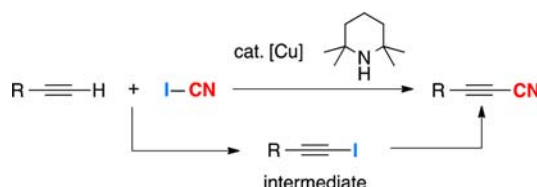


Copper-Catalyzed C—H Cyanation of
Terminal Alkynes with Cyanogen IodideKazuhiro Okamoto,* Masahito Watanabe, Naoki Sakata, Masahito Murai, and
Kouichi Ohe*Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering,
Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

kokamoto@scl.kyoto-u.ac.jp; ohe@scl.kyoto-u.ac.jp

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ABSTRACT



A copper-catalyzed reaction of terminal alkynes with cyanogen iodide (ICN) that produces alkynyl cyanides has been developed. The use of tetramethylpiperidine as a sterically congested base was successful in this reaction. Some control experiments revealed that the reaction involves the noncatalyzed formation of alkynyl iodides followed by copper-catalyzed cyanation of the iodides without the formation of copper(I) acetylide. This observation contrasts with what is normally observed in various copper-mediated reactions using terminal alkynes.

Direct carbon–carbon bond-forming transformation of hydrocarbons is one of the ideal types of synthetic reactions in terms of both availability and efficiency.¹ Cyanation, the simplest and most traditional way of adding C1 units, has also been applied to such reactions including cyanofunctionalization of C–C multiple bonds,^{2–4} direct C(sp²)–H cyanation,^{5–7} and direct conversion of C(sp³)–H bonds giving nitriles (Scheme 1).⁸ Among these, the direct acetylenic C(sp)–H cyanation, giving alkynyl cyanides, appears to be simple and easy to achieve because

acetylenic C–H bonds are relatively acidic and therefore readily deprotonated by strong bases. However, only two methods that use a stoichiometric amount of metal have been available for acetylenic cyanation until now (Scheme 2). One is the reaction of preformed lithium or copper acetylides with electrophilic cyanation agents,⁹ and the other is oxidative cyanation of terminal alkynes mediated by a stoichiometric amount of copper(I)

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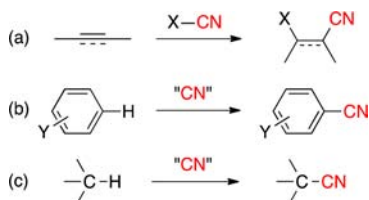
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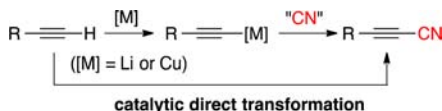
cyanide.¹⁰ Therefore, the development of a catalytic process that leads to alkynyl cyanides directly from the simple terminal alkynes is an important issue.

Scheme 1. Direct Cyanation of Hydrocarbons



Our research interest in this area has been focused on the utilization of cyanogen halides, which serve as viable electrophilic “CN⁺” sources and are complementary to the usual nucleophilic cyanation agents such as metal cyanides or cyanohydrins.¹¹ Herein, we report a copper-catalyzed C–H cyanation of terminal alkynes that uses cyanogen iodide (ICN) as the cyanation agent,^{12,13} for which the reaction pathway has now been revealed by stoichiometric reaction analysis and reaction monitoring.

Scheme 2. Acetylenic Cyanation Giving Alkynyl Cyanides



Our initial experiment was carried out with 1-dodecyne (**1a**), ICN, and 10 mol % of copper(I) triflate complex (CuOTf·toluene) in THF at 60 °C for 17 h, but no reaction occurred, and the starting alkyne was recovered intact

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(12) ICN (mp 146–147 °C; volatility 130 Pa at 25.2 °C) is stable to air and moisture and can be easily prepared from an aqueous solution of NaCN and I₂. See: Bak, B.; Hillebert, A. *Org. Synth.* **1952**, *32*, 29.

(13) **Caution!** All operations should be conducted in a well-ventilated fume hood because of the potential hazard from the generation of HCN in the catalytic conditions.

Table 1. Copper-Catalyzed Cyanation of 1-Dodecyne (**1a**) with Cyanogen Iodide^a

entry	base	conv (%) ^b 1a	yield (%) ^b 2a	3a	4a	5a
1	none	0	0	0	0	0
2	Et ₃ N	39	2	0	28	1
3	pyridine	74	2	1	38	16
5	K ₂ CO ₃	58	3	1	48	1
5	DBU	42	15	13	6	0
6	<i>i</i> Pr ₂ NH	52	17	0	28	2
7	<i>t</i> BuNH ₂	77	45	1	21	2
8	PMP	77	50	8	12	5
9	TEMP	95	78	3	2	9

^a Reaction conditions: 1-dodecyne **1a** (0.40 mmol), cyanogen iodide (1.0 mmol), base (0.60 mmol), copper catalyst (10 mol %) in THF (1.6 mL). ^b The yields and conversions were determined by ¹H NMR using nitromethane as an internal standard.

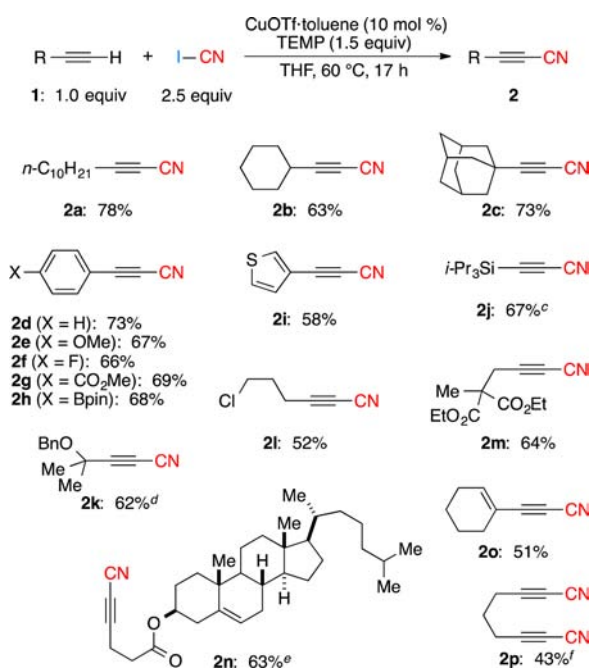
(Table 1, entry 1). Because it is well-known that copper-mediated cross-coupling of terminal acetylenes (e.g., Sonogashira–Hagihara coupling) usually requires bases to activate the copper acetylide formation, we employed triethylamine, pyridine, and potassium carbonate as representative bases (entries 2–4). A very small amount of the expected alkynyl cyanide **2a** together with alkynyl iodide **3a**, diiodoalkene **4a**, and triiodoalkene **5a** were obtained from the reaction mixture. The yield of **2a** was increased by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a stronger base or diisopropylamine as a secondary amine, but only by ~15% (entries 5 and 6). When *tert*-butyl amine was used as a primary amine or 1,2,2,6,6-pentamethylpiperidine (PMP) as a bulky tertiary amine, the yield of **2a** was increased to ~50% (entries 7 and 8). Eventually, 2,2,6,6-tetramethylpiperidine (TEMP) was shown to be the most efficient base for the present reaction, the yield of **2a** being 78% (entry 9). Under the optimized conditions, yields of the side products **3a–5a** were less than 10%.^{14,15}

The present acetylenic C–H cyanation reaction was expanded to the synthesis of alkynyl cyanides having various substituents (Scheme 3). Alkynes with primary, secondary, and tertiary alkyl groups could all be used in this reaction, with the corresponding alkynyl cyanides being obtained in good yield (**2a–2c**; 63–78%). Other than aliphatic alkynes, various aromatic acetylenes bearing *para*-substituents such as methoxy, fluoro, methoxycarbonyl, and Bpin also

(14) Although some other copper(I) or copper(II) salts could serve as catalysts for this reaction, the yields were generally lower than that obtained by using CuOTf·toluene as the catalyst.

(15) When the reaction temperature was raised up to 80 or 100 °C, the yield markedly decreased because of thermal isomerization of alkynyl cyanide into allenyl or propargyl cyanide. See: Wentrup, C.; Crow, W. D. *Tetrahedron* **1971**, *27*, 361.

Scheme 3. Copper-Catalyzed C–H Cyanation of Terminal Alkynes **1** with Cyanogen Iodide^{a,b}



^a Reaction conditions: alkyne **1** (0.40 mmol), cyanogen iodide (1.0 mmol), TEMP (0.60 mmol), and Cu(OTf)·toluene (10 mol %) in THF (1.6 mL). ^b Isolated yields were shown. ^c Cu(OTf)·toluene (20 mol %), at 80 °C for 36 h. ^d At 80 °C. ^e Cu(OTf)·toluene (20 mol %), for 36 h. ^f Cyanogen iodide (2.0 mmol), TEMP (1.2 mmol), and Cu(OTf)·toluene (20 mol %).

underwent the cyanation (**2d–2h**; 66–73%). It should be noted that the boronic pinacolester moiety was tolerated under the reaction conditions, despite its transmetalation activity, which enabled us to subject the product **2h** to a further transformation such as the Suzuki–Miyaura coupling reaction. The reaction of 3-thienylacetylene also afforded the cyanide **2i** in 58% yield. Aliphatic alkynes bearing various functional groups such as ether, chloro, ester, and alkene moieties, as well as a silylacetylene, were also tolerated in this reaction to afford the corresponding cyanides with these functional groups intact (**2j–2o**; 51–67%). Even cholesterol as a complex molecule was tolerated (**2n**; 63%). Double cyanation of 1,6-heptadiyne was also successfully achieved by using double the amounts of the reagents (**2p**; 43%).

To gain insight into the reaction mechanism, we monitored the catalytic reaction as a function of time using ¹H NMR. As shown in Figure 1, alkynyl iodide **3a** was formed initially, and the yield of **3a** reached a maximum of 95% at 45 min with almost full conversion of starting alkyne **1a**. After this period, the alkynyl iodide **3a** was gradually converted into the target cyanide **2a** with production of a minor amount of triiodide **5a**. The amount of diiodide **4a** was only at a trace level throughout the reaction. In addition to this result, alkynyl iodide **3a** was also obtained in high yield, even in the reaction without a copper salt (eq 1).

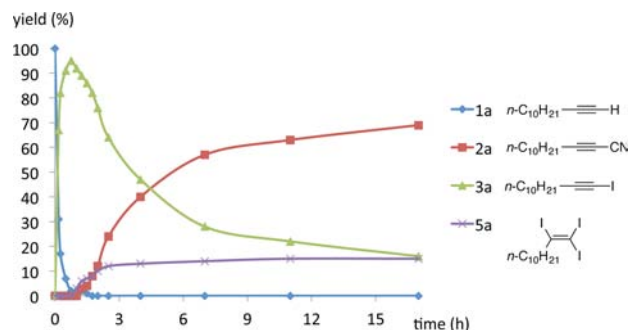
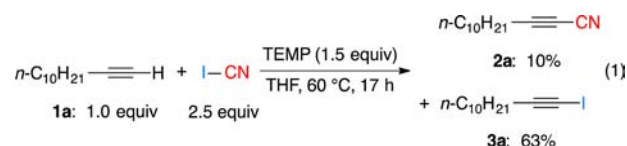


Figure 1. Copper-catalyzed cyanation of 1-dodecyne with cyanogen iodide in THF-*d*₈. Monitoring of the yields of the recovered reactant (**1a**) and the products (**2a**, **3a**, and **5a**) with time.



Therefore, we propose the reaction pathway described in Scheme 4. First, the base-mediated reaction of terminal acetylene **1** with ICN forms the alkynyl iodide **3** and TEMP·HCN (**6**) (Scheme 4a; step 1). Then, the copper iodide complex **7** undergoes ligand exchange by the initially generated ammonium cyanide **6** to form the cyanide complex **8** (Scheme 4b; step 2) as well as TEMP·HI (**9**).¹⁶ Alternatively, ICN can also react with complex **7** to give the cyanide complex **8** and molecular iodine (Scheme 4b; step 2'). Finally, the iodide **3** reacts with the generated copper(I) cyanide complex **8** to give the product cyanide **2**, regenerating the copper(I) iodide complex **7** (Scheme 4c; step 3).¹⁷

To confirm the proposed reaction mechanism, we conducted some control experiments using the preformed alkynyl iodide **3a**. First, the reaction of **3a** with a stoichiometric amount of CuCN in THF at 60 °C did not proceed at all; however, the addition of TEMP dramatically changed the reactivity and gave the cyanide in 45% yield (Scheme 5a). This result supports the mechanism of step 3 in Scheme 4c, where the cyanation of alkynyl iodide is caused by “CuCN” species and accelerated by TEMP.^{18–20}

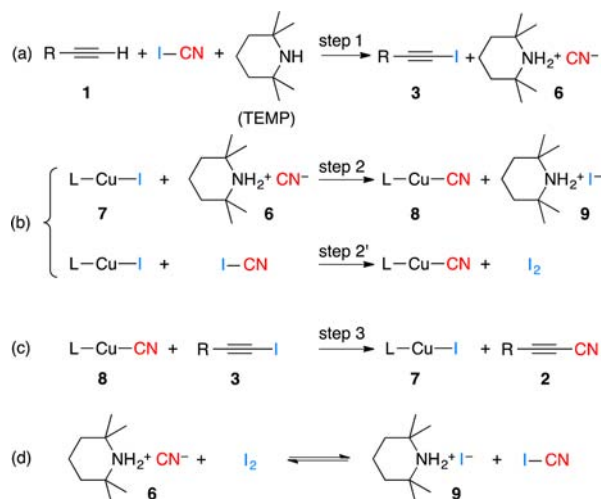
(16) The advantage of TEMP compared with other organic bases is due to its steric hindrance, which would maintain the cyanation activity by weakening the affinity with ICN (eq 2).



(17) Copper species **7** and **8** would be initiated into the catalytic cycle by the reaction of the copper catalyst precursor (CuOTf·toluene) with ICN.

(18) Formation of alkynyl cyanide from the reaction of alkynyl bromide with CuCN has been reported. See: Sladkov, A. M.; Ukhin, L. Y. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 13, 370.

(19) Very recently, the activation of alkynyl iodides with TEMP in a silver-catalyzed reaction was reported. See: Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, 135, 2955.

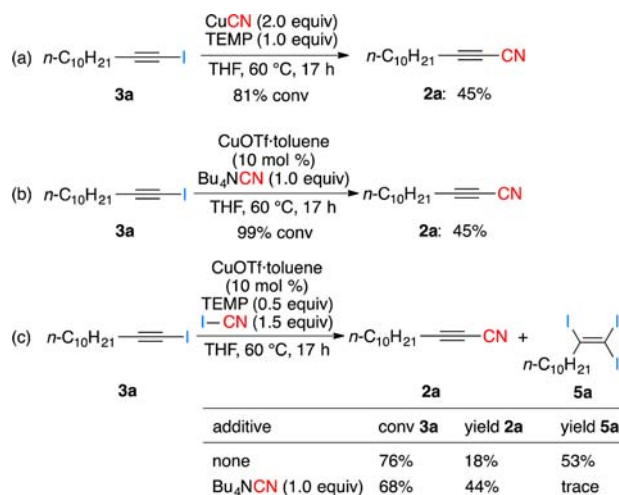
Scheme 4. A Proposed Reaction Mechanism

Second, the copper-catalyzed reaction of tetrabutylammonium cyanide (Bu_4NCN), a commercially available ammonium cyanide, also afforded the cyanide **2a** in 45% yield (Scheme 5b). This result shows that the ammonium cyanide serves as a cyanation agent in copper-catalyzed cyanation of alkynyl iodides. Third, we investigated the possibility of ICN as an alternative cyanation agent by performing the catalytic cyanation of alkynyl iodide with ICN (Scheme 4b; step 2'). For this purpose, we performed the copper-catalyzed reaction of alkynyl iodide **3a** with ICN in the standard conditions. However, cyanide **2a** was obtained in only 18% yield, and triiodide **5a** was obtained in 53% yield as the major product (Scheme 5c). This result indicates that the ICN serves as only a minor cyanation agent and that molecular iodine (I_2) as a byproduct causes the undesirable diiodination of alkynyl iodides.²¹ Moreover, the addition of Bu_4NCN in the above conditions markedly improved the selectivity toward the cyanide **2a** (44% yield), and only a trace amount of triiodide **5a** was observed. In the actual catalytic cyanation reaction, diiodination of alkynyl iodide **3a** is probably suppressed by the anion exchange reaction of ammonium cyanide **6** with I_2 (Scheme 4d).²²

(20) In the current system, additional cyanide salts (KCN or NaCN) greatly reduced the reactivity, which indicates that the neutral "CuCN" (not cuprate) acts as the catalyst.

(21) Alkynyl iodide **3a** might undergo diiodination with molecular iodine (I_2) generated by comproportionation of ICN.

(22) In a related experiment, ^{13}C NMR spectra (solvent: $\text{THF}-d_8$) of a mixture of Bu_4NCN (original peak of CN carbon at 165.0 ppm) and I_2 as well as a mixture of Bu_4NI and ICN (original peak at 44.0 ppm) both showed the same peak at 64.2 ppm (assigned to CN carbon). In the case of Scheme 4d, the two states will also be in a fast equilibrium.

Scheme 5. Copper-Mediated Cyanation Starting with Alkynyl Iodide **3a**

In conclusion, we have developed a copper-catalyzed direct cyanation reaction of terminal alkynes with cyanogen iodide which leads to alkynyl cyanides. Although the reaction appears to be simple, the actual mechanism supported by several experiments is more complicated, and every species generated in the reaction medium plays a crucial role for the selective conversion of alkynes to alkynyl cyanides. It is noteworthy that cyanogen iodide (ICN) acts as an iodinating agent of the terminal alkyne and that concomitantly produced ammonium cyanide ($\text{TEMP}\cdot\text{HCN}$) is diverted to a cyanation agent of the alkynyl iodide. Although the undesirable formation of the triiodoalkene occurred in the present system, ammonium cyanide should also suppress this side reaction effectively by consuming I_2 in the equilibrium.

Further mechanistic investigations, as well as the application of cyanation reactions through iodination as the intermediary reaction, are in progress.

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Supporting Information Available. Experimental Procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.