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Copper-Catalyzed Regio- and Stereoselective Iodocyanation and Dicyanation of Alkynes with Cyanogen Iodide

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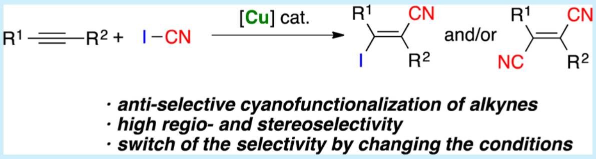
S *Supporting Information*

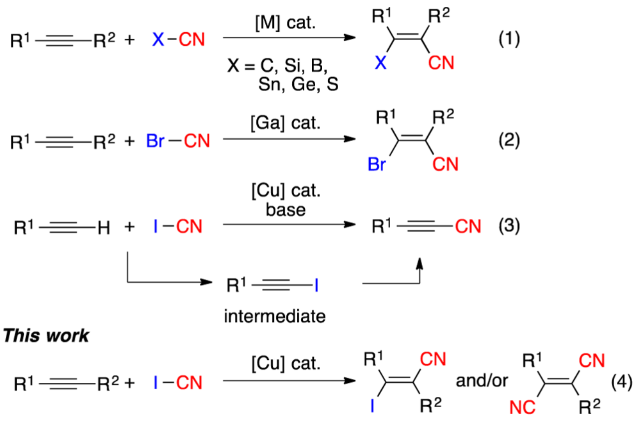
ABSTRACT: *anti*-Selective iodocyanation and dicyanation of various internal alkynes has been developed by means of a simple copper catalyst system. The selectivity of the products was switched by tuning the reaction conditions. Mechanistic studies have revealed all of the stepwise pathways including diiodide formation, selective monocyanation, and second cyanation processes.



Difunctionalization of alkynes is one of the most efficient ways of constructing complex olefinic moieties in short steps.[1] Of these reactions, metal-catalyzed direct addition of X−CN bonds (X = C, B, Si, Br, etc.) into alkynes has been extensively studied for decades in terms of its conceptual novelty, regio- and stereoselectivity, and product utility (Scheme 1, eq 1).[2−9] However, almost all of the cyanofunctionalization methods have provided only *syn*-selectivity. Therefore, development of *anti*-cyanofunctionalization methods is important for the diversity of stereodefined adducts.

During the course of our concurrent investigations based on the unique reactivities of cyanogen halides, our research interest has recently focused on the difference between cyanogen bromide (BrCN)[9a] and cyanogen iodide (ICN).[10] Cyanogen bromide serves as an electrophilic cyanation reagent and is effectively activated in the presence of Lewis acidic metals such as $GaCl_3$ (Scheme 1, eq 2).[9b,c] By contrast, cyanogen iodide does not work well as an electrophilic cyanation agent but can be used in combination with a copper catalyst. We have found that a copper catalyst was effective for the reaction of cyanogen iodide with alkynes giving alkynyl cyanides, and that the alkynyl cyanides were obtained through the formation of alkynyl iodides as an intermediate (Scheme 1, eq 3).[11] In this contribution, we report a copper-catalyzed *anti*-selective iodocyanation and dicyanation of alkynes using cyanogen iodide, in which the two reactions were switched simply by changing the reaction conditions (Scheme 1, eq 4).[12,13]

Scheme 1. Addition of X−CN Compounds to Alkynes



First, ester-containing alkyne **1a** was reacted with cyanogen iodide in the presence of 10 mol % of copper(I) acetate and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy) as a ligand in methanol at 80 °C for 20 h (Table 1, entry 1). Then the corresponding regioselective *anti*-iodocyanation product **2a** was obtained in 62% yield together with small amounts of dicyanide **3a** and diiodide **4a**. Two cyanation products were fully characterized by NMR and X-ray analysis (see Supporting Information). In the absence of the ligand and in a higher concentration, generation of dicyanation product **3a** was favored, and **3a** was obtained with high selectivity (Table 1, entries 2 and 3). When the reaction temperature was lowered to 60 °C, the major product formed then changed to iodocyanation product **2a** (Table 1, entry 4). The solvent was a key factor for the product selectivity, and a reaction in toluene selectively afforded the iodocyanation product **2a** (Table 1, entry 5). Finally, the copper catalyst could be changed into the more accessible copper(II) acetate, and the catalyst loading was lowered to 5 mol %. Under the optimized conditions using toluene or methanol as solvents, iodocyanation product **2a** was obtained in 89% isolated yield, and dicyanation product **3a** was obtained in 75% isolated yield (Table 1, entries 6 and 7). By contrast, the major product was diiodide **4a** in the absence of any copper catalysts, which indicates that the cyanation proceeds only in the presence of a copper catalyst (Table 1, entry 8).[14]

Various alkynes were applied to the present iodocyanation under the optimized reaction conditions (Table 2). Ester-containing alkynes were especially effective and gave the iodocyanation products regio- and stereoselectively. Methyl,

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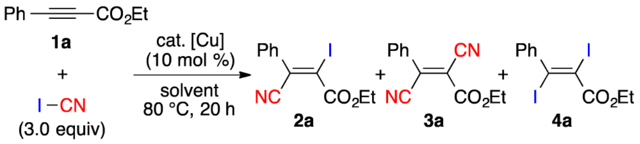
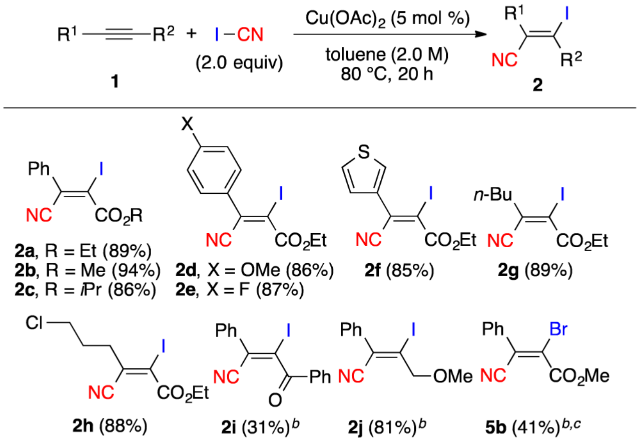
Table 1. Copper-Catalyzed Cyanation of Alkynes 1a with Cyanogen Iodide[a]



entry	[Cu]	yield (%)[b]			note
		2a	3a	4a	
1	CuOAc	62	2	7	MeOH (0.5 M) with dtbpy (10 mol %)
2	CuOAc	22	67	0	MeOH (0.5 M)
3	CuOAc	9	84	0	MeOH (2.0 M)
4	CuOAc	83	13	0	MeOH (2.0 M), 60 °C
5	CuOAc	84	15	0	toluene (2.0 M)
6[c,d]	$Cu(OAc)_2$	93(89)[e]	7	0	toluene (2.0 M)
7[c]	$Cu(OAc)_2$	12	81(75)[e]	0	MeOH (2.0 M)
8[f]	none	0	0	25	MeOH (2.0 M)

[a]Conditions: ethyl 3-phenylpropiolate (**1a**, 0.4 mmol), cyanogen iodide (1.2 mmol), and copper catalyst (40 μmol) at 80 °C for 20 h. [b]The yields were determined by ^{1}H NMR using 1,4-dioxane as an internal standard. [c]5 mol % of $Cu(OAc)_2$ was used. [d]2.0 equiv of ICN were used. [e]Isolated yield. [f]32% conversion of **1a**. dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

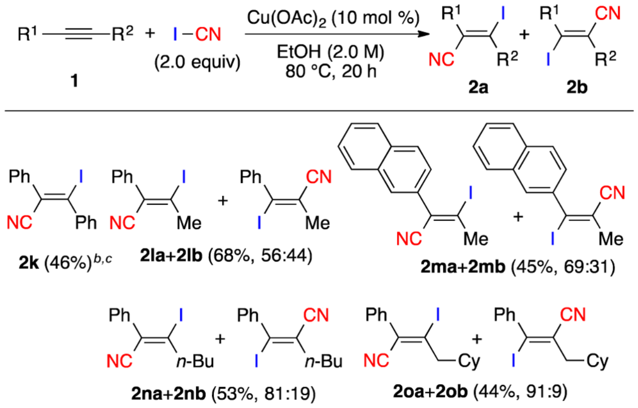
Table 2. Copper-Catalyzed Iodocyanation of Directing-Group-Tethered Alkynes with Cyanogen Iodide[a]



2a, R = Et (89%)
2b, R = Me (94%)
2c, R = *i*Pr (86%)
2d, X = OMe (86%)
2e, X = F (87%)
2f (85%)
2g (89%)
2h (88%)
2i (31%)[b]
2j (81%)[b]
5b (41%)[b,c]

[a]Conditions: alkyne **1** (0.40 mmol), cyanogen iodide (0.80 mmol), $Cu(OAc)_2$ (20 μmol) in toluene (0.20 mL). [b]$Cu(OAc)_2$ (40 μmol). [c]Cyanogen bromide (1.20 mmol) was used instead of cyanogen iodide.

Table 3. Copper-Catalyzed Iodocyanation of Simple Alkynes with Cyanogen Iodide[a]



2k (46%)[b,c]
2la+2lb (68%, 56:44)
2ma+2mb (45%, 69:31)
2na+2nb (53%, 81:19)
2oa+2ob (44%, 91:9)

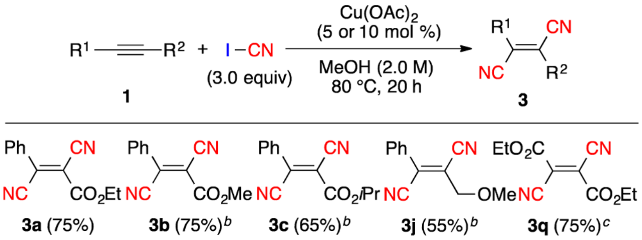
[a]Conditions: alkyne **1** (0.40 mmol), cyanogen iodide (0.80 mmol), $Cu(OAc)_2$ (40 μmol) in ethanol (0.20 mL). [b]The reaction was performed at 120 °C. [c]Toluene as a solvent.

ethyl, and isopropyl esters all reacted to give iodocyanation products **2a**−**c** in high yields. The reaction of alkynes having various aromatic moieties or an alkyl group also proceeded efficiently to give the iodocyanation products **2d**−**g**. When R^1 is a chloroalkyl group, the chloro group did not undergo the halogen exchange or cyanation (**2h**). Ketoalkyne **1i** also reacted to give the product **2i** in moderate yield. It is important that this reaction allows the use of alkynes without electron-deficient substituents. A methoxymethyl-group-substituted alkyne reacted to give adduct **2j** selectively in addition, which indicates that the ester and methoxymethyl groups might affect the regioselectivity in the same way. *anti*-Bromocyanation was also achieved by using cyanogen bromide (**5b**).

For simple alkynes, the use of ethanol as a solvent was effective for the selective iodocyanation (Table 3). The reaction of symmetric diphenylacetylene at 80 °C led to a single iodocyanation product **2k** in 46% yield. Arylalkylacetylenes also reacted to give regioisomers of *anti*-iodocyanation products (**2la**/**2lb** and **2ma**/**2mb**). Both regioisomers were characterized by X-ray crystallography (see Supporting Information). The steric bulkiness of alkyl moieties of R^2 seems to affect the regioselectivity of iodocyanation. When R^2 is *n*-butyl, the ratio of adducts **2na** and **2nb** was in a higher ratio (81:19). When R^2 is cyclohexylmethyl, the ratio of **2oa** and **2ob** reached 91:9.[15]

Table 4 summarizes the results of the dicyanation of alkynes using an excess amount of ICN. Alkynes having both a phenyl and an ester moiety all gave the *anti*-dicyanation products in high yields (**3a**−**c**). Even when the alkyne possesses a methoxymethyl group that can coordinate to the copper species, dicyanide **3j** was obtained in moderate yield. Diethyl acetylenedicarboxylate (**1q**) was much more reactive even in toluene and yielded unusually electron-deficient tetrasubstituted alkene **3q** in good yield.

Table 4. Copper-Catalyzed Dicyanation of Alkynes with Cyanogen Iodide[a]

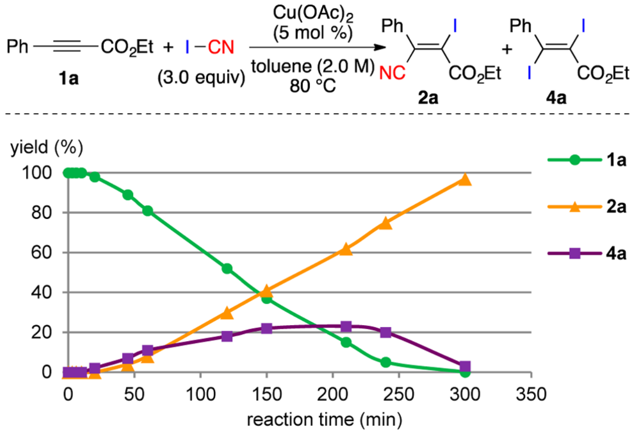


3a (75%)
3b (75%)[b]
3c (65%)[b]
3j (55%)[b]
3q (75%)[c]

[a]Conditions: alkyne **1** (0.40 mmol), cyanogen iodide (1.20 mmol), $Cu(OAc)_2$ (20 μmol) in methanol (0.2 mL). Isolated yields are shown. [b]$Cu(OAc)_2$ (40 μmol). [c]Toluene as a solvent.

The time-dependent reaction profile of the reaction of **1a** with ICN was observed continuously using ^{1}H NMR (Scheme 2). The amount of alkyne **1a** was gradually decreased after the 10 min induction period, generating iodocyanide **2a** and diiodide **4a**. While the yield of **2a** was gradually increased, the yield of **4a** increased and reached a ceiling at around 20%, and then decreased after 4 h. These observations indicate that the iodocyanide **2a** was generated from the intermediate of diiodide **4a**. Considering that the diiodination of alkynes could proceed

Scheme 2. Time-Dependent Distribution of the Recovered Reactant 1a and Products 2a and 4a in Copper-Catalyzed Cyanation of Alkynes with Cyanogen Iodide



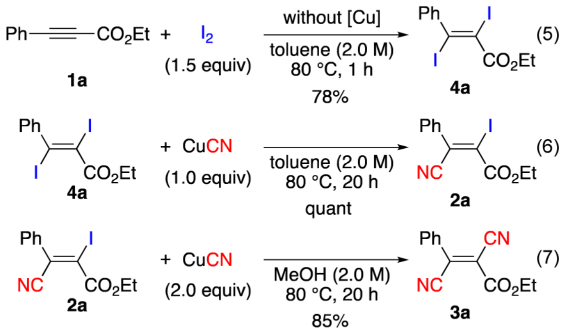
at least partly without any copper catalyst, albeit quite slowly (Table 1, entry 8), alkynes would undergo diiodination via molecular iodine that is generated by two pathways: one, the noncatalytic comproportionation of ICN, and the other, copper-mediated ligand exchange as shown in Scheme 3.[16]

Scheme 3

$$[\mathrm{Cu}]{-}\mathrm{I} + \mathrm{I}{-}\mathrm{CN} \longrightarrow \mathrm{I_2} + [\mathrm{Cu}]{-}\mathrm{CN}$$

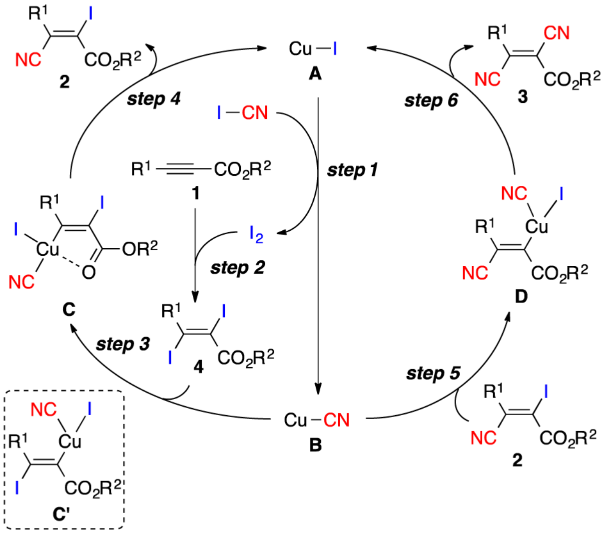
To gain insight into the mechanism generating each product **2a**, **3a**, and **4a**, a series of control experiments were conducted (Scheme 4). The reaction of alkyne **1a** with molecular iodine in the absence of copper in toluene at 80 °C produced diiodide **4a** in good yield (Scheme 4, eq 5).[17] The reaction of diiodide **4a** with a stoichiometric amount of copper(I) cyanide in toluene at 80 °C gave iodocyanide **2a** as a sole product quantitatively, of which the regio- and stereoselectivity was ideal (Scheme 4, eq 6). The isolated **2a** was further reacted with copper(I) cyanide in methanol at 80 °C, the dicyanide **3a** being obtained in high yield (Scheme 4, eq 7). These experiments suggest that two cyanation products **2a** and **3a** are produced stepwise from diiodide **4a** by cyanation with copper(I) cyanide.[18−20]

Scheme 4. Control Experiments



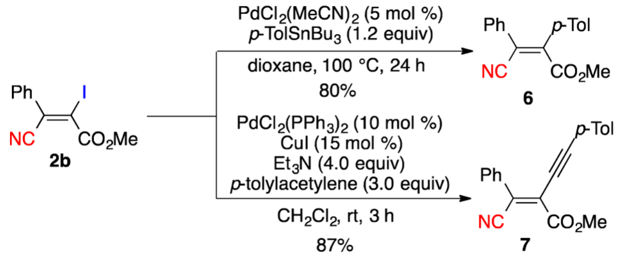
A proposed catalytic cycle for the present cyanation reactions using ester-containing alkyne **1** as a typical substrate is described in Scheme 5.[21] First, in situ generated low-valent copper iodide species **A** undergoes ligand exchange by cyanogen iodide to generate copper cyanide species **B** together with molecular iodine (Scheme 5, step 1). Molecular iodine is then quickly consumed for diiodination of alkyne **1** to afford diiodide **4** (Scheme 5, step 2). Oxidative addition of diiodide **4** to copper cyanide **B** forms intermediate **C** in a high oxidation state (Scheme 5, step 3), which leads to the iodocyanation product **2** by reductive elimination of **C**, regenerating copper iodide **A** (Scheme 5, step 4). In methanol, probably because of the acceleration of cyanation by a polar solvent effect, the second cyanation of **2** with copper cyanide **B** occurs through the oxidative addition−reductive elimination sequence to give dicyanide **3**, regenerating copper iodide **A** (Scheme 5, steps 5 and 6). The regioselectivity of the first cyanation of diodide **4** can be explained by assuming carbonyl oxygen-coordinating intermediate **C**. In intermediate **C**, the copper center in the higher oxidation state is highly stabilized by coordination of the internal carbonyl moiety, probably lowering the barrier for activation of cyanation compared with that from its regioisomer **C′**.

Scheme 5. A Proposed Catalytic Cycle for Copper-Catalyzed Iodocyanation and Dicyanation of Alkynes



The reaction products could be transformed by taking advantage of the iodide substituents (Scheme 6). Iodocyanation product **2b** was treated with a palladium catalyst and an arylstannane reagent to undergo the Stille coupling reaction with high efficiency, affording the tetrasubstituted alkene **6** in 88% yield. Similarly, Sonogashira−Hagihara coupling with an arylalkyne gave the enyne **7** in 87% yield.

Scheme 6. Derivatization of Iodocyanation Product 2b



In summary, we have developed regio- and stereoselective copper-catalyzed iodocyanation and dicyanation reactions of alkynes with cyanogen iodide. The stepwise mechanism for the formation of iodocyano- and dicyanoalkene has been revealed from NMR observations and stoichiometric experiments.

Obtained products could be useful as synthetic intermediates and further elaborated with high stereospecificity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01378.

Experimental procedures, additional experimental data, and compounds characterization data (PDF)
X-ray crystallographic analysis of compound **2b** (CIF)
X-ray crystallographic analysis of compound **2ma** (CIF)
X-ray crystallographic analysis of compound **2mb** (CIF)
X-ray crystallographic analysis of compound **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Other metal catalysts including Pd, Rh, Ni, Co, Fe, and Mn were examined, but only trace amounts of cyanation products were obtained.

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(16) CuI may be formed via initial ligand exchange of $Cu(OAc)_2$ by treatment of ICN forming CuI_2 followed by the decomposition of CuI_2 forming CuI and 1/2 I_2. The latter step is a well-known characteristic of copper iodide. See: Lee, J. D. *Concise Inorganic Chemistry*, 5th ed.; Wiley-Blackwell: Hoboken, NJ, 1998.

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