

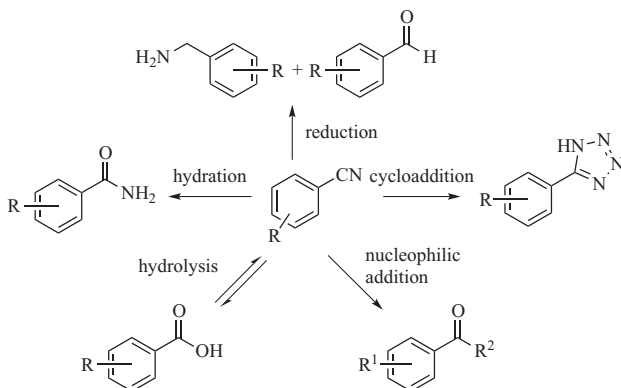
# COPPER-CATALYZED CYANATIONS OF ARYL HALIDES AND RELATED COMPOUNDS

THOMAS SCHAREINA AND MATTHIAS BELLER

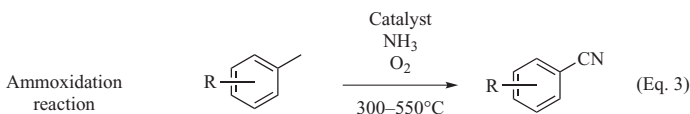
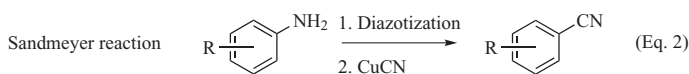
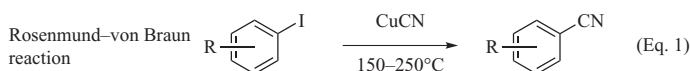
## 9.1 INTRODUCTION

Benzonitriles are of general interest for organic synthesis as integral parts of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.<sup>[1]</sup> In addition, the nitrile group serves as an important intermediate for a multitude of possible transformations into other functional groups, such as benzoic acid derivatives, benzylamines, benzaldehydes, and heterocycles (Scheme 9.1).

Typically, the introduction of a cyanide group is the most direct and versatile route to the preparation of functionalized benzonitriles. For more than a century, the synthesis of benzonitriles by stoichiometric methods prevailed in laboratory and industry (Scheme 9.2). Among these methods, the Rosenmund–von Braun reaction of aryl halides (see the Preface for a historical perspective)<sup>[2,3]</sup> and the diazotization of anilines with the subsequent Sandmeyer reaction were the most popular (Scheme 9.2, Eqs. 1 and 2).<sup>[4]</sup> However, due to (over)stoichiometric amounts of metal waste being generated, such processes do not meet today's criteria of sustainable synthesis. For the ton-scale production of benzonitriles, the method of choice in industry is ammoxidation,<sup>[5]</sup> whereby the corresponding toluene derivatives are reacted with oxygen and ammonia at high temperatures (300–550°C) in the presence of heterogeneous fixed-bed catalysts (Scheme 9.2, Eq. 3). However, lack of functional group



**Scheme 9.1** Representative synthetic applications of benzonitriles.



**Scheme 9.2** Traditional methods for the synthesis of benzonitriles.

tolerance and harsh reaction conditions make this method less suitable for the synthesis of functionalized benzonitriles.

In the early 1970s, the introduction and development of transition-metal-catalyzed carbon–carbon coupling reactions have dramatically changed the method of functionalizations of arenes. In this context, the first palladium-catalyzed cyanation of aryl halides was introduced in 1973 by Takagi and coworkers by reacting aryl bromides and iodides with potassium cyanide as the cyanating agent.<sup>[6]</sup> Since then, various palladium, nickel, and, more recently, copper catalysts were developed for the coupling of aryl halides with cyanides. Clearly, palladium complexes have dominated as catalysts in cyanation reactions so far because they tolerate a wider variety of functional groups and are less sensitive to air and humidity than nickel catalysts. They are also more active than copper catalysts. On the other hand, copper catalysts and the nitrogen ligands used mostly for their activation are much cheaper than the palladium catalysts and the phosphine ligands necessary to activate them, in many cases also outweighing the higher cost for the more reactive substrates

that are usually needed for copper. A slight downside of copper complexes as catalysts is their biological activity. While higher animals (vertebrates) are relatively inert against copper uptake, even very low concentrations can be biocidal for microorganisms, including those used in waste water treatment.\*.[7,8] Thus, apart from cost arguments, the application of a low amount of the catalyst is desirable.

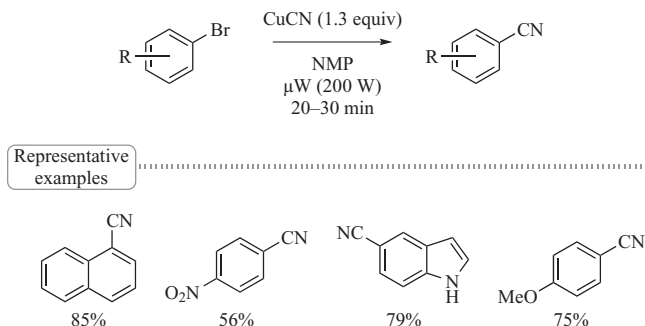
A general problem of metal-catalyzed cyanations is the high affinity of cyanide toward typical palladium-, nickel-, and copper-based catalysts. Often, a fast deactivation of the catalytic system is observed due to the formation of stable metal cyanide complexes; and catalysis proceeds in general with low efficiency. Notably, all mechanistic investigations in this direction have been performed with palladium-based systems.<sup>[9]</sup> One solution for overcoming this problem relies on the use of solvents in which standard cyanide sources such as sodium cyanide, potassium cyanide, and zinc(II) cyanide<sup>[10]</sup> have very low solubility.<sup>[3b]</sup> Beller and others have shown that organic (e.g., tetramethylethylenediamine [TMEDA])<sup>[11]</sup> and inorganic (e.g., zinc and zinc salts)<sup>[12]</sup> additives are beneficial for the regeneration of the catalytically active palladium metal center. Another elegant approach has been the slow dosage of the corresponding cyanide source<sup>[3g]</sup> (e.g., acetone cyanohydrin<sup>[13]</sup> or trimethylsilyl cyanide),<sup>[14]</sup> which keeps the cyanide concentration low and leads to a higher catalyst productivity. Other recent developments include microwave activation<sup>[15]</sup> and the application of novel or modified catalyst systems.<sup>[16]</sup> However, most of these developments have drawbacks such as toxicity of the cyanide source and comparably high catalyst costs (low catalyst productivity).

In the following sections, the classical copper-mediated Rosenmund–von Braun and Sandmeyer reactions are described followed by procedures using only catalytic amounts of copper salts in conjunction with mild sources of cyanide such as acetone cyanohydrin or potassium hexacyanoferrate(II). The final section is devoted to a blooming area of the cyanation reactions, the copper-catalyzed oxidative cyanation.

## 9.2 MODIFICATIONS AND UPDATES OF CLASSICAL CYANATION REACTIONS (ROSENMUND–VON BRAUN, SANDMEYER)

Since the first report of a copper-catalyzed cyanation of bromo-anthraquinone by the Farbwerke Hoechst Company in the patent literature in 1913,<sup>[2c]</sup> considerable progresses have been reported in the Rosenmund–von Braun reaction. Cai and coworkers were able to decrease the reaction time of this venerable transformation to 20–40 minutes by microwave heating in *N*-methylpyrrolidinone at ambient pressure (Scheme 9.3).<sup>[17]</sup> Simple standard aryl bromides were converted to the corresponding benzonitriles by reaction

\* For humans, the daily uptake of 0.5 mg.kg<sup>-1</sup> is considered nonhazardous.



**Scheme 9.3** Copper(I)-mediated cyanation reaction of aryl bromides using microwave irradiation.

with copper(I) cyanide in 68–90% yield. While the method is fast and easy to apply, still, an overstoichiometric amount of copper(I) cyanide has to be used.

Wang and coworkers identified L-proline as an effective additive to promote the Rosenmund–von Braun reaction at lower temperature (80–120°C) in dimethylformamide (DMF).<sup>[18]</sup> This modified Rosenmund–von Braun cyanation of aryl bromides exhibits good functional-group compatibility since nitro, amino, amide, hydroxyl, and ester substituents were tolerated. Once again, an overstoichiometric amount of copper(I) cyanide has to be used, which limits the usefulness of the method.

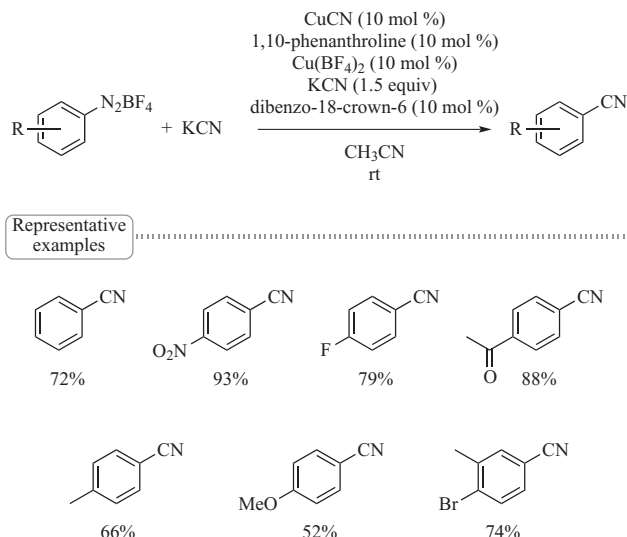
Beletskaya and coworkers introduced another interesting improvement of a classical cyanation reaction. Catalytic Sandmeyer reactions using copper(I) cyanide (10 mol %) in the presence of 1,10-phenanthroline (phen) as a ligand, copper(II) tetrafluoroborate (10 mol %, to suppress radical side reactions), and potassium cyanide as cyanating agent in acetonitrile could be performed at room temperature starting from reactive aryl diazonium tetrafluoroborate salts (Scheme 9.4).<sup>[19]</sup> However, electron-rich substrates gave lower yields of the desired aryl cyanides.

A logical evolution of the cyanation reaction of aryl halides has focused on the development of an efficient copper-catalyzed version. The efforts toward this important goal, both from an academic and an industrial point of view, are discussed in the next section.

### 9.3 COPPER-CATALYZED CYANATIONS OF ARYL HALIDES

After the first example of a copper-catalyzed (5 mol %) cyanation of an aryl bromide in the open literature appeared,<sup>\*,[20]</sup> a general protocol for catalytic

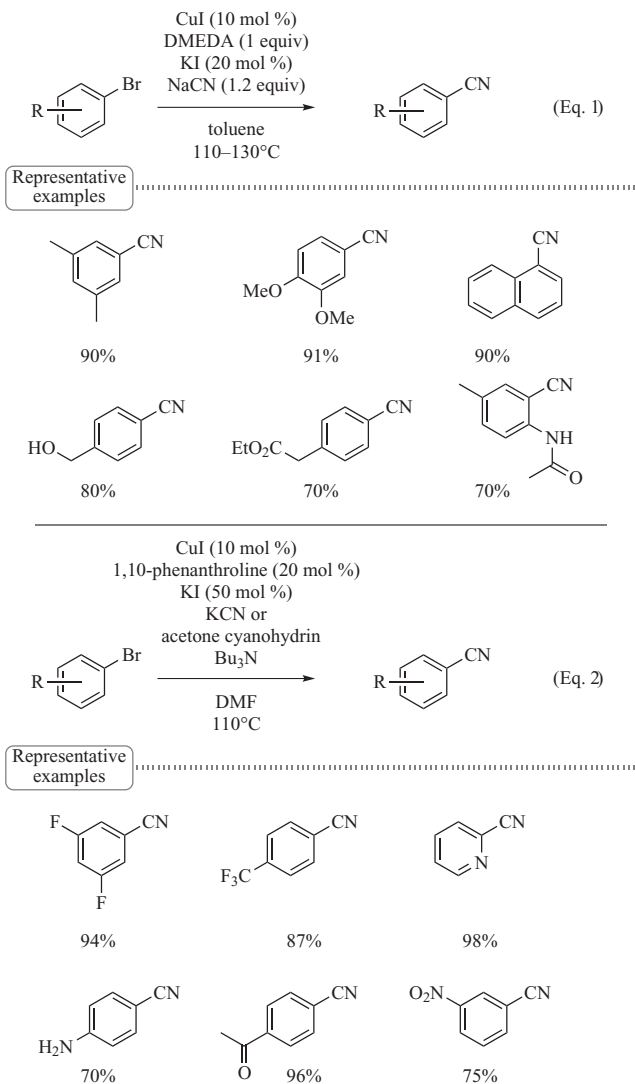
\* One example of copper-catalyzed (5 mol %) cyanation of an aryl bromide (2-bromonaphthalene) has been reported to proceed with 55% conversion when the reaction is carried out in an ionic liquid.



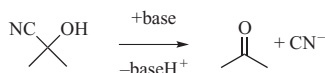
**Scheme 9.4** Copper-catalyzed Sandmeyer reaction.

Rosenmund–von Braun reaction was reported by Buchwald and coworkers.<sup>[21]</sup> The latter used copper(I) iodide (10 mol %), potassium iodide (20 mol %), and *N,N'*-dimethylethylenediamine (DMEDA, 100 mol %), the cyanide source being sodium cyanide (1.2 equiv). Subsequently, Cristau, Taillefer, and coworkers<sup>[22]</sup> demonstrated that this reaction also proceeds in the presence of 1,10-phenanthroline (20 mol %) as ligand. Both methods relied upon cheap but highly toxic cyanide sources like sodium cyanide or potassium cyanide (Scheme 9.5). Both groups also stated that a catalytic amount of iodide is necessary as additive to convert aryl bromides into the corresponding aryl iodide, which then undergoes the substitution reaction with cyanide (see Chapter 6 for details on the aromatic Finkelstein reaction). It should be noted that in both cases, the corresponding patents have been issued as early as 2001.<sup>[23,24]</sup>

Additionally, Cristau, Taillefer, and coworkers reported, for the first time in the same publication, the use of acetone cyanohydrin as a cyanide source for copper-catalyzed cyanation reactions.<sup>[22]</sup> Acetone cyanohydrin decomposes quantitatively to acetone and cyanide anion in the presence of a base (Scheme 9.6). Thus, a controlled amount of cyanide can be introduced into the reaction vessel by slow addition, for example, with the help of a syringe pump, to prevent the above-mentioned deactivation of the metal catalyst. Beller and coworkers developed a similar protocol in which the use of acetone cyanohydrin allowed the reduction of the amount of catalyst by fine-tuning the addition rate of the cyanation reagent, thus avoiding catalyst poisoning.<sup>[13]</sup>



**Scheme 9.5** Copper(I)-catalyzed domino halide exchange–cyanation sequence.



**Scheme 9.6** Decomposition of acetone cyanohydrin under basic conditions.

Historically, the latest cyanation reagent for the preparation of benzonitriles is potassium hexacyanoferrate(II),  $K_4[Fe(CN)_6]$ .<sup>\*,[26]</sup> After establishing its value for the palladium-catalyzed cyanation of aryl halides,<sup>[27]</sup> Beller was also able to use it for the copper-catalyzed cyanation reaction.<sup>[28]</sup> Potassium hexacyanoferrate(II) has the advantage of being essentially the least toxic cyanide source conceivable: While all known other cyanation sources are highly poisonous (potassium cyanide has a lethal dose low of 2.86 mg.kg<sup>-1</sup> orally in humans),  $K_4[Fe(CN)_6]$  is nontoxic (the lethal dose 50 of  $K_4[Fe(CN)_6]$  is lower than the one of sodium chloride!) and is even used in food industry for metal precipitation.<sup>†</sup> Importantly, for practical applications, potassium hexacyanoferrate(II) is commercially available on ton-scale and its price per mole of cyanide is comparable to potassium cyanide.<sup>‡</sup> Notably, all six cyanide ligands can be used for the catalytic cyanation reactions.

In the first report on the use of potassium hexacyanoferrate(II) for copper-catalyzed cyanation of aryl halides, copper(II) tetrafluoroborate and DMEDA<sup>[21]</sup> as ligand were used as the catalytic system.<sup>[28]</sup> In later reports, a modified procedure using copper(I) iodide (10 mol %) and 1-butylimidazole (200 mol %) as an additive or 1-methylimidazole as a solvent was developed (Scheme 9.7).<sup>[29]</sup> Despite comparably high reaction temperatures (up to 160°C in the majority of cases), excellent selectivities were achieved. Additionally, the scope of the cyanation reaction was increased in comparison with palladium-based methods, including the derivatization of heterocyclic and sterically hindered aromatic bromides.

More recently, other groups used 1,10-phenanthroline in combination with copper(I) iodide (20 mol %) and the same cyanide source (Scheme 9.8).<sup>[30]</sup> Aryl iodides gave marginally higher yields of benzonitrile products than aryl bromides and aryl chlorides did not react at all.

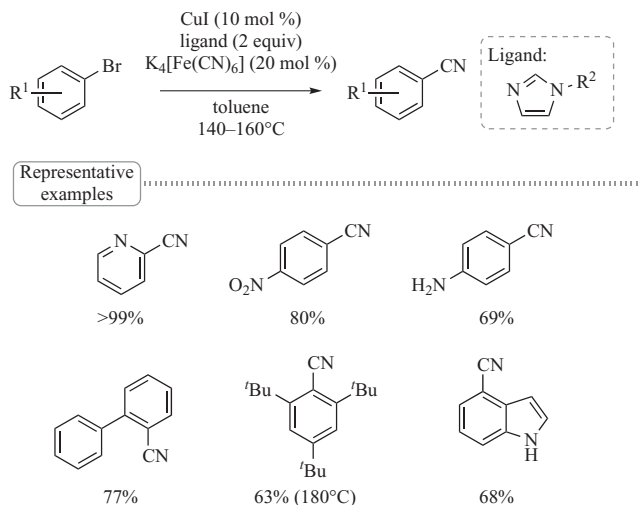
An even more simple and inexpensive ligand, ethylenediamine, was introduced by Wang and coworkers (Scheme 9.9).<sup>[31]</sup> However, the copper(II) acetate loading was relatively high (30 mol %). The method worked well for aryl bromides and highly activated aryl chlorides, and potassium iodide had to be used as an additive in this reaction.

Another option for the production of aryl nitriles from low-toxicity starting materials is the method called “combined cyanide source” by Cheng and coworkers (Scheme 9.10).<sup>[3g,32]</sup> Cyanide is produced *in situ* from ammonium salts and the solvent, DMF, and the copper mediator seems to play an

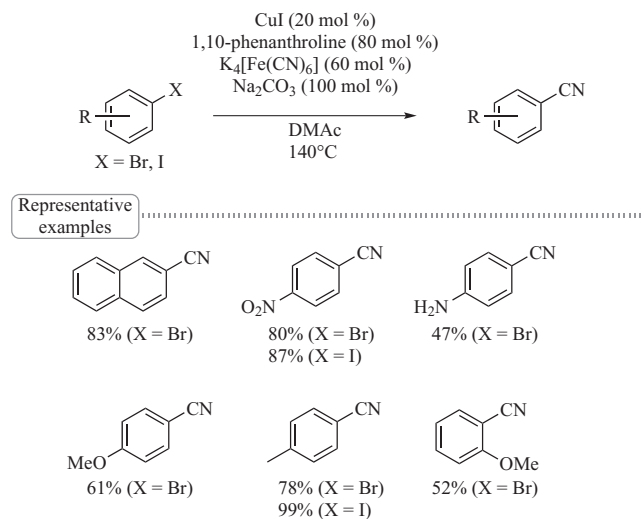
\* The first use of potassium ferrocyanide as cyanating reagent in a noncatalytic reaction.

† The risk and safety statements and the Material Safety Data Sheets (MSDS) of fine chemical providers differ considerably on the topic of the toxicity of potassium hexacyanoferrate(II) and other ferrocyanides. In any case, contact with acids should be avoided due to the potential danger of HCN evolution, for the same reasons ingestion of substantial amounts should be definitely avoided. The use in the food industry is limited to low concentrations.

‡ The price per mole of cyanide is €14 for  $K_4[Fe(CN)_6]$  and €1 for potassium cyanide (ACS quality both). Source: Aldrich Chemicals Catalogue 2012.



**Scheme 9.7** Copper(I)-catalyzed cyanation of aryl bromides with potassium ferrocyanide and alkylimidazoles as ligands.

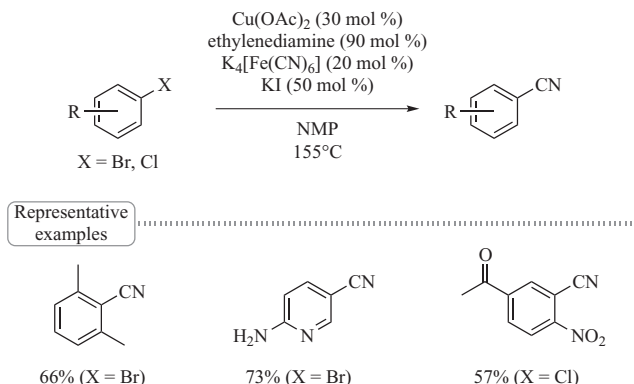


**Scheme 9.8** Copper(I)-catalyzed cyanation of aryl iodides and bromides with potassium ferrocyanide and 1,10-phenanthroline as ligand.

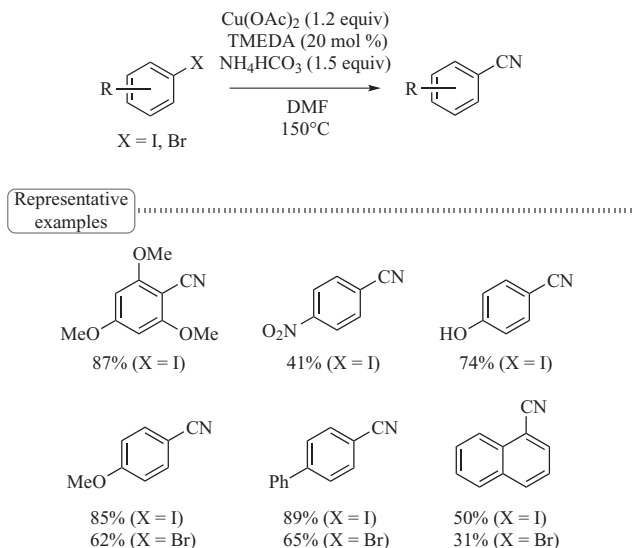
important role in the formation of cyanide. Mostly aryl iodides were tested in this reaction, aryl bromides giving inferior results. Alkyl, alkenyl, and alkynyl iodides did not work under the standard reaction conditions.

Water as a reaction medium is a popular way to render procedures more ecologically and economically friendly. However, simple inorganic cyanides



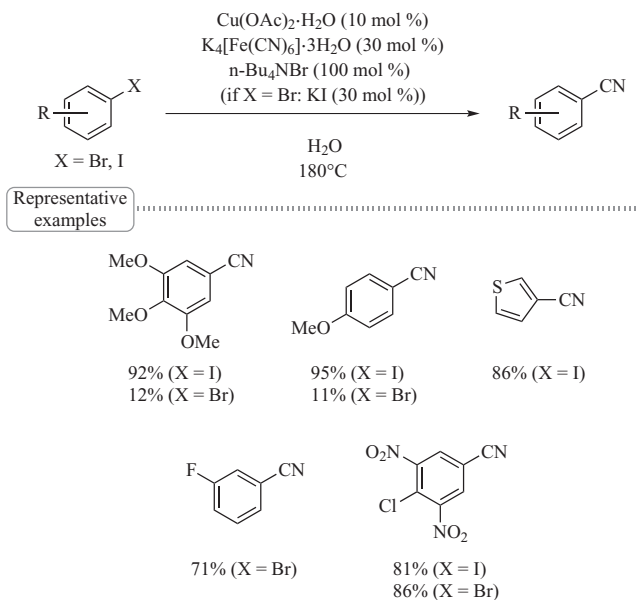


**Scheme 9.9** Copper(II)-catalyzed cyanation of aryl bromides and activated aryl chlorides with ethylenediamine as ligand.

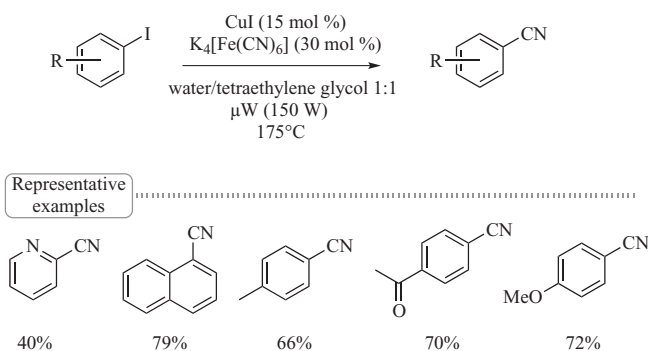


**Scheme 9.10** Copper(II)-mediated cyanation of aryl halides with *in situ* generated cyanide from ammonium hydrogencarbonate and dimethylformamide.

such as sodium- and potassium cyanide decompose in water, resulting in the evolution of highly toxic gaseous hydrogen cyanide, and are therefore hardly relevant in aqueous solutions. Due to the stability of potassium hexacyanoferrate(II) in water, the cyanation reaction can also be performed in aqueous media with this reagent, as shown by the group of Wang (Scheme 9.11).<sup>[33]</sup> While all types of aryl iodides react reasonably well, only aryl bromides with strongly electron-withdrawing substituents gave the desired



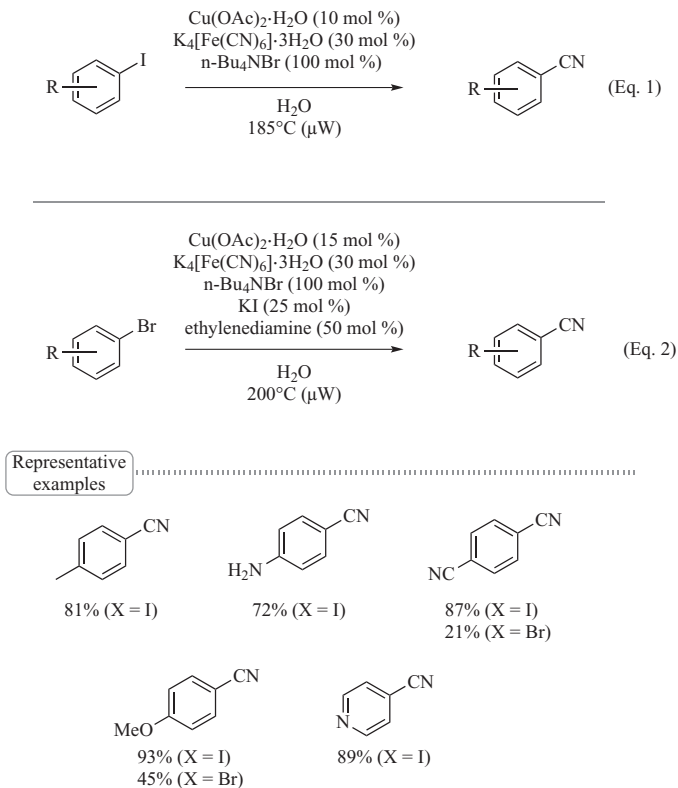
**Scheme 9.11** Ligand-free copper(II)-catalyzed cyanation in aqueous media.



**Scheme 9.12** Microwave-heated copper(I)-catalyzed cyanation of aryl iodides in aqueous media.

products. Moreover, potassium iodide (30 mol %) has to be added to ensure significant reactivity.

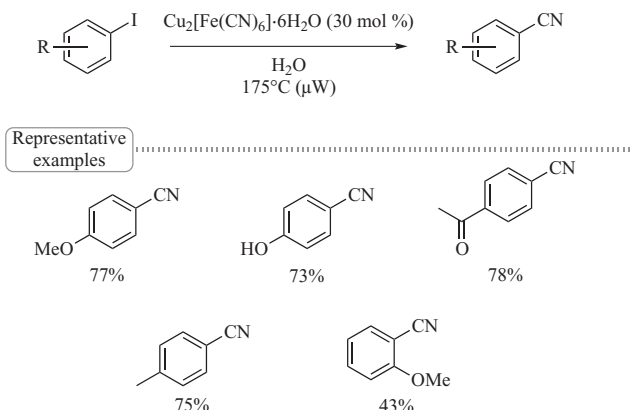
Besides economical and ecological aspects, water is an ideal solvent for the application of microwave heating. DeBlase and Leadbeater showed that the reaction times of catalytic cyanations could be reduced to 30 minutes thanks to microwave irradiation at  $175^\circ\text{C}$  (Scheme 9.12).<sup>[34]</sup> The yield of the reaction is sensitive to the water concentration, and tetraethylene glycol seems to act as a phase transfer reagent. A very similar procedure, based on palladium catalysis, has been published earlier by the same group.<sup>[35]</sup>



**Scheme 9.13** Ligand-free copper(II)-catalyzed cyanation of aryl halides with microwave irradiation in aqueous media.

The Wang group converted mainly aryl iodides to the corresponding benzonitriles with a similar set of conditions (Scheme 9.13).<sup>[36]</sup> A corrigendum revealed some errors in the first article, resulting in slightly different conditions for the conversion of aryl bromides and aryl iodides. Aryl bromides could be cyanated in good yields with the help of additives, potassium iodide and ethylenediamine, and higher reaction temperature. After pentane extraction of the final product, the aqueous phase containing the catalytic system could be reused up to six times in the cyanation of iodobenzene with a slightly diminished yield (see Chapter 20 for an overview of reusable copper-based catalytic systems).

Another microwave-based approach by Leadbeater used  $\text{Cu}_2[\text{Fe}(\text{CN})_6]$  as both catalyst and cyanide source for the cyanation of aryl iodides (Scheme 9.14).<sup>[37]</sup> In the few model reactions of standard substrates, 0.3 equiv of  $\text{Cu}_2[\text{Fe}(\text{CN})_6]$ , corresponding to 0.6 equiv catalytic copper, gave in the best case 78% yield of the nitrile product starting from 1-(4-iodophenyl)ethanone. In the case of one particularly hydrophobic substrate, 4-iodotoluene, 1 equiv of the



**Scheme 9.14** Ligand-free copper(II)-catalyzed cyanation of aryl bromides with microwave irradiation in aqueous media.

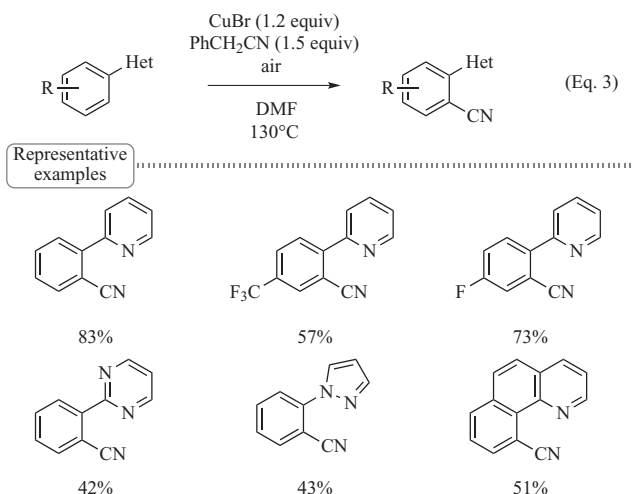
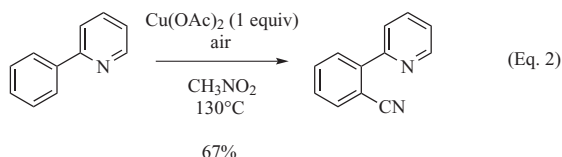
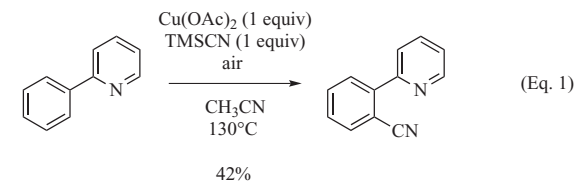
phase transfer reagent tetrabutylammonium bromide (TBAB) had to be added to increase the yield from 35% (without TBAB) to 75% (with TBAB).

As shown by all examples described in this section, efficient copper-catalyzed cyanation reactions are now available to the synthetic chemist to prepare benzonitriles using nontoxic cyanide sources<sup>[3g]</sup> such as potassium hexacyanoferrate(II) or powerful combined copper- and cyanide sources such as  $\text{Cu}_2[\text{Fe}(\text{CN})_6]$ . The last section of this chapter is devoted to copper-catalyzed oxidative cyanation reactions that are currently blossoming due to their intrinsic synthetic potential.

## 9.4 COPPER-MEDIATED OXIDATIVE CYANATIONS

The direct activation of aromatic C–H bonds gained increasing interest in recent years and, in this context, impressive oxidative cyanation reactions have been reported using very simple cyanide sources such as trimethylsilyl cyanide, nitromethane, benzyl cyanide, and even acetonitrile.<sup>[3g]</sup>

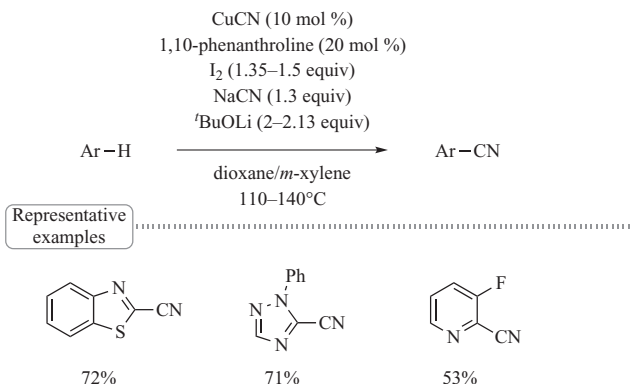
In a copper(II) acetate-mediated functionalization reaction with oxygen as the final oxidant, chelating 2-arylpyridines were cyanated in the *ortho*-position using trimethylsilyl cyanide (Scheme 9.15, Eq. 1) or nitromethane (Scheme 9.15, Eq. 2), although the detailed mechanism for this transformation still has to be elucidated.<sup>[38b]</sup> More recently, Wang and coworkers described a copper(I) bromide-catalyzed cyanation of 2-aryl heteroaromatics using benzyl cyanide as a mild source of cyanide (Scheme 9.15, Eq. 3).<sup>[38a]</sup> This very efficient transformation relies on the aerobic copper oxidation of the benzylic position of the latter to the corresponding benzoyl cyanide that could undergo a retro-cyanohydrin. In parallel, a copper(II) aerobic C–H functionalization that is thought to proceed via single-electron transfers allows a clean cyanation reaction. Pyridines, pyrimidines, and pyrazoles were shown to be efficient



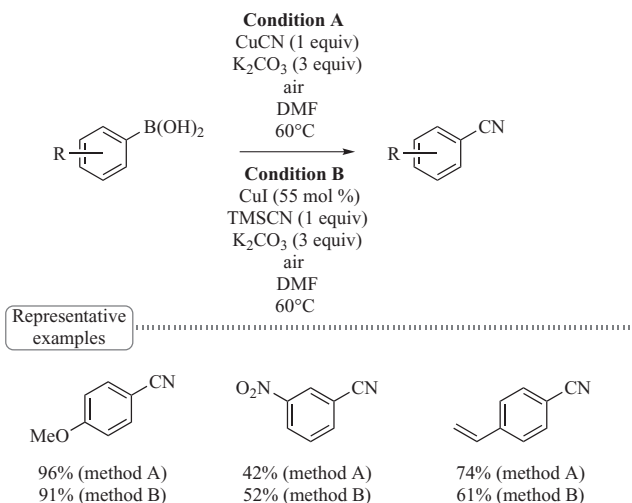
**Scheme 9.15** Ligand-free copper-mediated oxidative cyanation of 2-aryl heterocycles by C–H activation using trimethylsilyl cyanide, nitromethane, and benzyl cyanide.

directing groups in this reaction. A related cyanation reaction of indoles in position 3 using benzyl cyanide and copper(I) iodide (100 mol %) in DMF under air was also reported by Kwong in 2013.<sup>[38c]</sup>

Most recently, Do and Daugulis reported a direct copper-catalyzed cyanation of heterocyclic C–H bonds with iodine as the final oxidant.<sup>[39]</sup> Heterocycles with relatively acidic hydrogens, as oxazoles, thiazoles, imidazoles, triazoles, and azole are selectively cyanated with of copper(I) cyanide (10 mol %) and sodium cyanide as stoichiometric cyanide source in the presence of the strong base lithium *tert*-butoxide (Scheme 9.16). This overall transformation into heteroaryl cyanide involves a lithiation followed by iodination, the transient heteroaryl iodide being then converted into the desired nitrile in the only copper-catalyzed step of this domino sequence.



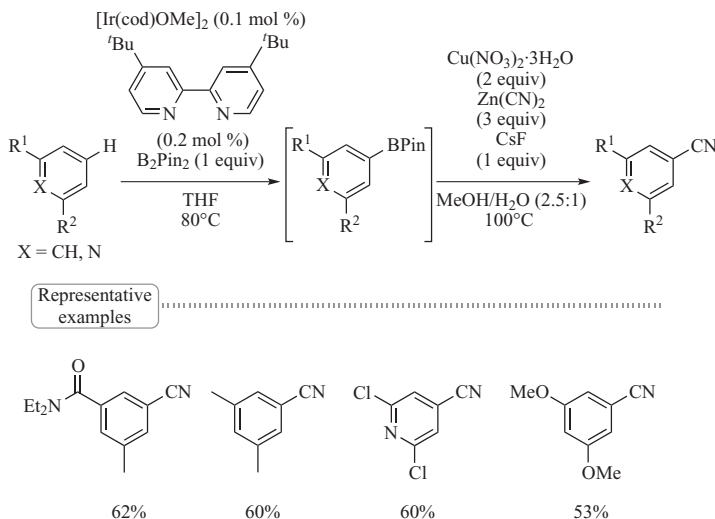
**Scheme 9.16** Copper(I)-catalyzed regioselective cyanation reaction of heterocycles.



**Scheme 9.17** Copper(I)-mediated oxidative cyanation reaction of boronic acids.

In addition to aryl halides, the cyanation of arylboronic acids has been achieved using copper(I) cyanide (1 equiv) and potassium carbonate in dry DMF under air at 60°C.<sup>[40]</sup> Alternatively, a combination of copper(I) cyanide (0.55 equiv), trimethylsilyl cyanide, and potassium carbonate in dry DMF can be used for this transformation. Thanks to the ease of activation of the carbon–boron bond, this method could be performed under mild reaction conditions and with an excellent functional group tolerance (Scheme 9.17).

Hartwig and coworkers developed a one-pot sequence to convert 1,3-disubstituted or 1,2,3-trisubstituted arenes and heteroarenes to aromatic and heteroaromatic nitriles by an iridium-catalyzed direct C–H borylation followed by a copper-mediated oxidative cyanation of the arene (Scheme 9.18).<sup>[41]</sup> The substrates are limited to 3,5-substituted and 3,4,5-substituted arenes, and



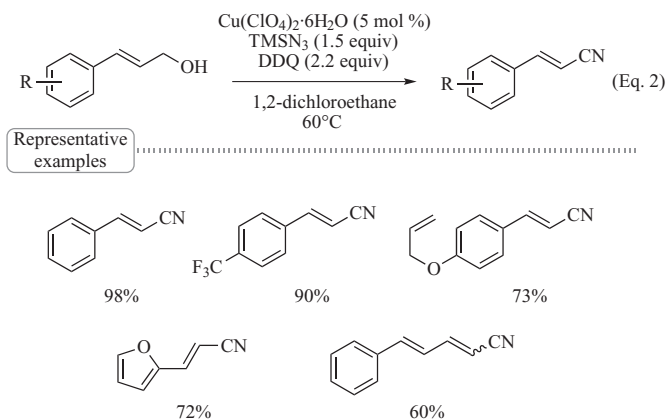
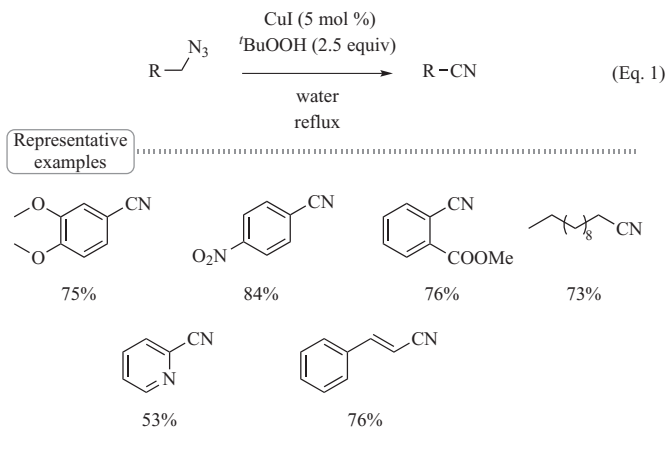
**Scheme 9.18** One-pot sequential C–H borylation and cyanation of arenes.

halide, ketone, ester, amide, and protected alcohol may be present in the coupling partner.

Finally, a totally different approach developed by Lamani and Prabhu is noteworthy.<sup>[42a]</sup> In the presence of copper(I) iodide (5 mol %) and *tert*-butyl hydroperoxide in refluxing water, a wide range of primary azides are oxidized to the corresponding nitriles (Scheme 9.19, Eq. 1). The method is applicable to both aromatic and aliphatic azides. A clever extension of this concept was reported in 2012 by the same research group (Scheme 9.19, Eq. 2): Using trimethylsilyl azide as a nitrogen source in the presence of copper(II) perchlorate, benzylic and cinnamyl alcohols were smoothly converted to the corresponding nitriles in good yields via the intermediate azides that were further oxidized with dichlorodicyanoquinone.<sup>[42b]</sup>

A new development based on the combined cyanide source (see Scheme 9.10) was introduced by Chang and coworkers (Scheme 9.20).<sup>[43a]</sup> With copper(II) nitrate mediation under oxidative conditions, aryl boron compounds (boronic acids, boronate esters, and potassium trifluoroborate) as well as electron-rich aromatics were converted to the corresponding aryl nitriles. A key intermediate is ammonium iodide, which delivers the nitrogen atom of the cyanide group and the iodide as a transient leaving group for the substrate. A related transformation was reported by Chang in 2013 for the cyanation of aryl and styrylsilanes.<sup>[43b]</sup>

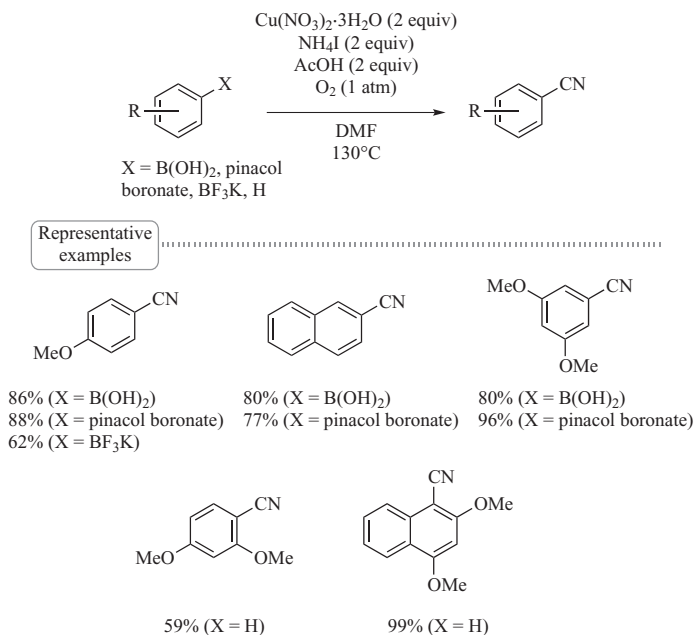
Li and coworkers reported a very simple copper(I)-catalyzed oxidative cyanation of aryl halides using acetonitrile as the cyanide source in the presence of triphenylphosphine oxide as a ligand (40 mol %) and silver oxide (1 equiv) at  $125^\circ\text{C}$  under air (Scheme 9.21).<sup>[44]</sup> In this catalytic system, the aryl copper(II) intermediate complexes the nitrile moiety of acetonitrile, followed



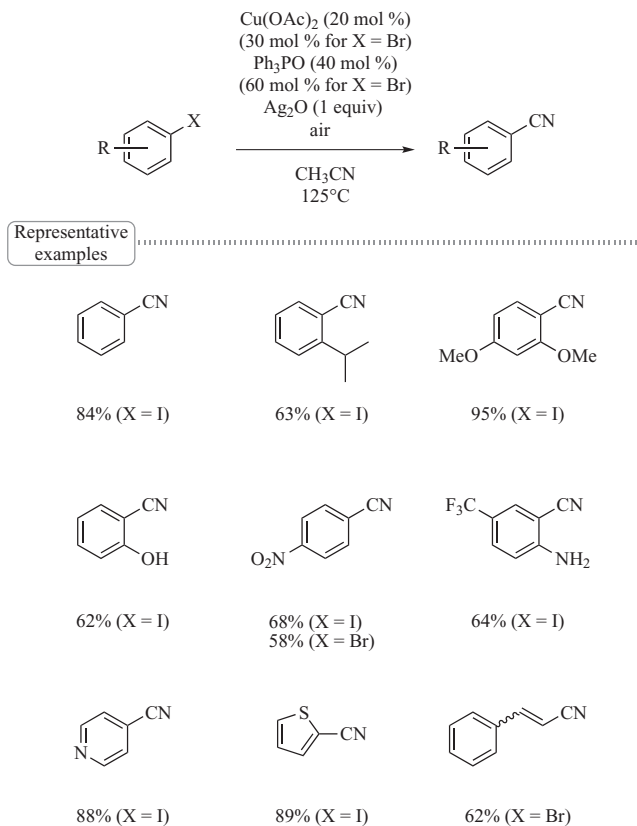
**Scheme 9.19** Copper(I) and (II)-catalyzed oxidative synthesis of nitriles from azides and alcohols.

by oxidative cleavage of the carbon–carbon  $\sigma$ -bond of acetonitrile mediated by oxygen and silver oxide. Reductive elimination of the copper(III) intermediate finally delivers the desired nitrile and regenerates the active copper(I) catalyst. Electron-rich and electron-poor aryl iodides and bromides could be converted in moderate-to-good yields to the corresponding benzonitriles under these conditions. It is worth noting that phenolic motifs were tolerated, which is in sharp contrast with previous metal-catalyzed cyanation reactions that, upon reaction of the metal cyanide with the free phenol, liberate cyanhydric acid that immediately deactivates the catalyst. Other cyanide sources were screened such as benzyl cyanide, benzonitrile, and ethylcarbonocyanide, all leading to the desired nitriles, although in lower yields. To close this section, a recent copper-mediated direct cyanation of aromatic C–H bond through a radical pathway ought to be mentioned (Scheme 9.22).<sup>[45]</sup> Han

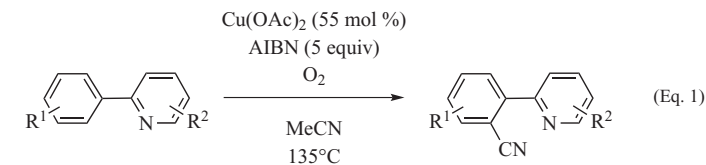




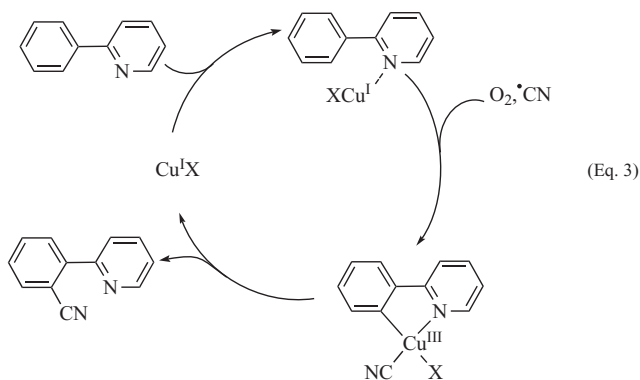
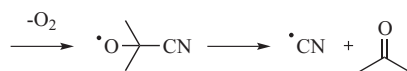
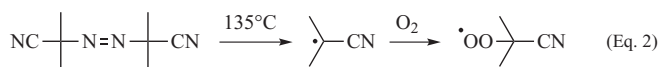
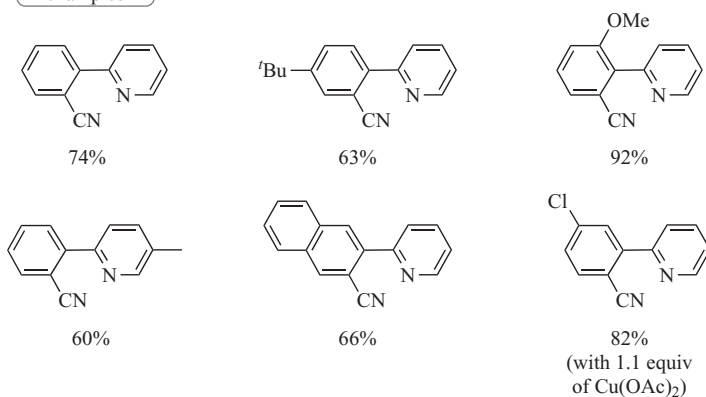
**Scheme 9.20** Copper-mediated cyanation reaction of boron derivatives and electron-rich aromatics to nitriles.



**Scheme 9.21** Copper(II)-catalyzed oxidative cyanation of aryl halides using acetonitrile as the cyanide source.



Representative  
examples



**Scheme 9.22** A free-radical copper(I)-mediated direct cyanation reaction of 2-phenyl pyridines.

reported that thermolysis of 2,2'-azobisisobutyronitrile (AIBN) under an oxygen atmosphere smoothly generated a CN radical (Scheme 9.22, Eq. 2) that could combine with a copper(I) species to lead to a copper(III) species under oxidative conditions. Upon reductive elimination, the desired cyanated aromatic was obtained (Scheme 9.22, Eq. 3). This conceptually novel cyanation reaction clearly opens a new chapter between copper salts and cyanide sources.

## 9.5 CONCLUSION

The synthesis of nitriles continues to be an important topic in organic synthesis. In general, the synthesis of benzonitriles is still far away from being benign, although in the last two decades, significant progress has been achieved in metal-catalyzed cyanations of substituted arenes. Most notable was the introduction of less toxic cyanation agents such as potassium hexacyanoferrate(II),  $K_4[Fe(CN)_6]$ , or purely organic sources of cyanide such as benzyl cyanide or acetonitrile. In parallel, the development of novel catalysts with improved efficiencies still triggers a lot of interest. However, in spite of all progress, catalytic cyanations of aryl halides and related compounds are still far away from being catalytically efficient. While some of the copper-catalyzed procedures—especially using potassium hexacyanoferrate(II),  $K_4[Fe(CN)_6]$ , or zinc cyanide as cyanide source—have been upscaled in the pharmaceutical industry up to the kilogram scale, none of these reactions have been so far applied in industry on a larger scale. Clearly, more general and more efficient procedures are needed to achieve this. In order to be applied in the fine chemical industry, the conversion of less expensive aryl chlorides is most desirable. However, this goal is also far away from being solved in a general manner. Finally, and from an academic perspective, the mechanistic foundations of the copper-catalyzed cyanation reactions is desired. Hopefully, this knowledge will lead to improved and “greener” cyanations in the future.

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