

Aerobic Copper-Promoted Radical-Type Cleavage of Coordinated Cyanide Anion: Nitrogen Transfer to Aldehydes To Form Nitriles

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S Supporting Information

ABSTRACT: We have disclosed for the first time the copper-promoted C≡N triple bond cleavage of coordinated cyanide anion under a dioxygen atmosphere, which enables a nitrogen transfer to various aldehydes. Mechanistic study of this unprecedented transformation suggests that the single electron-transfer process could be involved in the overall course. This protocol provides a new cleavage pattern for the cyanide ion and would eventually lead to a more useful synthetic pathway to nitriles from aldehydes.

Transition-metal-mediated complete cleavage of C≡X (X = C, N, O) triple bonds is believed to be the important source of new organic reactions, but it represents a challenging topic of considerable interest due to the inherent stability of multiple bond linkages.¹ Over the past decades, noteworthy progress for the cleavage of C≡C triple bonds has been made.^{1c,e,f,h} The rupture of C≡N triple bonds as a mechanism for the reorganization of organonitrile molecular skeletons has also been demonstrated. The established metal-mediated methods for the complete cleavage of C≡N bond in organonitriles are mainly dependent on double protonation at the coordinated nitrile carbon, reductive cleavage, and metathesis-type process of metal complexes with organonitriles, resulting in metal nitrile complexes capable of nitrogen transfer (Scheme 1a).^{2–4} In contrast to the CN triple bond of organonitriles, however, the C≡N bond cleavage of a coordinated cyanide anion (CN[−]) remains greatly underrepresented in the literature. Intuitive chemical knowledge would suggest that the cleavage of a

coordinated cyanide anion is significantly more challenging. The negatively charged cyanide anion is commonly regarded as pseudohalide and exists as an integrated component in many chemical reactions. The coordinated cyanide anion in metal complexes exhibits very high stability; experimental and computational investigations have demonstrated that the metal-mediated cleavage of a cyanide anion is difficult to achieve.⁵ Even though a few computational studies on the cleavage of cyanide anion have emerged in recent years, experimentally successful examples are very rare. A representative example of the complete cleavage of a coordinated CN[−], reported by Fehlhammer et al., demonstrates that the dinuclear Na[Fe₂(CN)Cp₂(CO)₃] complex reacts with phthaloyl dichloride to give a tetraferriooxaallenium species and phthalimide (Scheme 1b).⁶ Herein, we wish to disclose a novel transition-metal-promoted radical-type cleavage pattern of a coordinated cyanide anion under a dioxygen atmosphere.

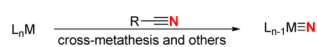
Over the past few years, stoichiometric copper salts as mediators have received great attention as inexpensive, rich, and effective alternatives to noble metal species in organic transformations.^{7,8} The conversion between the different oxidation states of copper (Cu⁰, Cu^I, Cu^{II}, and Cu^{III}) via one- or two-electron process can occur readily. This ability has inspired organic chemists to discover a wide range of stoichiometric and catalytic transformations including both one-electron radical pathways and two-electron reductive elimination pathways. Molecular oxygen is an atom-economical, abundant, and environmental-friendly oxidant. The oxidation of copper in the presence of O₂ can allow ready access to the higher-value peroxy-copper species,⁹ which enables a rich range of transformations involving single electron-transfer (SET) processes.¹⁰

In the course of our research on C(sp³)–H bond activation, we initially aimed to realize the cyanation of C(sp³)–H bond of 8-methylquinoline with potassium hexacyanoferrate(III) (K₃[Fe(CN)₆]). To our surprise, we found that the methyl group of 8-methylquinoline was replaced unexpectedly by the cyano group, affording 8-cyanoquinoline **2v** in 58% instead of 2-(quinolin-8-yl)acetonitrile in the presence of Pd(OAc)₂/CuCl₂ under an oxygen atmosphere (eq 1). Further GC-MS analysis indicated the presence of quinoline-8-carbaldehyde in the reaction system. Subsequently, we found that quinoline-8-carbaldehyde could also smoothly undergo the nitrogenation in 64% yield in the presence of only CuBr₂, whereas the

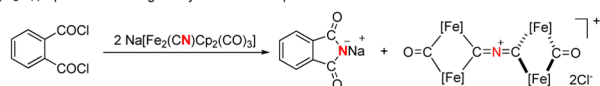
Scheme 1. Transition-Metal-Mediated Complete Cleavage of C≡N Triple Bonds

Previous work

(a) C≡N triple bond cleavage of organonitriles



(b) C≡N triple bond cleavage of cyanide iron complex

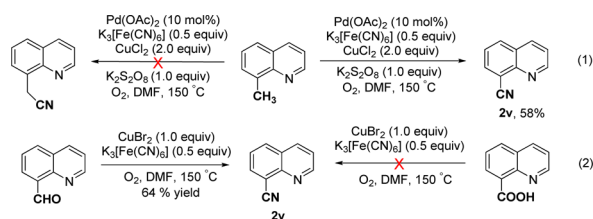


This work



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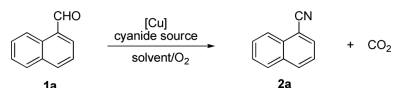
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corresponding carboxylic acid failed to convert to the nitrile (eq 2). These preliminary observations excluded the pathway of decarboxylative cyanation of quinoline-8-carboxylic acid and indicated that the aryl aldehyde was the most likely intermediate.

To gain a better understanding of this unexpected result, we systematically studied the function of each component (Table 1;

Table 1. Nitrogenation of 1-Naphthaldehyde^a



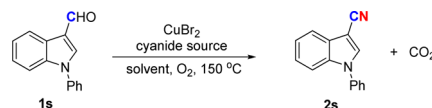
entry	Cu source	cyanide	solvent	yield (%) ^b
1	CuCl ₂	K ₃ [Fe(CN) ₆]	DMF	49
2	CuBr ₂	K ₃ [Fe(CN) ₆]	DMF	80
3	CuBr ₂	K ₃ [Fe(CN) ₆]	DMSO	37
4	CuBr ₂	K ₄ [Fe(CN) ₆]	DMF	20
5	CuBr ₂	KCN	DMF	50
6	CuBr ₂	CuCN	DMF	76
7	CuBr ₂	–	DMF	NR
8	–	K ₃ [Fe(CN) ₆]	DMF	NR
9 ^c	CuBr ₂	K ₃ [Fe(CN) ₆]	DMF	NR
10 ^d	CuBr	K ₃ [Fe(CN) ₆]	DMF	25
11 ^d	CuCl	K ₃ [Fe(CN) ₆]	DMF	30
12 ^d	–	CuCN	DMF	70

^aReaction conditions: **1a** (0.25 mmol), copper source (0.25 mmol), K₃[Fe(CN)₆] (0.125 mmol), or KCN (0.5 mmol) or CuCN (0.5 mmol) at 150 °C under O₂ for 12 h. ^bIsolated yield based on **1a**. ^cUnder N₂ atmosphere. ^dUsing an additional O₂ balloon. NR: no reaction.

for details, see Table S1). We started our investigation on the aldehyde nitrogenation employing 1-naphthaldehyde as a model substrate. The combination of CuCl₂ and K₃[Fe(CN)₆] in DMF at 150 °C provided the cyanated product **2a** in 49% yield (Table 1, entry 1). Subsequently, the copper source proved to be fairly important (Table S1). CuBr₂ gave an improved yield of 80% (Table 1, entry 2). It is notable that O₂ is crucial to this cyanation. Conducting the reaction in an exclusive nitrogen atmosphere shut down the transformation (Table 1, entry 9). Cu^I salts such as CuBr and CuCl, instead of Cu^{II} salts, could also generate the nitrile product, but in relatively lower yields (Table 1, entries 10–11). The use of KCN instead of K₃[Fe(CN)₆] and the employment of CuCN without CuBr₂ both led to the nitrogenation of 1-naphthaldehyde (Table 1, entries 5 and 12). In addition, no desired product was obtained without either copper salt or CN source (Table 1, entries 7 and 8). It can thus be concluded that copper salt, cyanide, and dioxygen are all essential ingredients, whereas the iron(III) ion is not indispensable. Although K₃[Fe(CN)₆] and CuCN gave **2a** in comparative yields (Table 1, entries 2, 6, and 12), from the viewpoint of safety, K₃[Fe(CN)₆] was chosen as the cyanide source for continued investigations. Further GC-MS detection of the gas phase of the cyanation process revealed the generation of carbon dioxide (CO₂).

Next, isotope incorporation experiments were performed. To our surprise, the reaction of ¹³C-labeled aldehyde **1s** (with ¹³C-enriched carbonyl carbon atom) gave rise to almost complete isotopic incorporation into the cyano moiety, which certainly excluded the decarbonylative cyanation of the aryl aldehyde (Table 2, entries 1 and 2; Figures S2–S3). Notably, the use of

Table 2. Isotope Incorporation Experiment and GC-MS Detection of the Nitrogenation of 1-Phenyl-1H-indole-3-carbaldehyde



entry	-CHO	cyanide	-CN (isotope incorporation)	solvent
1 ^a	¹³ CHO	K ₃ [Fe(CN) ₆]	¹³ CN (98% ¹³ C)	DMF
2 ^a	¹³ CHO	K ₃ [Fe(CN) ₆]	¹³ CN (98% ¹³ C)	DMSO
3 ^b	CHO	Cu ¹⁵ N	C ¹⁵ N (97% ¹⁵ N)	DMF
4 ^b	CHO	Cu ¹⁵ N	C ¹⁵ N (99% ¹⁵ N)	DMSO

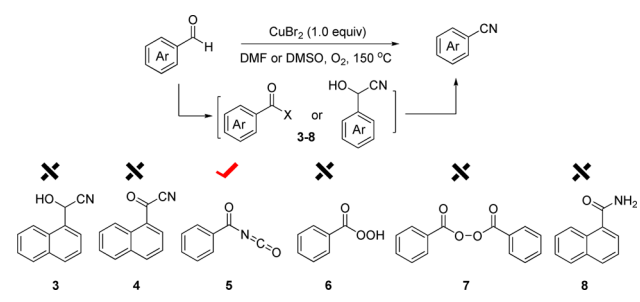
^a¹³C-labeled **1s** (0.25 mmol), CuBr₂ (0.25 mmol), and K₃[Fe(CN)₆] (0.125 mmol) under O₂ for 12 h. ^b**1s** (0.25 mmol), CuBr₂ (0.25 mmol), and ¹⁵N-labeled CuCN (0.5 mmol) under O₂ for 12 h.

DMSO as the solvent instead of DMF could also result in the ¹³C-labeled product ¹³C-**2s**, implying that the nitrogen source originates from K₃[Fe(CN)₆] rather than the solvent DMF. GC-MS analysis of the gas phase of these reactions disclosed the formation of CO₂ (*m/z* value of 44) rather than ¹³C-labeled carbon dioxide (¹³CO₂) (Table 2; Figures S6–S8). Thus, we rationalized that the generation of CO₂ originates from the dissociation of cyanide. When **1s** reacted with ¹⁵N-labeled CuCN instead of K₃[Fe(CN)₆] in DMF or DMSO, 97% and 99% isotopic ¹⁵N, respectively, incorporated into the cyanated product. This result conclusively indicates that the cyanide salt is the nitrogen source (Table 2, entries 3–4; Figures S4–S5).

It is noteworthy that the cyanation was inhibited in the presence of radical scavengers, including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), ascorbic acid, and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (for details, see Table S2), suggesting the possibility of a radical pathway. To explore this possibility, an electron paramagnetic resonance (EPR) experiment was performed with the addition of free-radical spin-trapping agent DMPO (5,5-dimethyl-1-pyrroline *N*-oxide).^{10d,f,11} When DMPO was added to the mixture of 1-naphthaldehyde, CuBr₂, and K₃[Fe(CN)₆] in DMF, a EPR signal was identified (Figure S9), further implying the existence of radical species.

Given that it is notoriously difficult to cleave the triple bond of a coordinated cyanide anion, we were puzzled by such an unprecedented aerobic copper-promoted nitrogen-transfer process. It is known that both the carbon and nitrogen ends of the cyanide anion could act as a reactive site. First, we proposed a plausible reaction pathway involving an intermediate such as a cyanohydrin or acyl nitrile through the nucleophilic attack of the carbon end of cyanide on the aldehyde carbon. However, neither 2-hydroxy-2-(naphthalen-1-yl)acetone nitrile (**3**) nor 1-naphthoyl cyanide (**4**) gave 1-naphthonitrile (**2a**) in the presence or absence of K₃[Fe(CN)₆] (Scheme 2). Thus, we postulated that another plausible pathway could involve the formation of an *N*-functionalized isocyanide via the coupling of the nitrogen end of the cyanide anion with an acyl radical¹² or the corresponding acylium ion¹³ generated from the aldehyde through the promotion of copper. The commercially available benzoyl

Scheme 2. Control Experiments for Investigating the Possible Intermediates for the Cyanation Reaction



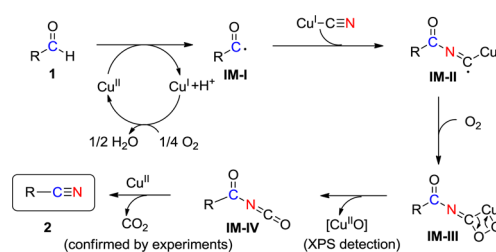
isocyanate (**5**) gave the desired benzonitrile (**2q**) in a comparative yield, implying that the nitrogen transfer of cyanide could undergo the isocyanide process. The Hammett analysis of a series of para-substituted benzaldehydes ($X = \text{NO}_2$, Cl, H, Ph, and OPh) reveals a linear free energy relationship ($R = 0.96$) with the Hammett constant σ^+ (Figure S12).¹⁴ A small Hammett value of 0.46 was observed, suggesting the possibility of a radical pathway.¹⁵ It is well-known that aldehydes can be oxidized to peroxy acids under similar conditions of Cu/ O_2 . However, the reactions of both peroxybenzoic acid (**6**) and benzoyl peroxide (**7**) failed to give the nitrile products, excluding the possibility of peroxy acid and peroxide as a suitable precursor. Finally, a trace amount of 1-naphthamide (**8**) was observed in the reaction mixture by GC-MS detection. Subjecting independently prepared **8** to the reaction conditions could not afford any of the cyanated product **2a**, ruling out the possibility of an amide intermediate. We assume that **8** could originate from the hydrolysis of the isocyanate.

Subsequently, we performed an X-ray photoelectron spectroscopy (XPS) experiment. The XPS analysis of a solid sample of the reaction indicated the formation of CuO (Figure S13), providing important information about the reaction mechanism. This observation also demonstrates why a stoichiometric amount of copper salt is required to achieve good conversion. It is noteworthy that CuO could also promote the generation of benzonitrile from benzoyl isocyanate, but only a 17% yield was obtained.

Considering that a more common route to nitriles is the condensation of ammonia onto the aldehyde, followed by oxidation of the subsequent imine,¹⁶ an alternative to the Cu-mediated C–N cleavage is the release of ammonia from cyanide, by first oxidation of cyanide to cyanate,¹⁷ followed by hydrolysis. To explore this possibility, sodium cyanate (NaOCN) instead of $\text{K}_3[\text{Fe}(\text{CN})_6]$ was subjected to the standard reaction conditions. However, only a trace amount of 1-naphthonitrile was detected by GC-MS analysis. Furthermore, NH_3 was not determined by GC-MS in the either presence or absence of aldehyde. Therefore, although the details of nitrogen transfer are not entirely clear at the present stage, the pathway involving the oxidation of cyanide to cyanate and the subsequent release of NH_3 seems less favored.

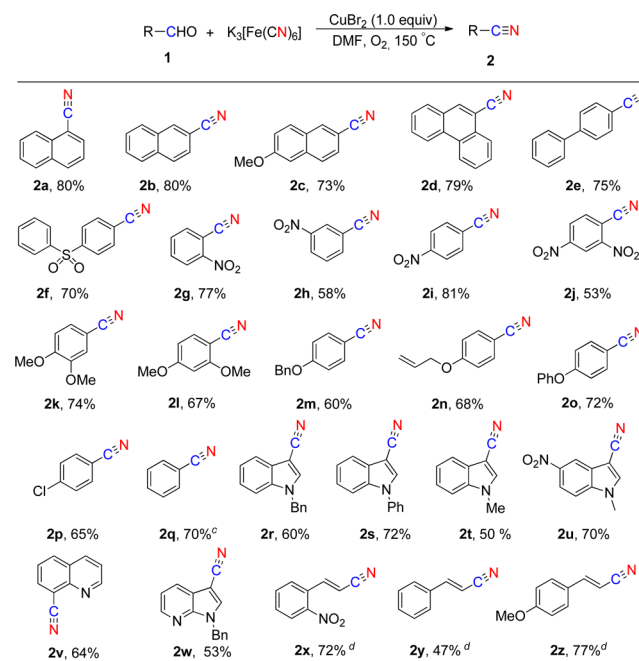
On the basis of the aforementioned observations and previous reports, a plausible mechanism is illustrated in Scheme 3. Considering that CuCN alone could afford the desired nitrile (Table 1, entry 12), we selected CuCN instead of the $\text{CuBr}_2/\text{K}_3[\text{Fe}(\text{CN})_6]$ system to demonstrate the pathway for clarity.¹⁸ First, Cu^I is oxidized to Cu^{II} under the dioxygen atmosphere.^{9b} Next, Cu^{II} serves as a single electron oxidant to convert the aldehyde **1** to the acyl radical species **IM-I**. The Cu^ICN species then combines with **IM-I** to generate the Cu^I -bonded carbon-centered radical intermediate **IM-II**.¹² The copper cation (as a

Scheme 3. Plausible Mechanism for the Copper-Mediated Cyanide Cleavage and Nitrogenation of Aldehydes



“protective metal”) could protect the carbon end from the attack of the acyl radical probably due to the coordination to the carbon end,¹² leading to the regioselectivity of C–N bond formation vs C–C bond formation. Subsequently, the radical species **IM-II** is intercepted by molecular oxygen to generate the copper(II) species **IM-III**.¹⁹ The following elimination of CuO affords intermediate **IM-IV** with the formation of a C=O double bond. The resulting isocyanate species gives the cyanated product **2** with concomitant release of CO_2 .²⁰

With the optimized reaction conditions in hand, we next turned to investigate the aldehyde scope (Table 3). To our

Table 3. Copper-Promoted Nitrogen Transfer of Cyanide to Aldehyde^{a,b}

^aReaction conditions: aldehyde (0.25 mmol), CuBr_2 (0.25 mmol), $\text{K}_3[\text{Fe}(\text{CN})_6]$ (0.125 mmol) in DMF under O_2 at 150 °C for 12 h. ^bIsolated yield based on **1**. ^cGC-MS yield. ^dReaction time: 16 h.

delight, a relatively broad scope of aldehydes including aryl aldehydes, heteroaryl aldehydes, and cinnamaldehydes afforded the desired products in moderate to good yields.

In conclusion, contrary to a deep-rooted prejudice, the $\text{C}\equiv\text{N}$ triple bond cleavage of coordinated cyanide anion is promoted by a copper salt in combination with molecular oxygen, enabling nitrogen transfer to aldehydes to form nitriles. The current work discloses cyanide as a source of nitrogen and opens a hardly accessible bond cleavage for further reaction development, which could have pronounced implications in future work.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10945.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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- (18) In the $\text{CuBr}_2/\text{K}_3[\text{Fe}(\text{CN})_6]$ system, CuBr_2 and $\text{K}_3[\text{Fe}(\text{CN})_6]$ could undergo redox reaction, affording the $[\text{Cu}^{\text{I}}-\text{CN}]$ species as the active cyano-transfer agent. For the reaction of Cu^{II} and MCN (e.g., $\text{K}_3\text{Fe}(\text{CN})_6$, KCN and $\text{K}_4\text{Fe}(\text{CN})_6$) to lead to the formation of the $[\text{Cu}^{\text{I}}-\text{CN}]$ species with the reduction of Cu^{II} to Cu^{I} by cyanide or other reagents, see: (a) Domínguez-Vera, J. M.; Moreno, J. M.; Colacio, E. *Inorg. Chim. Acta* **2004**, *357*, 611. (b) He, X.; Lu, C.-Z.; Yuan, D.-Q.; Chen, S.-M.; Chen, J.-T. *Eur. J. Inorg. Chem.* **2005**, *2005*, 2181. (c) Huang, R.-Y.; Xu, H.; Ye, S.-Y.; Wu, G.-H.; Zhao, X.-Q.; Wang, Y.; Liu, G.-X. *J. Mol. Struct.* **2013**, *1036*, 235. To gain more information of the reaction of CuBr_2 and $\text{K}_3[\text{Fe}(\text{CN})_6]$, low-temperature EPR experiments were performed. During the reaction of CuBr_2 with $\text{K}_3[\text{Fe}(\text{CN})_6]$ in the absence of substrate, the EPR signal strength of $\text{Cu}(\text{II})$ weakens gradually, indicating the possibility of the reduction of $\text{Cu}(\text{II})$ to $\text{Cu}(\text{I})$ (for details, see Figures S10–11).
- (19) Cu^{I} bonded or coordinated radical species could capture O_2 to form a cyclic Cu^{II} peroxide intermediate, see: (a) Jin, S.-J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011. (b) Cossy, J.; Belotti, D.; Bellost, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089. Also see Schemes 270, 284, 286, 292, 296, 298, 303, 309, and 460 in ref 9b.
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