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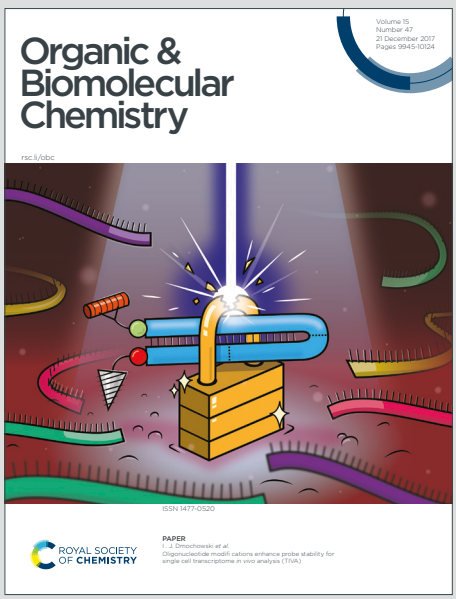




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# An aerobic and green C-H cyanation of terminal alkynes†

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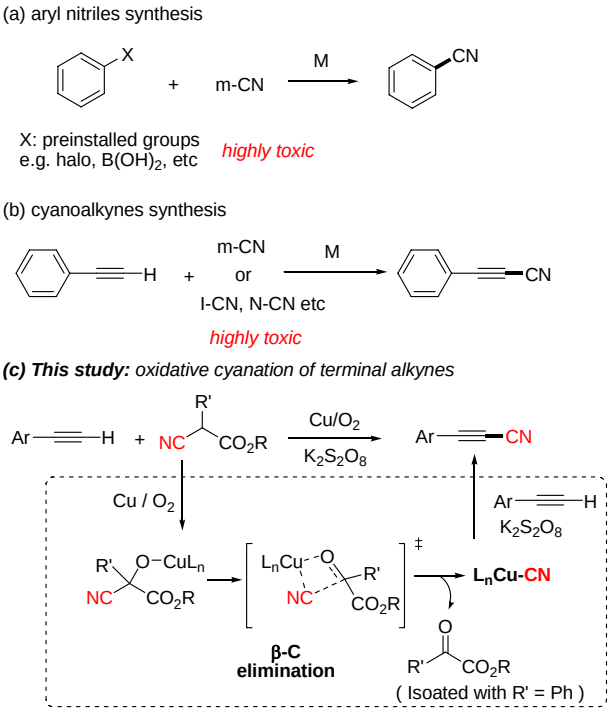
**Abstract:** This study describes a benign C-H cyanation of terminal alkynes with α-cyanoesters serving as a nontoxic cyanide source. In-situ generation of key copper cyanide intermediate is proposed by a sequence of α-C-H oxidation and copper-mediated β-carbon elimination of α-cyanoesters, releasing α-ketoesters byproduct observed experimentally. Ensuing reaction of the copper cyanide with terminal alkynes delivers preferentially cyanoalkynes, and surpasses possible Glaser type dimerization of terminal alkynes or the undesired accumulation of HCN under protic conditions. The presence of co-oxidant $K_2S_2O_8$ is crucial to this selectivity, probably by promoting oxidative transmetalation and the resulting formation of Cu(III)(acetylide)(CN) intermediate. All the reagents and salts used are commercially available, cheap and nontoxic, avoiding the use of highly toxic cyanides salts typically required in cyanation studies. The scope of this reaction is demonstrated with a set of alkynes and α-cyanoesters. Application of this method to late-stage functionalization of terminal alkyne group in an estrone derivative is also feasible, showing its practical value for drug design.

The prevalence of nitrile-containing compounds in pharmaceuticals, agrochemicals and materials,[1] and the versatile reactivity of cyano group[2] have boosted continuous efforts to the synthesis of nitriles. Traditionally, nitriles are prepared by methods such as dehydration of amides or oximes in the presence of dehydrating agents, or nucleophilic aromatic cyanation of aryl diazonium salts or halides with a stoichiometric amount of toxic CuCN.[3,4] Recent endeavor in transition metal catalysis has allowed catalytic cyanation of aryl halides or boronic acids/esters by cyanide salts (Scheme 1a).[5-7] However, inherent drawbacks associated with the current methods, in particular the need for highly toxic cyanide salts, have brought about safety concerns, and greatly impeded the practical application of these methods. This has prompted recent efforts to pursue safer cyanation chemistry avoiding the manipulation of toxic cyanide salts.[8-10]

Cyanoalkynes are useful synthetic building blocks with broad applications, in particular in the preparation of heteroarenes. Currently, the preparation of cyanoalkynes has been dominated by cyanation of terminal alkynes with toxic cyanide salts (e.g. NaCN, CuCN), I-CN and amino-CN sources (Scheme 1b),[11] as well as other peculiar methods using azides.[12,13] Direct terminal alkyne C-H cyanation by a nontoxic organic cyano source remains very rare.[14]

Our recent efforts using α-cyanoesters as a type of readily available, green and easy-to-handle cyano source have enabled the development of efficient and green cyanation of aryl iodides, boronic acids, and styrenes.[15] These reactions occur in the presence of a copper salt under aerobic conditions[16] to facilitate the C-CN bond cleavage in α-cyanoesters,[17,18] thus offering the prerequisite cyanide in a safe and green way without the manipulation of toxic cyanide salts or reagents. To probe the probability of direct C-H cyanation of terminal alkynes using α-cyanoesters as the nontoxic source, we noticed that several potential challenges are waiting to be resolved. The first one is the effective in-situ formation of the putative $L_nCu$-CN intermediate via $Cu/O_2$ accelerated C-CN bond cleavage of α-cyanoesters. Second, the acceleration and selectivity of reaction of $L_nCu$-CN intermediate with terminal alkynes to forge the alkynyl-CN bond. While the Glaser type dimerization of terminal alkynes is a very typical and privileged reaction under $Cu/O_2$ oxidative conditions,[19] it requires that reaction of $L_nCu$-CN intermediate with terminal alkynes is quick enough to suppress Glaser type dimerization. Finally, the avoidance of generation of flammable HCN is a superior task for any cyanation reactions under protic conditions. This also requires that $L_nCu$-CN intermediate generated in-situ is consumed quickly through productive reaction with terminal alkynes.

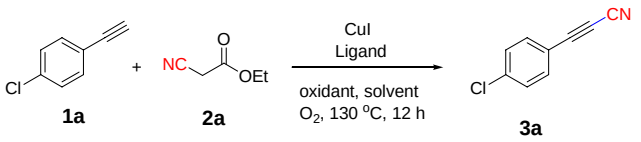



**Scheme 1** Methods for nitriles synthesis.

To meet the above demands, we report herein the development of direct C-H cyanation of terminal alkynes by α-cyanoesters serving as the safe and convenient cyano source

(Scheme 1c). This reaction is convenient, robust and selective to produce propiolonitriles, which can suppress potential Glaser-type oxidative alkyne dimerization and the undesired formation of flammable and dangerous HCN gas despite the protic environment. This is a great advantage compared to methods using cyanides salts where HCN is believed to be a severe byproduct under protic conditions. The choice of a suitable co-oxidant is crucial to achieve this high reactivity and selectivity. Interestingly, this method can also allow cyanation of aryl and vinyl halides and boronic acids, significantly broadens the scope of nitriles accessible. The synthetic potential of this method is demonstrated in the late-stage functionalization of estrone derivatives. Finally, the mechanism of this reaction is discussed.

**Table 1** Optimization study [ae]




**1a** **2a** **3a**

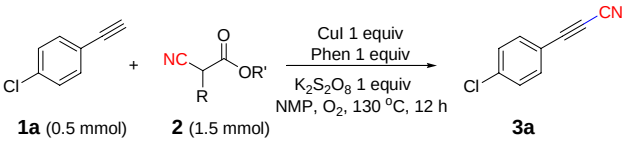
| entry | Ligand | Oxidant | solvent | yield (%)[b] |
|---|---|---|---|---|
| **1** | **Phen** | **$K_2S_2O_8$** | **NMP** | **55** |
| 2 | $PPh_3$ | $K_2S_2O_8$ | NMP | trace |
| 3 | $PCy_3$ | $K_2S_2O_8$ | NMP | trace |
| 4 | DPPF | $K_2S_2O_8$ | NMP | trace |
| 5 | - | $K_2S_2O_8$ | NMP | 25 |
| 6 | Phen | $K_2S_2O_8$ | DMF | trace |
| 7 | Phen | $K_2S_2O_8$ | DMSO | trace |
| 8 | Phen | $K_2S_2O_8$ | DMA | trace |
| 9 | Phen | $K_2S_2O_8$ | NMP/DMF(1:1) | trace |
| 10 | Phen | TBHP | NMP | trace |
| 11 | Phen | $H_2O_2$ | NMP | trace |
| 12 | Phen | - | NMP | trace |
| 13[c] | Phen | $K_2S_2O_8$ | NMP | trace |
| **14[d]** | **Phen** | **$K_2S_2O_8$** | **NMP** | **60** |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), CuI (0.5 mmol), ligand (0.5 mmol), co-oxidant (0.5 mmol) and solvent (3 mL) under $O_2$ balloon at 130 °C for 12 hours. [b] Isolated yields of **3a** by column chromatography. [c] Reaction at RT or 40 °C. [d] **2a** used in 1.5 mmol. [e] Phen, 1,10-phenanthroline; $PCy_3$, tricyclohexylphosphane; DPPF, bis(diphenylphosphanyl) ferrocene; NMP, *N*-methylpyrrolidinone.

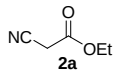
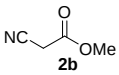
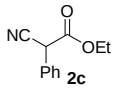
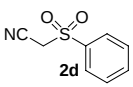
Our study began by reaction of *para*-chlorophenyl acetylene and ethyl α-cyanoacetate under copper/oxygen condition (Table 1), with the anticipation of generation of cyanide from α-cyanoacetate via oxidative C-CN bond cleavage.[15,16] After great efforts, it was found that the desired **3a** was produced in 55% isolated yield promoted with CuI/phenanthroline (phen) using $K_2S_2O_8$ as the co-oxidant in NMP (entry 1). Phenanthroline is found to perform better than other ligands, such as phosphines (entries 2-5). NMP is a preferred solvent that likely stabilizes the cyanide generated in situ (entries 6-9). $K_2S_2O_8$ is a crucial co-oxidant for this reaction (entries 1 & 10-12), which likely accelerates the desired reaction of in-situ generated Cu-CN with terminal alkyne, and thereby minimizes potential side reaction of Glaser-type dimerization of terminal alkynes toward conjugated diynes, or cyanide protonation to the undesired HCN. In cases where the desired cyanoalkyne **3a** was obtained in low yield, byproducts were observed including diynes arising from Glaser-type dimerization, oligomers of alkynes from Sonogashira-type coupling and other identified byproducts in some cases. This also highlights the optimized conditions in promoting the selective formation of **3a** and suppressing the formation of byproducts. Finally, it was found that the yield can further be improved to 60% with 3 equivalents of cyanoester (entry 14).

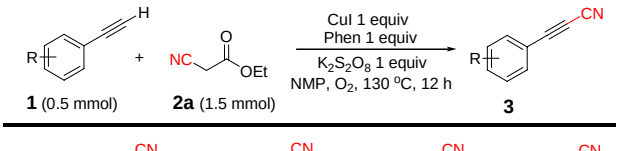
Notably, other α-cyanoacetic esters analogous to **2a** were also examined for this cyanation reaction, but gave lower yields than **2a** (Table 2). For example, **2b**, **2c** and **2d** gave the desired **3a** in 51%, 40% and 46% yields under the conditions of entry 14.

**Table 2**. Various α-cyanoesters sources evaluated

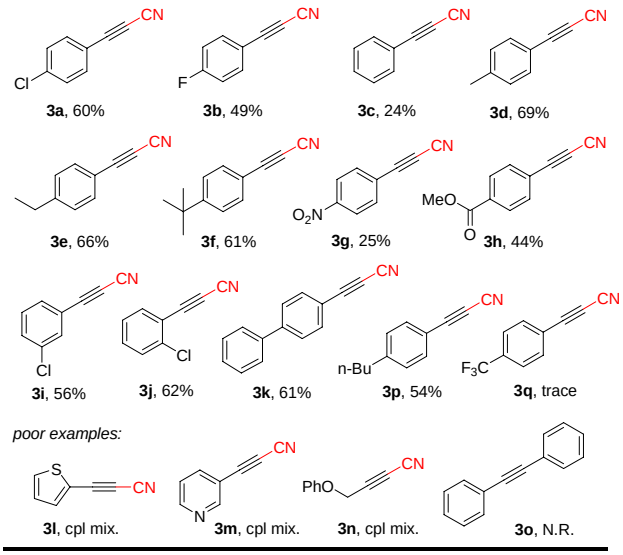



**1a** (0.5 mmol) **2** (1.5 mmol) **3a**

| entry | α-cyanoester **2** | yield of **3a** |
|---|---|---|
| 1 |  **2a** | 60 |
| 2 |  **2b** | 51 |
| 3 |  **2c** | 40 |
| 4 |  **2d** | 46 |




**1** (0.5 mmol) **2a** (1.5 mmol) **3**



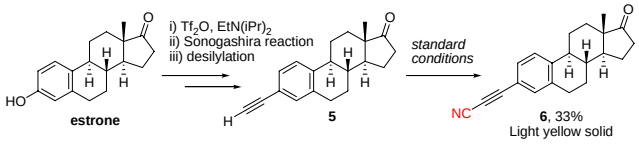

**3a**, 60% **3b**, 49% **3c**, 24% **3d**, 69%
**3e**, 66% **3f**, 61% **3g**, 25% **3h**, 44%
**3i**, 56% **3j**, 62% **3k**, 61% **3p**, 54% **3q**, trace
**3l**, cpl mix. **3m**, cpl mix. **3n**, cpl mix. **3o**, N.R.

**Scheme 2** Substrate scope of C-H cyanation of various terminal alkynes. Isolated yields are reported. Symbol "cpl mix." means complex mixture; N.R. means no reaction. **3c** suffers from severe lost during workup due to volatile property.

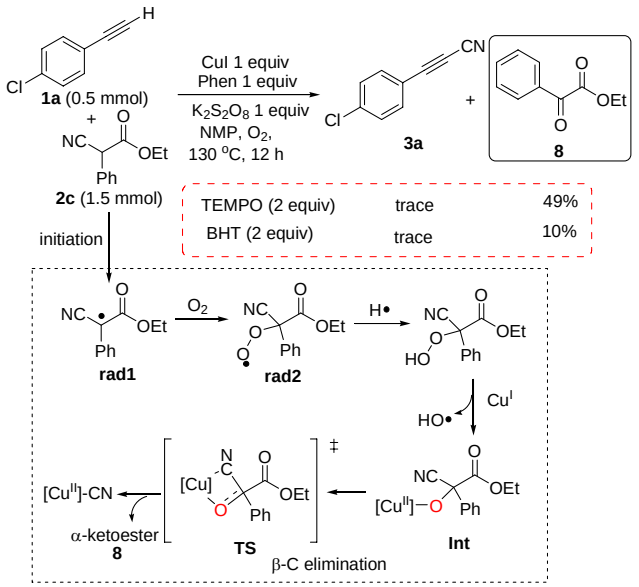
With the optimized conditions developed (entry 14, Table 1), terminal alkynes with a range of substituents on the aromatic ring were studied (Scheme 2). Substituents including halo, alkyl, phenyl, nitro and ester are tolerated on the aromatic ring. Interestingly, substituents at either *para*-, *meta*- or *ortho*-position have no appreciable impact on the reaction efficiency, as reflected by the yields of **3a**, **3i** and **3j**. However, 2-thiophenyl and 3-pyridyl acetylenes were poor substrates, giving complex mixtures. This is attributed to the coordinating ability of the heteroaryl ring to copper that might trap the Cu-CN generated in-situ and thus impedes the approach and installment of cyanide to the alkyne terminus.

Gratifyingly, this method was found to also enable cyanation of aryl and vinyl halides, and boronic acids (please see ESI† for more details).

To show the capability of this method for practical drug design, late-stage functionalization of an estrone derivative **5** is demonstrated (Scheme 3). The desired product **6** was obtained introducing a propiolonitrile to replace the original hydroxyl group in estrone.[20]

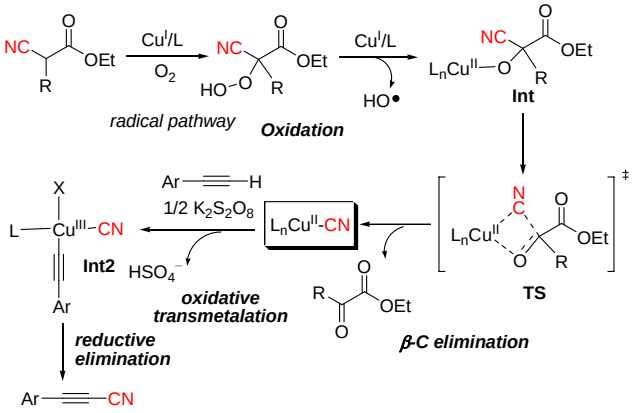



**Scheme 3** Late-stage functionalization of an estrone derivative **5**.




**Scheme 4** Radical trapping study and characterization of an α-ketoester intermediate.

To shed light on the reaction, radical trapping studies were conducted. Under the optimized conditions, when two equivalents of additional TEMPO (2,2,6,6-tetramethylpiperidinyloxo) or BHT (2,6-ditertbutyl-4-methylphenol) were added in the reaction solution, the desired **3a** was obtained in trace amounts. Interestingly, a new compound was found as the major product by TLC and isolated in 49% and 10% yields, which was identified to be α-phenyl-α-ketoester **8** (Scheme 4).[21] This finding indicates that radical species might probably be involved in the reaction. Possibly, radical species **rad1** is initially generated, followed by oxygen insertion to give **rad2** which can abstract a hydrogen to give a peroxide compound (Scheme 4).[16] Oxidation of the Cu(I) precatalyst by this peroxide gives a Cu(II)-oxide intermediate **Int**. Then, β-carbon elimination occurs from **Int** through a typical four-membered ring transition state **TS** releases α-ketoester **8** observed, and a Cu(II)-CN intermediate.[18]




**Scheme 5** Mechanism proposed.

Thus, a plausible mechanism is proposed to involve initial copper-mediated oxidation of the cyanoacetate to produce copper(II) alkoxide compound **Int** following a radical pathway (Schemes 4 and 5).[16] From **Int**, β-C elimination occurs to produce key intermediate $L_nCu^{II}$-CN through a typical four-membered ring transition state **TS**,[17,18] with the release of α-ketoester observed experimentally. This oxidation/C-C cleavage sequence to generate cyanide is reminiscent of the metabolism of nitrile compounds in biological systems. At this stage, the oxidative transmetalation of the $L_nCu^{II}$-CN with terminal alkyne assisted by $K_2S_2O_8$ likely gives preferentially a $Cu^{III}$(acetylide)(CN) type intermediate **Int2** (Scheme 5). The $K_2S_2O_8$ co-oxidant plays a crucial role to promote this oxidative transmetalation, which thereby suppresses the competing Glaser type dimerization of alkynes and other side reactions. Finally, reductive elimination from **Int2** produces the cyanoalkyne target compound.

## Conclusions

In summary, this study reports a copper-mediated C-H cyanation of terminal alkynes using α-cyanoacetates as the nontoxic cyano source. A sequence of oxidation/C-CN bond cleavage is proposed to generate Cu-CN intermediate with the release of α-ketoesters observed experimentally. This reaction is robust, selective and most importantly safe, avoiding the use of toxic cyanide salts previously required. This reaction

can be extended to allow cyanation of aryl/vinyl halides and boronic acids, further broadening the synthetic scope. This method is also demonstrated in the late-stage functionalization of estrone derivatives.

## Conflicts of interest

There are no conflicts of interest to declare.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, spectroscopic characterization data, and copies of $^{1}H$ and $^{13}C$ NMR spectra. See DOI: 10.1039/b000000x/

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21 The fate of radical scavengers could not be determined after the reactions despite great efforts.

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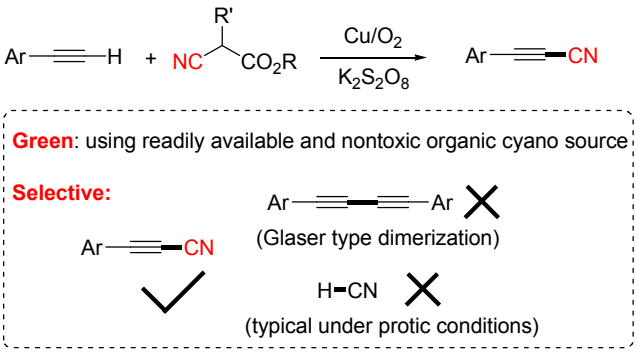


This study reports C-H cyanation of terminal alkynes with α-cyanoacetates serving as readily available and friendly cyano source under $Cu/O_2$ conditions.