in good yield (Table 2, entries 10–13).

Highlighting the utility of this transformation, some representative acetophenone derivatives were selected and subjected to the standard conditions. When α,β-unsaturated ketone was employed as the substrate, the reaction proceeded smoothly and gave the desired product in 61% yield (Table 3, entry 1). It was found that aliphatic ketone **1p** could also achieve this conversion (Table 3, entry 2). Unfortunately, propiophenone or benzophenone did not deliver the corresponding nitrile under the same reaction conditions (Table 3, entries 3 and 4).

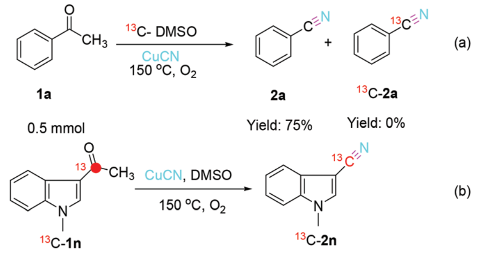
In order to have some information on the reaction mechanism of this cyanation process, some control experiments were carried out. It was found that ^{13}C-DMSO instead of DMSO as the solvent could not lead to the ^{13}C-labelled product under standard conditions, which eliminated the possibility of the

Table 3 Scope of ketones[a]

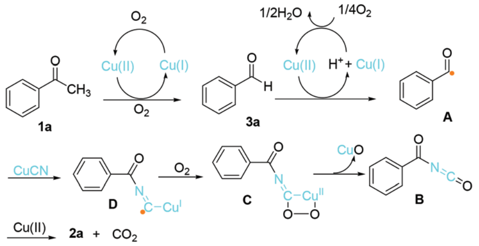


Entry	Ketone **1**	Product **3**	Yield[b] (%)
1	 **1o**	 **2o**	61
2	 **1p**	 **2a**	70
3	 **1q**	 **2a**	0
4	 **1r**	 **2a**	0

[a] Reaction conditions: **1a** (0.5 mmol), CuCN (0.7 mmol), DMSO (2 mL), 150 °C in O$_2$ for 16 h. [b] Isolated yield.



Scheme 2 Experiments for mechanistic studies.



Scheme 3 Possible mechanism.

carbon atom in the cyano group derived from DMSO (Scheme 2a). A ^{13}C-labelled product was generated in 73% yield using a ^{13}C-carbonyl-labelled ketone **1n** as the reagent, which certainly excluded the deacylative cyanation reaction of the aryl methyl ketone (Scheme 2b). The replacement of CuCN with sodium cyanate resulted in a trace amount of benzonitrile.[10] Further GC-MS detection of the gas phase of the reaction revealed that no NH$_3$ was generated during the reaction. The results indicate that the conversion of the C═O bond of the aryl methyl ketone to a C≡N bond *via* an imine intermediate, followed by oxidation of the imine to the nitrile could be ruled out.

We supposed that methyl benzoate might be the intermediate. To probe this, methyl benzoate was treated under the standard reaction conditions. To our surprise, no desired product was observed, which provided evidence that the reaction does not proceed *via* an ester intermediate. It has been reported that an aryl methyl ketone can be transformed into an aryl aldehyde.[11] Then, the aldehyde undergoes the cyanation reaction to form a nitrile. Benzaldehyde **3a** was subjected to the optimized reaction conditions. The desired benzonitrile **2a** was obtained in 49% yield. The results indicate that benzaldehyde may be involved in this process. When 5.0 equivalents of TEMPO, a radical-trapping reagent, were added to the reaction under standard conditions no desired product was obtained, suggesting that free radical intermediates may be involved in the reaction.

On the basis of these preliminary results and previous studies,[8,9] the catalytic cycle of this transformation was hypothesized as shown in Scheme 3. Firstly, Cu^I is oxidized to Cu^{II} under an O$_2$ atmosphere.[12] With the help of Cu^{II} and O$_2$, the substrate **1a** is oxidized to give the corresponding benzaldehyde **3a** *via* cleavage of the C–C bond. Subsequently, the key intermediate **A** is formed through a single electron transfer. At this stage, the reaction of intermediate **A** with CuCN will give the Cu^I-bonded carbon-centered radical intermediate **B** *via* the regioselectivity of C–N bond formation. The subsequent aerobic oxidation of intermediate **B** generates species **C**.[13] At this juncture, the resulting Cu^{II} intermediate **C** will produce benzoyl isocyanate **D**, which will decompose to give benzonitrile **2a** with extrusion of CO$_2$ gas.

In summary, we have developed a Cu-mediated C$_{sp^2}$–C$_{sp^3}$ cleavage reaction toward the formation of aromatic nitriles, using cyanide anions as the nitrogen source. A wide range of functional groups were tolerated under the optimized reaction conditions. In addition, molecular oxygen, the most environmentally friendly oxidant, was employed at a pressure of 1 atmosphere. Due to the easy availability of the starting materials and potential applications of the products, this method is highly promising in organic synthesis. Mechanistic, scope, and limitation studies of the reaction are in progress in our laboratory.

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Notes and references

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