



Copper-mediated cyanation reactions



Qiaodong Wen, Jisong Jin, Lianpeng Zhang, Yan Luo, Ping Lu*, Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

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ABSTRACT

Aryl nitriles can be efficiently synthesized through transition-metal-mediated cyanation of aryl halides, arenes, aryl boronic acids, and so on. Among those most commonly used transition-metals, copper catalysts are surely much more inexpensive and easier to handle, compared to any other metal catalysts. Considering the high-efficiency of copper catalysts in the activation of C–X, C–H, and C–B bond as well as in the formation of C–CN bond, this Letter summarizes various copper-mediated cyanations based on the different kinds of cyanide reagents, such as metal cyanides, potassium hexacyanoferrate(II), acetone cyanohydrins, DDQ, AIBN, benzyl cyanide, malononitrile, nitromethane, and DMF. Our group's recent contributions to this area are also demonstrated.

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Introduction

Aryl nitriles are an important class of organic compounds. They are present as a key motif of natural products, pharmaceuticals, agrochemicals, dyes, and herbicides.¹ Moreover, aryl nitriles are well-known as versatile intermediates for the preparation of amines, amidines, amides, aldehydes, carboxylic acids, and tetrazoles.² Take the synthesis of losartan, which is an angiotensin II receptor antagonist, for example.³ Losartan is a tetrazole derivative like many other sartans drugs. The part of tetrazole structure can be synthesized from aryl nitrile and sodium azide. Hence, 4'-methyl-[1,1'-biphenyl]-2-carbonitrile is the key precursor in this conversion (Scheme 1).

Undoubtedly, the preparation of aryl nitriles shows great importance in organic synthesis. Among these preparation processes, the most popular synthetic strategies are the classical Rosenmund-von Braun reaction and Sandmeyer reaction, starting from aryl halides and aryl diazonium salts, respectively (Scheme 2).⁴ However, both of them utilize stoichiometric amounts of CuCN as cyanating reagent under relatively high temperature, which indicates equal amounts of metal waste and pollution.

The transition metal-mediated cyanation reactions have been more and more attractive in these years, among which palladium and copper are most commonly involved.⁵ Researchers have established lots of cyanation methods based on these metal catalysts and also disclosed a series of cyanating reagents.^{6,7} While comparing to Cu-catalyzed cyanation reactions, Pd-catalyzed cyanation

reactions suffer from several drawbacks, in spite of their high efficiencies. The most obvious disadvantage is that many palladium catalysts are relatively expensive, as are their corresponding ligands. Moreover, in some cyanation reactions, excess dissociative cyanide anion (CN⁻) would poison the palladium catalyst and restrain the reactions, owing to the high affinity of CN⁻ to palladium.⁸

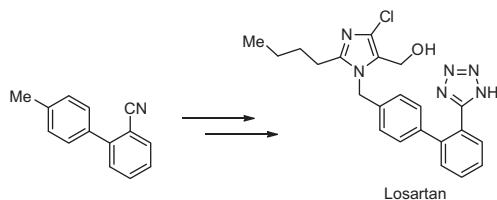
Given the unfavorable factors mentioned above, copper catalysts show several distinctive advantages in cyanation reactions. Cheap and commercially available copper sources make various cyanations possible under much milder reaction conditions, including copper-mediated cyanation of aryl halides, arenes, as well as aryl boronic acids. Most of them show great efficiency in each reaction. Although several recent reviews about cyanation reactions mainly discussed palladium-catalyzed cyanation of aryl halides,^{5b,c} synthesis of aryl nitriles using nonmetallic cyanosources,^{5d} and transition-metal-catalyzed C–CN bonds couplings,^{5e} there are no specific reviews focused on the copper-mediated cyanation reactions. Herein, we describe recent developments in copper-mediated cyanations, classified by the cyanide source.

Metal cyanides

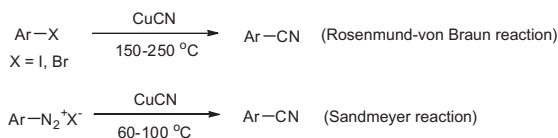
Metal cyanide (MCN) has been commonly used in direct cyanation reactions, such as KCN, NaCN, CuCN, Zn(CN)₂, AgCN, TMSCN, etc. A serious issue in common with all is their high toxicity. However, such drawback has not limited their wide applications in transition metal-mediated cyanation reactions. Besides palladium-catalyzed cyanations with these cyanides, copper-catalyzed cyanations are also universal.

* Corresponding authors. Tel./fax: +86 571 87952543.

E-mail addresses: pinglu@zju.edu.cn (P. Lu), orgwyg@zju.edu.cn (Y. Wang).



Scheme 1. Preparation of Losartan from 4'-methyl-[1,1'-biphenyl]-2-carbonitrile.



Scheme 2. Classical Rosenmund-von Braun reaction and Sandmeyer reaction.

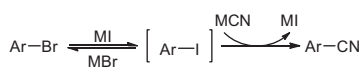
In 2003, Buchwald demonstrated copper-catalyzed cyanation of aryl bromides via a halide exchange (Scheme 3).⁹ They disclosed that CuI worked much better than CuBr or CuCN in the cyanation of aryl bromides. The result was explained as copper-catalyzed conversion of aryl bromide into aryl iodide, which was more reactive in cyanation reaction. Thus, by addition of 20 mol % KI to the reaction, the efficiency of this cyanation reaction was improved. Moreover, addition of ligand seemed to be very beneficial for this cyanation. This reaction had a wide substrate scope with a great tolerance of functional groups (Table 1). And various heteroaryl bromides also preformed excellently via this cyanation, including some indoles, benzothiophenes, quinolines, and pyrazoles (Table 2).

In 2010, Daugulis and co-workers reported a copper-catalyzed cyanation of heterocycles using copper cyanide as catalyst, NaCN as the cyanide source, and iodine as an oxidant (Table 3).¹⁰ The cyanation was thought to be a stepwise reaction. Benzothiazole was firstly iodinated to 2-iodobenzothiazole under the help of *t*-BuOLi, followed by a copper-catalyzed cyanation with NaCN as cyanating reagent. In relation to the substrate scope, many heterocycles were cyanated smoothly in good yields. Furthermore, by minor modifications of general conditions, *N*-methylindole and azulene could be cyanated via this method.

CuCN can function as both copper catalyst and cyanating reagent.¹¹ One classical example is the Rosenmund-von Braun reaction, which is both catalyzed and cyanated by CuCN at a high temperature (150–250 °C). As a modification of Rosenmund-von Braun reaction, Ding and co-workers reported *L*-proline-promoted CuCN-mediated cyanation of aryl halides in 2008 (Table 4).¹² Employing *L*-proline as ligand, the reaction occurred at a lower temperature (80–120 °C) than in its absence.

Cheng and co-workers also reported a copper-mediated cyanation with CuCN in the cyanation of boronic acids (Table 5).¹³ Here, CuCN activated the C–B bond and served as a cyanide source. Reactions were conducted under much milder reaction conditions, which were run in DMF solution at 60 °C for 2 h. Various boronic acids, with different functional groups, afforded the corresponding aryl nitriles in good yields.

In the same report,¹³ TMS-CN, AgCN, and Zn(CN)₂ were also examined as cyanide sources (Table 6). 0.55 equiv of CuI was



Scheme 3. Halide exchange in cyanation.

Table 1
Cyanation of aryl bromides with NaCN

Ar-Br	Yield (%)	Conditions
Ar-Br	91%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110–130 °C, 24 h
Ar-Br	90%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 130 °C
Ar-Br	98%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 130 °C
Ar-Br	80%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110 °C, 20 h
Ar-Br	70%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 130 °C
Ar-Br	70%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 130 °C

Table 2
Cyanation of heteroaryl bromides with NaCN

Het-Br	Yield (%)	Conditions
Het-Br	95%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110 °C, 24 h
Het-Br	74%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110 °C, 24 h
Het-Br	78%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110 °C, 24 h
Het-Br	80%	10 mol% CuI, 20 mol% KI, 1.0 equiv ligand 1, 1.2 equiv NaCN, Toluene, 110 °C, 24 h

Table 3
CuCN-catalyzed cyanation with NaCN

Ar-H	Yield (%)	Conditions
Ar-H	63%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	72%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	51%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	71%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	71%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	53%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	90%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C
Ar-H	36%	CuCN (10 mol%), phenanthroline (20 mol%), I ₂ , NaCN, <i>t</i> BuOLi, dioxane/ <i>m</i> -xylene, 110 °C

Table 4
Cyanation of aryl halides with CuCN

R-Ar-X	Yield (%)	Conditions
R-Ar-X	X = I, 98%; X = Br, 81%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = I, 80 °C, 24 h; X = Br, 120 °C, 45 h
R-Ar-X	X = I, 92%; X = Br, 56%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = I, 80 °C, 24 h; X = Br, 120 °C, 45 h
R-Ar-X	X = I, 90%; X = Br, 76%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = I, 80 °C, 24 h; X = Br, 120 °C, 45 h
R-Ar-X	X = Br, 85%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = Br, 120 °C, 45 h
R-Ar-X	X = Br, 87%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = Br, 120 °C, 45 h
R-Ar-X	X = Br, 78%	2.0 equiv CuCN, 1.0 equiv <i>L</i> -proline, DMF, X = Br, 120 °C, 45 h

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