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Cyano-Group Sources

Synthesis of Aromatic Nitriles Using Nonmetallic Cyano-Group Sources

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arenes · aryl halides · aryl nitriles · cyanides · nonmetallic cyano-group sources

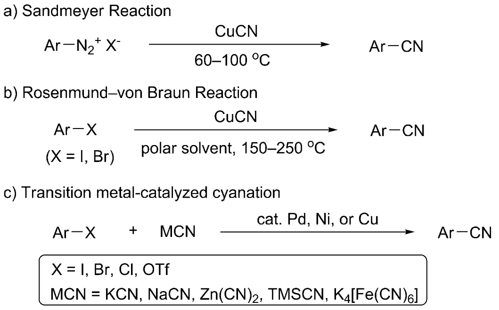
Aromatic nitriles are prepared efficiently through transition-metal-mediated cyanation of aryl (pseudo)halides with metallic cyano-group sources, such as CuCN, KCN, NaCN, $Zn(CN)_2$, TMSCN, or $K_4[Fe(CN)_6]$. However, this approach often suffers from drawbacks, such as the formation of stoichiometric amounts of metal waste, the poisoning of the metal catalysts, or the generation of toxic HCN gas. As a result, a range of "nonmetallic" organic cyano-group sources have been explored for the cyanation of aryl halides and arene C−H bonds. This Minireview summarizes types of nonmetallic cyano-group sources and their applications in the preparation of aryl nitriles.

1. Introduction

Nitriles are an important building unit in organic synthesis, and in particular aryl nitriles are widely present as a key motif in numerous products, such as dyes, herbicides, agrochemicals, pharmaceuticals, and electronic materials.[1] Moreover, the nitrile group serves as a versatile precursor for various functional groups, such as amines, amidines, tetrazoles, aldehydes, amides, or other carboxy derivatives.[2] The most conventional synthetic routes to aryl nitriles are the Sandmeyer reaction (Scheme 1 a)[3] and the Rosenmund–von Braun protocol (Scheme 1 b),[4] which have been reliably utilized, even on a preparative scale. However, they suffer from a critical drawback, because both reactions require stoichiometric amounts of CuCN under relatively harsh conditions. As a result, a variety of new procedures have been extensively investigated for in the synthesis of aryl nitriles.[5] In particular, the successful development of transition-metal-catalyzed cyanation of aryl halides or their derivatives is considered to be highly promising.[6] In this approach, reaction partners for the coupling with aryl halides are mainly metal- or metalloid-bound cyanide sources, such as KCN,[7] NaCN,[8] $Zn(CN)_2$,[9] TMSCN,[10] or $K_4[Fe(CN)_6]$[11] (Scheme 1 c).

Although metal-catalyzed cyanation reactions have attractive features, they also have some drawbacks: 1) the cyano-group sources employed are generally toxic and need careful handling to prevent the generation of hazardous HCN gas, 2) metal waste is produced in stoichiometric amounts, thus inducing an environmental issue, and 3) a careful control of the cyanide concentration is often required to maintain the catalyst activity, which is frequently influenced by the formation of inactive cyano group/transition-metal complexes.[12]

In order to deal with those problems mentioned above, the use of nonmetallic cyano-group sources has been scrutinized as an alternative in recent years. Although the development of such sources is still in an early stage, they show promise in the metal-mediated cyanation of aryl halides and arene C−H bonds. Therefore, it is anticipated that this approach of using nonmetallic cyano-group sources can be further developed with a high level of efficiency, selectivity, and practicability with minimum environmental concerns. Herein, recent progress in the search for nonmetallic cyano-group sources and their applications in the cyanation of



Scheme 1. Cyanation methods that lead to aryl nitriles.

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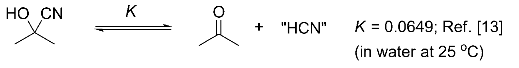
various substrates is described. Organic cyano-group sources are classified according to whether they contain the "CN" unit in their molecular skeleton or whether the precursors generate the "CN" unit in situ through additional reactions.

2. Organic Precursors with a "CN" Unit

Recently, different organic compounds that contain a CN moiety were successfully used as efficient cyano-group sources in the transition-metal-catalyzed cyanation of diverse substrates. Unlike metal cyanide precursors, the CN moiety in these compounds is connected to a C, O, S, or N atom by covalent rather than ionic bonds. Obviously, one of the most notable advantages in using these organic cyano-group sources in the metal-catalyzed cyanation is that they do not produce any metal wastes, and that deactivation of transition-metal catalysts by a high concentration of cyanide ions is also minimized. However, an additional synthetic effort to prepare the cyano-group-containing organic compounds is often necessary.

2.1. Acetone Cyanohydrin

Acetone cyanohydrin forms an equilibrium with acetone and hydrogen cyanide (HCN), although the concentration of HCN is insignificant at ambient conditions (Scheme 2).[13]



Scheme 2. Acetone cyanohydrin, a useful HCN surrogate.

Because the equilibrium will shift toward the right side upon the progress of any plausible cyanation reaction, acetone cyanohydrin can be regarded as one of the safe and inexpensive surrogates of HCN with minimum environmental concern.[14] Although recent focus in this regard has been mainly in metal-catalyzed reactions of epoxides, aziridines, olefins, and tertiary amines,[15] research efforts on the catalytic cyanation of aryl halides using acetone cyanohydrin started only in recent years.

In 2003, Beller and co-workers demonstrated that the constant dosage of acetone cyanohydrin solves the problem associated with an excess amount of cyanide ions during the metal-catalyzed cyanation of aryl halides.[16] Using a syringe pump to maintain a continuous addition of a small volume of the liquid reagent, they reported the first example of the Pd-catalyzed cyanation of aryl halides using acetone cyanohydrin (Scheme 3). Slow addition of acetone cyanohydrin allowed lowering the reaction temperature and decreasing the catalyst loading in comparison with to their previous cyanation conditions, in which KCN was employed.[12c,17] By a careful tuning of the ratio of palladium catalyst/phosphine ligand and the dosage rate, a high turnover number (TON; up to 1900) was observed.

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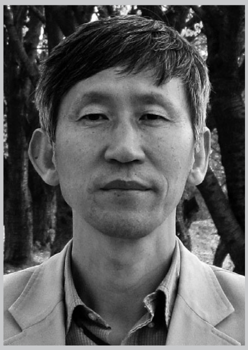
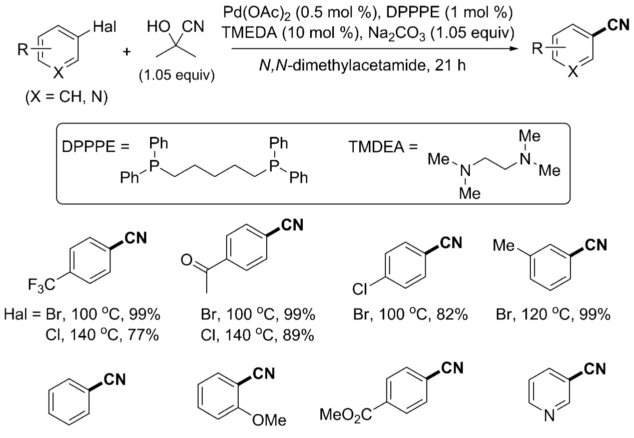


Sukbok Chang received his B.Sc. degree in chemistry from Korea University in 1985, and his M.Sc. degree from KAIST under the guidance of Professor Sunggak Kim in 1987. In 1996, he earned his PhD degree in organic chemistry at Harvard University, working with Professor Eric N. Jacobsen. After his postdoctoral experience with Professor Robert H. Grubbs at Caltech, he joined Ewha Womans University (Seoul) as an assistant professor in 1998, and then moved to KAIST (Daejeon) in 2002. His research interests are the development, understanding, and synthetic applications of transition-metal catalysis.

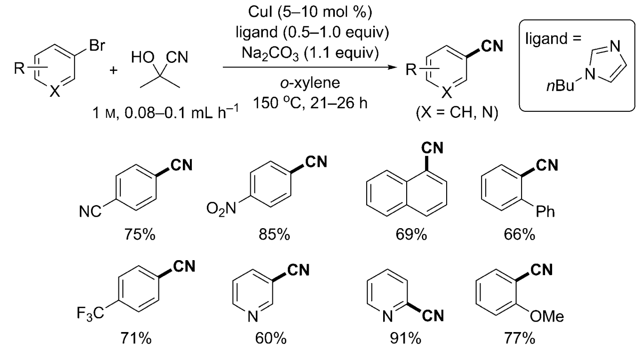
The substrate scope of aryl halides was investigated using $Pd(OAc)_2$ (0.5 mol %), 1,5-bis(diphenylphosphanyl)pentane (DPPPE, 1 mol %), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 10 mol %), and Na_2CO_3 (1.05 equiv) in *N,N*-



Scheme 3. Pd-catalyzed cyanation of (hetero)aryl halides.

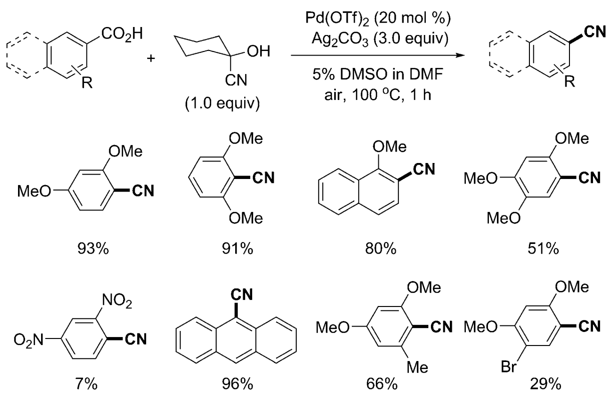
dimethylacetamide (DMAc) as solvent. Relative to the aryl halides, 1.05 equiv of acetone cyanohydrin (1M, dosage rate: 0.1 mL h^{-1}) was employed. While electron-poor and electron-rich aryl bromides gave excellent product yields, *ortho*-substituted aryl bromides resulted in lower conversion and yields. In addition to aryl bromides, heteroaryl bromides and activated aryl chlorides were smoothly converted to the corresponding benzonitriles with good yields, albeit at slightly higher temperatures. It is interesting to note that both DPPPE and TMEDA additives were required to achieve high efficiency, and only poor conversion was observed without the TMEDA ligand. The present study can be regarded as a significant advance in the related areas, eventually leading to practical applications.

Beller and co-workers also reported the Cu-catalyzed cyanation of (hetero)aryl bromides with acetone cyanohydrin in 2011 (Scheme 4).[18] The highest catalytic activity was obtained by the combined use of CuI and 1-butylimidazole as ligand. Various aromatic nitriles were produced in good yields by fine tuning of the dosage rate of acetone cyanohydrin. Compared to the previous Pd-catalyzed cyanation,[16] the yields in this Cu-catalyzed version were generally lower, even at higher temperature (150 °C). However, *ortho*-substituted aryl bromides were smoothly cyanated under these conditions, while their cyanation was problematic under palladium catalysis.



Scheme 4. Cu-catalyzed cyanation of (hetero)aryl bromides.

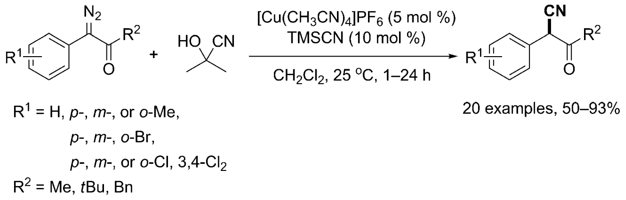
Similar to acetone cyanohydrin, cyclohexanone cyanohydrin was also used as a source of cyanide ions. In 2010, Taran and co-workers reported the Pd-catalyzed decarboxylative cyanation of arene carboxylic acids by using cyclohexanone cyanohydrin (Scheme 5).[19] To optimize the reaction conditions, they employed the Heck-type olefination protocol developed by Myers et al.[20] in the cyanation of 2,4-dimethoxybenzoic acid. The solvent system, which consisted of 5% dimethylsulfoxide (DMSO) in *N,N*-dimethylformamide (DMF), played a crucial role to achieve high cyanation efficiency. The use of crown ethers or soluble cyanide salts, such as ammonium cyanide, resulted in the decrease of product yields, thus suggesting that deactivation of the catalyst by an excess amount of cyanide ions occurred during the reaction. To solve this deactivation problem, cyclohexanone cyanohydrin was successfully utilized as the liquid cyanide source. Finally, the use of $Pd(OTf)_2$ and Ag_2CO_3 in the DMSO/DMF solvent system was optimized by the slow addition of cyclohexanone cyanohydrin.



Scheme 5. Decarboxylative cyanation of arene carboxylic acids.

Interestingly, it was found that in the substrates, the presence of at least one *ortho* substituent with electron-donating properties was necessary to obtain high product yields, although the reason for this result is not clear. Halides turned out to be compatible with the present reaction conditions. Although it is the first application of organic cyanohydrin reagents in the decarboxylative cyanation, there are some unsolved limitations, such as the necessity for a high loading of palladium catalyst and the requirement of an *ortho* substituent in the substrates.

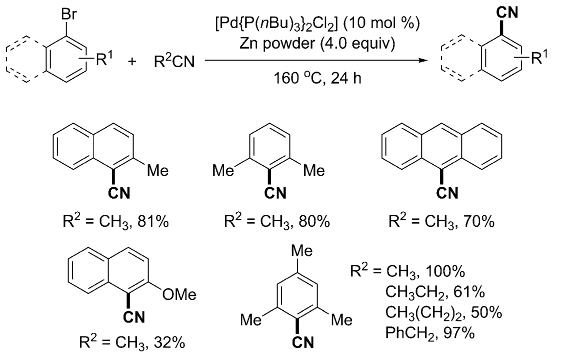
In addition, Chang and co-workers demonstrated the synthetic utility of acetone cyanohydrin in the hydrocyanation of diazoacetates.[21] In the presence of catalytic amounts of a copper species and TMSCN, α-aryl diazoacetates readily reacted with acetone cyanohydrins to afford the corresponding α-aryl cyanoacetates in moderate to high yields under mild conditions (Scheme 6).



Scheme 6. Cu-catalyzed hydrocyanation of α-aryl diazoacetate.

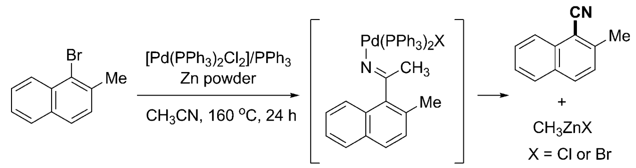
2.2. Carbon-Bound Cyano-Group Sources

In 1998, Cheng and co-workers reported the Pd- or Ni-catalyzed cyanation of aryl halides with alkyl nitriles (Scheme 7).[22] In this reaction, alkyl nitriles act as both solvent and cyanide source. In addition to acetonitrile, other alkyl nitriles, such as propionitrile, *n*-butyronitrile, and benzyl nitrile, reacted to afford the benzonitrile products, and the yields were greatly dependent on the amount of phosphine ligand and zinc powder employed. Interestingly, only *ortho*-substituted bromoarenes, such as 1-bromo-2-methylnaphthalene and 2-bromomesitylene, showed higher reactivity. Based on a mechanistic investigation, it was suggested that the



Scheme 7. Pd-catalyzed cyanation of aryl bromides with alkyl nitriles.

cyanation occurs through the formation of palladoimine **1** followed by the C–C bond cleavage (Scheme 8). Upon the analysis of the side products, an alkyl–zinc complex (RZnX) was proposed to have formed. Importantly, both palladium and zinc species were required for the C–C bond formation and cleavage. This example demonstrated that acetonitrile could be used as one of the most convenient and cheap cyano-group sources in the transition-metal-catalyzed cyanation of aryl halides. However, the requirement of a phosphine ligand and excessive amounts of zinc powder in addition to the necessity of an *ortho* substituent in aryl halides have to be addressed in order to make this cyanation method more practical.



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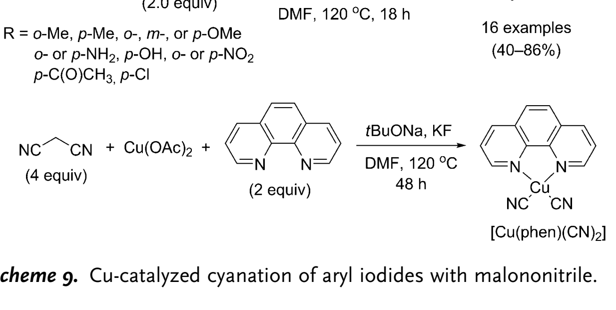
Scheme 8. Mechanistic proposal for the Pd-catalyzed cyanation with acetonitrile.

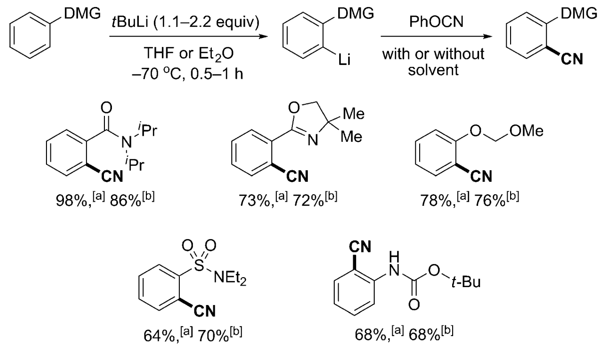
Very recently, Zhou and co-workers developed the Cu-catalyzed cyanation of aryl iodides with malononitrile (Scheme 9).[23] Although malononitrile was previously known to react with aryl halides to give aryl malononitriles[24] or arene carboxylic acids[25] under copper catalysis, cyanation of aryl halides with malononitrile was first achieved with $Cu(OAc)_2$ in the presence of 1,10-phenanthroline, KF, and *t*BuONa in DMF. Without copper or 1,10-phenanthroline, the cyanation did not occur. Aryl iodides substituted with electron-donating groups were smoothly transformed to the corresponding nitriles, whereas the reaction of substrates that bear electron-withdrawing groups was rather sluggish. Mechanistic studies showed that copper–cyano complex $[Cu(phen)(CN)_2]$ was generated in situ through the Cu-mediated cleavage of a C–CN bond of malononitrile. The observation that KF did not affect the cyanation of aryl halides with a preformed $[Cu(phen)(CN)_2]$ species led the authors to propose that KF is only involved in the cleavage process of C–CN bond of malononitrile.



Scheme 9. Cu-catalyzed cyanation of aryl iodides with malononitrile.

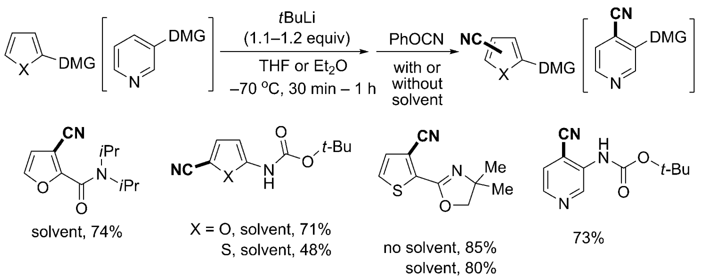
2.3. Oxygen- and Sulfur-Bound Cyano-Group Sources

Sato and Yue reported a two-step cyanation procedure of (hetero)arenes through lithiation followed by electrophilic cyanation with phenyl cyanate (PhOCN),[26] which can be easily prepared from phenol and BrCN (Scheme 10).[27] After the lithiation of arenes that bear a directing metalation group (DMG) with *tert*-butyllithium, the reaction of lithiated arenes with phenyl cyanate (without solvent or in diethyl ether or THF) afforded the desired products, which were cyanated at the *ortho* position relative to the DMG. Among various DMGs, the diisopropylamide group gave an especially high efficiency both under conditions with and without solvent.



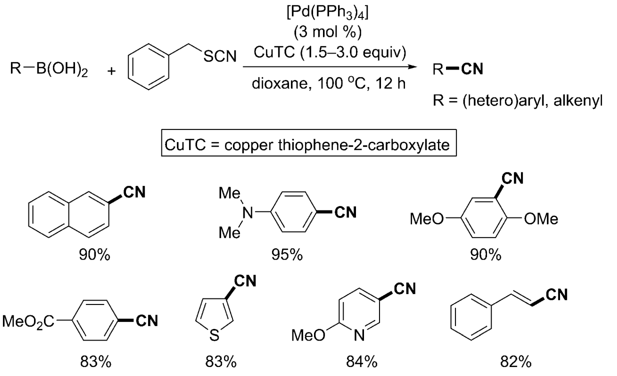
Scheme 10. Electrophilic cyanation of arenes with phenyl cyanate. [a] Without solvent. [b] With solvent.

In addition to arenes, heteroarenes, such as furans and thiophenes, were also readily converted to cyanated products (Scheme 11). It is noteworthy that the cyanation of N-Boc-substituted furan or thiophene led to the exclusive formation of products cyanated at the 5 position, unlike the cyanation of substrates with other DMGs. The observed regioselectivity was rationalized by the preferential lithiation at the α position relative to heteroatoms in the heterocycles, presumably because of the weaker directing ability of the Boc-protected amino substituent. However, 3-(*N*-Boc-amino)pyridine was cyanated selectively at the 4 position rather than the *ortho* sites (2 or 6 position).



Scheme 11. Cyanation of heteroarenes with phenyl cyanate.

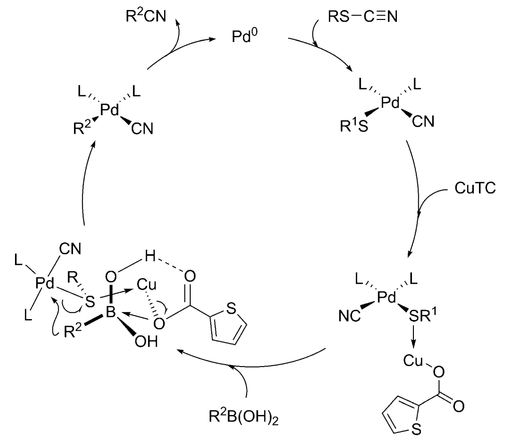
Zhang and Liebeskind reported the Pd-catalyzed cross-coupling of thiocyanates with boronic acids in the presence of copper(I) thiophene-2-carboxylate (CuTC; Scheme 12).[28]



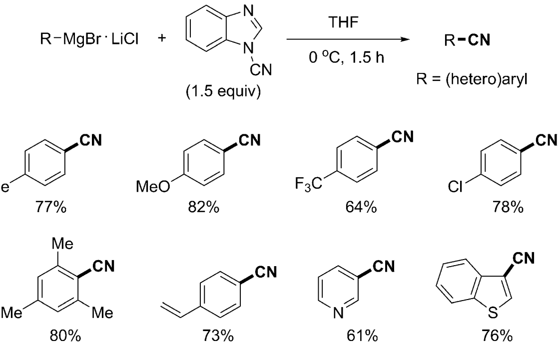
Scheme 12. Cyanation of (hetero)aryl and alkenyl boronic acids with benzyl thiocyanate.

The nature of the organic thiocyanates did not have much influence on the reaction efficiency, and commercially available benzyl thiocyanate was thus employed in this reaction. While high cyanation yields were obtained with electron-rich substrates under the optimized conditions, the reaction of electron-poor aryl boronic acids was rather sluggish. In addition, alkenyl boronic acids were also cyanated in high yield, but aryl boronate esters and boroxines were ineffective substrates.

It was proposed that the cyanation may start with an oxidative addition of benzyl thiocyanate to Pd^0,[29] followed by the transmetalation from boron to palladium and then reductive elimination (Scheme 13). In addition, on the basis of previous reports, it was suggested that the copper additive acts as a thiophilic agent to enhance the polarization of the palladium−thiolate bond, while simultaneously providing borophilic activation by coordination of carboxylate to the boron atom.[30]



Scheme 13. Mechanistic proposal for the catalytic cyanation with benzyl thiocyanate.

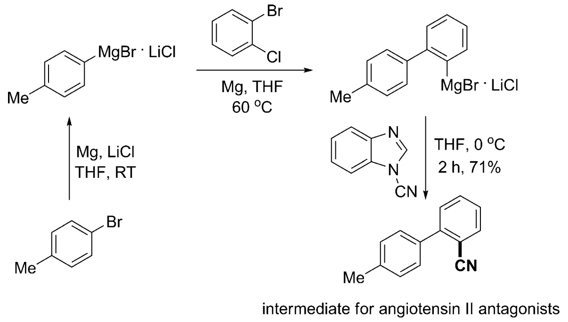


Scheme 14. Electrophilic cyanation with *N*-cyanobenzimidazole.

2.4. Nitrogen-Bound Cyano-Group Sources

Beller and co-workers recently reported the electrophilic cyanation of aryl Grignard reagents with a nitrogen-bound cyano-group source (Scheme 14).[31] Among the various nitrogen-bound cyano-group sources examined, *N*-cyanobenzimidazole,[32] which can be prepared by the reaction of imidazole with cyanogen bromide, exhibited the highest reaction efficiency. Careful tuning of temperature and solvent gave an improvement in yield and selectivity, and cyanation in THF at 0 °C constituted optimal conditions. Electron-rich, electron-poor, and sterically demanding benzonitriles were readily accessible in good yields from the corresponding arylmagnesium bromides.[33]

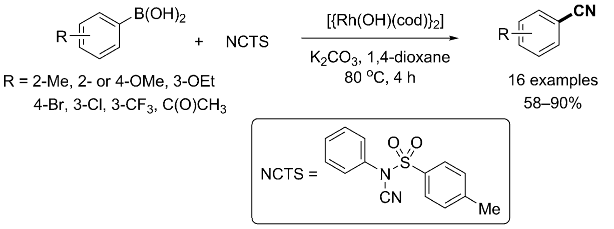
Interestingly, the above-mentioned electrophilic cyanation could be applied in a domino Grignard coupling/cyanation sequence to produce 2-biarylnitriles (Scheme 15). For example, the coupling of 4-tolylmagnesium bromide with



Scheme 15. Domino-Grignard-coupling and cyanation.

benzyne, generated in situ from magnesium and 2-chloro-1-bromobenzene, followed by cyanation with *N*-cyanobenzimidazole gave 2-(4-tolyl)benzonitrile in 71 % overall yield. This protocol provides a facile approach for central intermediates for several angiotensin II antagonists.

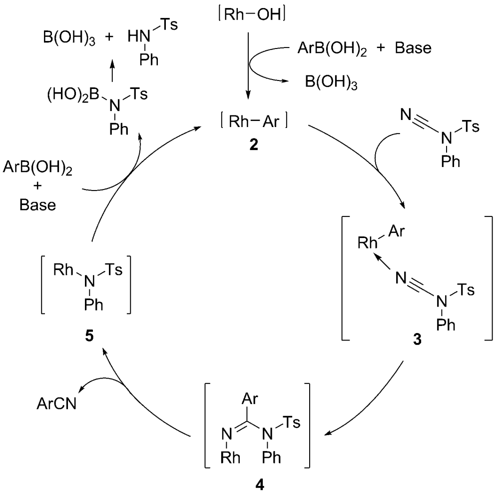
Subsequently, Beller and co-workers developed the Rh-catalyzed cyanation of aryl boronic acids with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) in 2011 (Scheme 16).[34] NCTS was readily synthesized by the reaction of phenylurea with *p*-toluenesulfonyl chloride in pyridine. The cyanation of aryl boronic acids proceeded smoothly using [{Rh(OH)(cod)}$_2$] (1 mol %; cod = 1,5-cyclooctadiene) and of K_2CO_3 (1.0 equiv) in 1,4-dioxane at 80 °C. While the use of boric acid (H_3BO_3) instead of K_2CO_3 afforded products in excellent yields, K_2CO_3 was superior to H_3BO_3 with respect to substrate diversity. Various arylboronic acids that contained a large range of functional groups as well as *ortho* substituents were readily converted to the corresponding nitriles in high yields. Synthetically useful halogenated benzonitriles were also synthesized from aryl boronic acids in good yield. Moreover, it was interesting to note that alkenyl boronic acids were also cyanated. While phenyl boronic acid pinacolate did not undergo cyanation, phenyl boronate neopentylglycol ester was converted smoothly into the corresponding benzonitrile in moderate yield.



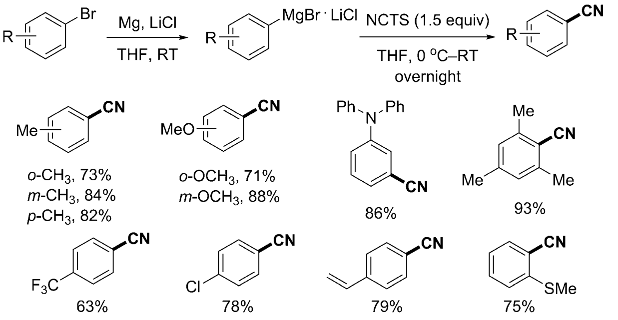
Scheme 16. Rh-catalyzed cyanation of aryl boronic acids with NCTS.

The authors proposed the cyanation mechanism based on the precedent Rh-catalyzed addition of aryl boronic acids to unsaturated bonds (Scheme 17).[35] First, transmetalation of aryl boronic acids with a rhodium complex would generate an aryl–rhodium species **2**. Upon coordination of **2** with NCTS to form **3**, a (imido)rhodium species **4** can be formed by the transfer of an aryl group to the carbon atom of the nitrile group. Then, rearrangement of **4** produces benzonitrile and rhodium species **5**. Finally, transmetalation affords aryl–rhodium species **2**, thus completing the catalytic cycle.

In addition, NCTS was employed by Beller and co-workers in the electrophilic cyanation of aryl Grignard reagents (Scheme 18).[36] Similar to their previous report,[31] lithiation of aryl bromides and subsequent addition of NCTS gave nitrile products. While cyanation of the pregenerated aryl Grignard reagents with NCTS was sluggish at 0 °C in different solvents, increasing the temperature of reactions in THF to room temperature improved the product yields, irrespective of electronic and steric demand of the substrates.

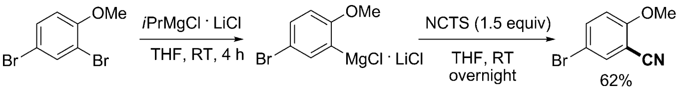


Scheme 17. Mechanistic proposal for the Rh-catalyzed cyanation of boronic acids.



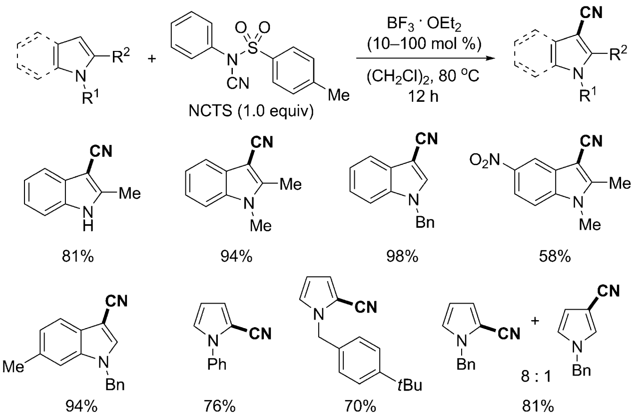
Scheme 18. Cyanation of aryl bromides with NCTS.

Interestingly, Beller and co-workers observed a selective cyanation of dibromo arenes. For example, formation of a Grignard reagent at the *ortho* position in 2,4-dibromoanisole was selectively achieved by a bromine–magnesium exchange with *i*PrMgCl·LiCl (Scheme 19). Consequently, cyanation of in situ generated Grignard reagent with NCTS produced 4-bromo-2-cyanoanisole at room temperature in acceptable yield. In addition, several intermediates of pharmaceuticals and agrochemicals were synthesized to demonstrate the general utility of the present cyanation protocol.



Scheme 19. Regioselective cyanation of 2,4-dibromoanisole.

Another example of the electrophilic cyanation with NCTS was recently reported by Wang and co-workers (Scheme 20).[37] They observed that $BF_3{\cdot}OEt_2$ catalyzed the direct cyanation of a C–H bond of indoles with NCTS at 80 °C. The use of other Lewis acids, such as $Zn(OTf)_2$ and $AlCl_3$, or Brønsted acids, such as trifluoroacetic acid, was ineffective. The reactions of both protected and unprotected indoles proceeded smoothly to afford the corresponding 3-cyano indoles in high yields. The presence of substituents at C2 did not affect the efficiency and regioselectivity in the



Scheme 20. $BF_3{\cdot}OEt_2$-mediated cyanation of indoles and pyrroles.

present cyanation. While electron-rich indoles showed excellent yields when catalytic amounts of $BF_3{\cdot}OEt_2$ were used, electron-poor indoles required 1.0 equiv of the Lewis acid in order to give acceptable yields. Pyrroles and electron-rich benzenes were also found to be suitable substrates for this reaction, although higher amounts of $BF_3{\cdot}OEt_2$ were required to give slightly lower product yields compared to those of indoles.

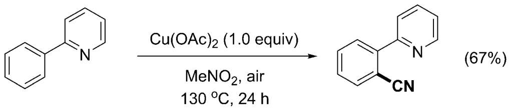
Up to now, organic cyano-group sources that contained the "CN" unit within the molecule were discussed. These organic precursors were often employed in the electrophilic cyanation of electron-rich arenes or analogues, including Grignard reagents and indoles. In addition, aryl boronic acids were readily cyanated with organic cyano-group sources. One of the most significant features in this study with CN-containing cyano-group sources is the relative ease of design and synthesis of those compounds to test their efficiency in cyanation reactions. It is anticipated that a variety of more efficient and practical CN-containing cyano-group sources will be developed in the near future, eventually leading to highly attractive cyanation procedures using those precursors.

3. Cyano-group Sources Without a "CN" unit

Very recently, certain organic precursors, which do not bear a "CN" unit, were applied to the cyanation reactions, either alone or in combination with other reactants. Because they do not have the cyano unit in their molecular skeletons, the detailed pathway that delivers the cyano group from those compounds is not fully understood in most cases. In addition, cyanation reactions that utilize these precursors sometimes require stoichiometric amounts of co-catalysts or additives under rather harsh conditions. Despite these difficulties, cyanation procedures based on this approach can provide a practical tool with minimum environmental concerns.

3.1. Nitromethane

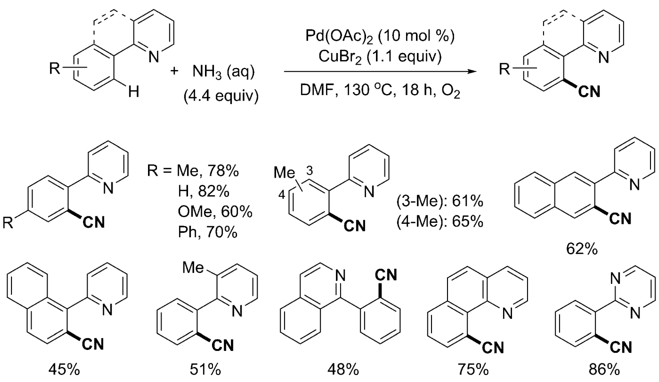
During the course of a study on the Cu-catalyzed functionalization of arene C–H bonds using O_2 as an oxidant, Yu and co-workers observed that nitromethane ($MeNO_2$) could be a "CN" group source in the cyanation of 2-phenylpyridine (Scheme 21).[38] In the reaction of 2-phenylpyridine with copper(II) acetate (1.0 equiv) in nitromethane at 130 °C, cyanation occurred at the 2 position of the phenyl moiety of the substrate to give 2-(2-cyanophenyl)pyridine in moderate yield. Although a single-electron-transfer (SET) pathway involving a copper species was proposed, the exact mechanism for the formation of the cyano unit from nitromethane needs to be further elucidated in due course.



Scheme 21. Cu-mediated cyanation with nitromethane.

3.2. Combined Cyano-Group Sources

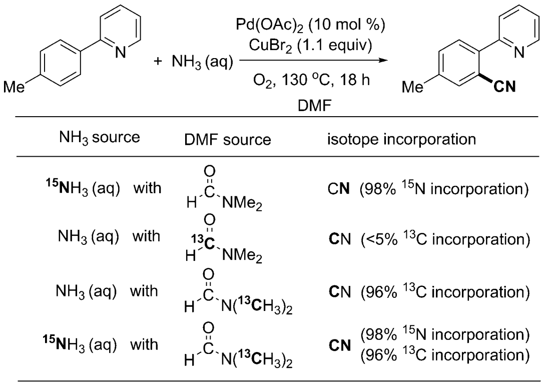
DMF is used in organic synthesis both as a polar reaction solvent and as a multipurpose precursor for the formation of various units, including O, CO, NMe_2, $CONMe_2$, Me, and CHO.[39] In 2010, Kim and Chang found that a combined use of DMF and aqueous ammonia provided the cyano group under Cu-mediated oxidative conditions (Scheme 22).[40] This unprecedented protocol was utilized in the direct cyanation of 2-phenylpyridine and derivatives that bear chelating groups and in which arene C–H bonds are activated by the palladium catalyst that is employed.[41]



Scheme 22. Cyanation of arene C–H bonds with DMF and ammonia.

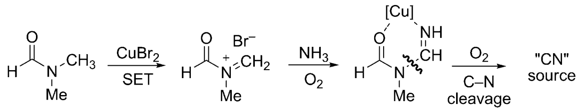
Palladium, copper, DMF, and NH_3 (aq.) were all required for the cyanation under these conditions. A variety of 2-phenylpyridine derivatives were cyanated to give benzonitrile products in moderate to high yields. The reaction was highly regioselective, affording only one isomeric product, even in cases in which two reacting sites existed. Based on a series of labeling experiments, it was concluded that the nitrogen and carbon atom of the introduced CN moiety originated from ammonia and the *N*,*N*-dimethyl group of DMF, respectively

(Scheme 23). Interestingly, a doubly labeled nitrile product could be readily accessed by using $^{15}NH_3$ and $(^{13}CH_3)_2NCHO$ under the present conditions.



Scheme 23. Labeling experiments with isotopic ammonia and DMF.

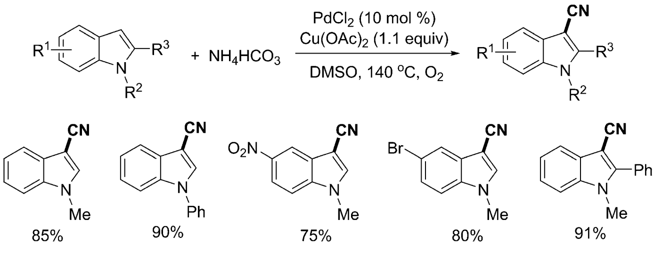
The mechanistic pathway for the generation of the CN unit was also proposed (Scheme 24). A Cu^{II}-mediated consecutive single-electron transfer was assumed to take place first, converting DMF to an iminium species,[42] which reacts with ammonia to afford an amidine intermediate. The C–N bond cleavage of amidine was believed to proceed under the employed oxidative conditions, thus releasing the cyano moiety.[43]



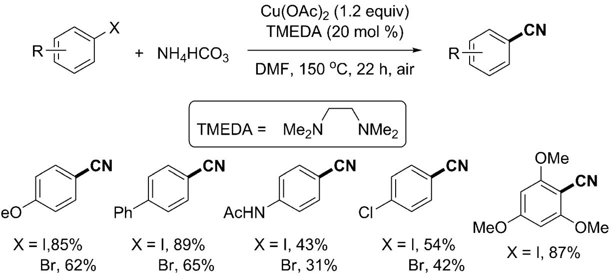
Scheme 24. Proposed major pathway for the generation of the "CN" group.

Cheng and co-workers reported that ammonium bicarbonate and DMSO could also be employed as combined cyano-group sources in the Pd-catalyzed cyanation of indoles (Scheme 25).[44] Similar to the above-mentioned results of isotope experiments, the nitrogen and carbon atoms originated from the ammonium salt and the methyl group of DMSO, respectively. In addition, cyanide anions were formed under the conditions, as evidenced by an indicator test.

Subsequently, Cheng and co-workers applied similar conditions by using combined cyano-group sources for the cyanation of aryl halides (Scheme 26).[45] In this report, aryl halides were cyanated with NH_4HCO_3 and DMF instead of DMSO in the presence of $Cu(OAc)_2$ (1.2 equiv) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 0.2 equiv) at 150 °C. While electron-rich reactants showed good reactivity, cyanation of electron-poor iodides and bromides was rather sluggish. Aryl iodides bearing an *ortho* substituent were good substrates in the present cyanation.

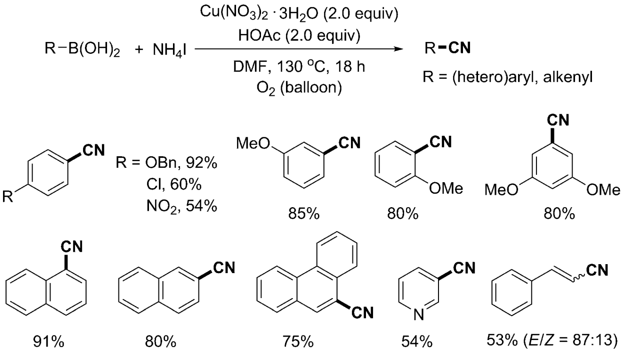


Scheme 25. Cyanation of indoles with NH_4HCO_3 and DMSO.



Scheme 26. Cyanation of aryl halides with NH_4HCO_3 and DMF.

More recently, Chang and co-workers demonstrated that the new strategy of generating the CN group in situ from two combined sources, ammonium iodide and DMF, could be readily applied to the cyanation of aryl boronic acids (Scheme 27).[46] Smooth cyanation occurred in the presence of $Cu(NO_3)_2{\cdot}3H_2O$ and acetic acid at 130 °C under O_2 atmosphere. It is noteworthy that aryl boronic esters and borate salts as well as aryl boronic acids were all cyanated with similar efficiency. Cinnamonitrile was obtained from (*E*)-styreneboronic acid as a mixture of two stereoisomers in moderate yield.



Scheme 27. Cyanation of (hetero)aryl and alkenyl boronic acids with NH_4I and DMF.

The cyanation of aryl boronic acids or esters proceeded via an aryl iodide intermediate, which was formed within a short period of time after the start of the reaction (Figure 1). This result suggests that ammonium iodide plays a dual role as a supplier of an iodide anion for the formation of an iodobenzene intermediate, as well as a source of the nitrogen atom of the CN group in the product.

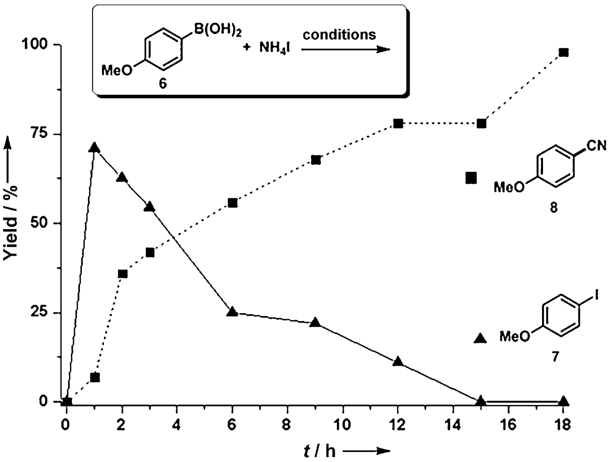
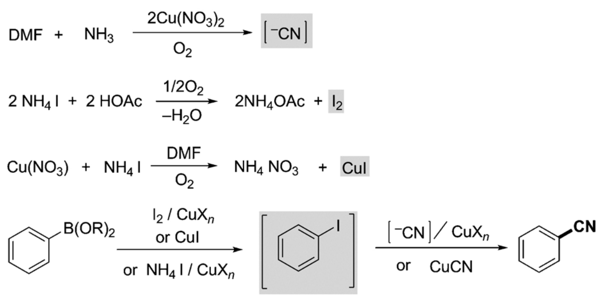


Figure 1. Reaction profile in the Cu-mediated cyanation of 4-methoxyphenyl boronic acid with ammonium iodide and DMF.

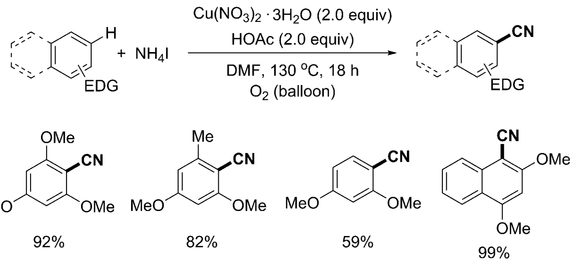
In this cyanation method, the in situ generation of the cyanide anion was confirmed by a cyanide detection test with a picric acid strip. In addition, it was confirmed that both CuI and molecular iodine were formed under the reaction conditions,[47] thus confirming the original mechanistic proposal that the cyanation of boronic acids or esters proceeds through initial iodination followed by subsequent Cu-mediated cyanation (Scheme 28).



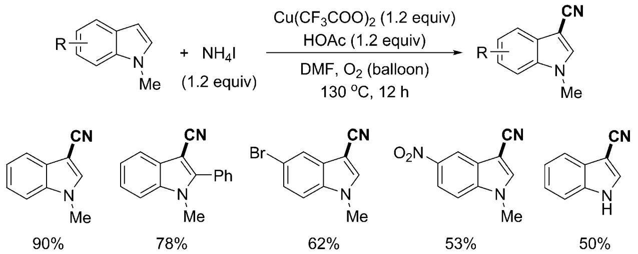
Scheme 28. Proposed mechanistic pathway. Species with grey background were identified by experiments

Based on the above-mentioned mechanistic postulate, this cyanation strategy was logically extended to various electron-rich benzenes, because they are prone to undergo the initial iodination process (Scheme 29). Interestingly, the observed cyanation position of arene C–H bonds is in a good agreement with the electronic demand predicted from the electrophilic aromatic iodination.

Chang and co-workers also developed the regioselective cyanation of indoles and 2-phenylpyridines under "palladium-free" conditions (Scheme 30).[48] While the procedure developed by Cheng and co-workers required a palladium catalyst for the cyanation of indoles with NH_4HCO_3 and DMSO,[44] the use of ammonium iodide allowed the development of a new protocol that did not require palladium catalysts. Similar to the previous report,[46] the cyanation of indoles proceeded through two sequential steps: initial iodination followed by cyanation. The presence of substituents at the 2 position of indoles did not lower reaction efficiency and regioselectivity.

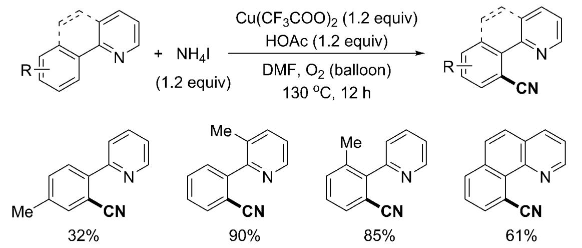


Scheme 29. Cu-mediated cyanation of electron-rich arenes.



Scheme 30. Cyanation of indoles with NH_4I and DMF.

The present cyanation system was also applied to the "palladium-free" cyanation of 2-phenylpyridines (Scheme 31). In previous studies reported by Chang and co-workers, the presence of a palladium catalyst was important to activate the C–H bond of 2-phenylpyridine when aqueous ammonia was employed,[40] however, the use of ammonium iodide allowed the same conversion in the absence of a palladium catalyst.

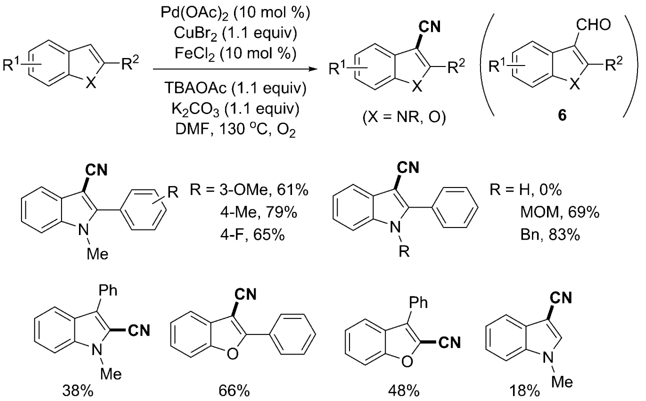


Scheme 31. Cyanation of 2-phenylpyridines and benzo[*h*]quinoline in the absence of palladium species.

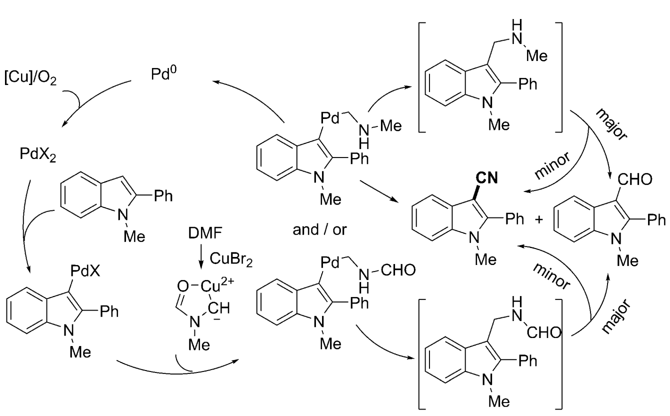
Although the recently developed cyanation procedures, in which combined sources are used for the in situ generation of CN unit, are conceptually novel, there are several limitations to overcome in order to make them more attractive and practical. For example, the mechanistic pathway needs to be fully elucidated in order to understand the formation of the cyano group. Also, the requirement of more than stoichiometric amounts of copper species needs to be addressed, presumably on the basis of mechanistic understanding.

3.3. N,N-Dimethylformamide

In 2011, Ding and Jiao reported the Pd-catalyzed cyanation of indoles with DMF alone, but under rather complicated conditions that required the use of various reagents and additives (Scheme 32).[49] A range of indoles were converted to the corresponding 3-cyanoindoles in the presence of Pd(OAc)$_2$, CuBr$_2$, FeCl$_2$, tetrabutyl ammonium acetate (TBAOAc) and K$_2$CO$_3$ in DMF under O$_2$ atmosphere. While the palladium and copper salts and the O$_2$ atmosphere were essential, the use of FeCl$_2$, K$_2$CO$_3$, and TBAOAc additives enhanced the reaction efficiency and selectivity for the desired 3-cyanoindole over the 3-formylindole side product. The presence of a 2-aryl substituent was required to produce 3-cyanoindoles efficiently. Interestingly, 3-substituted indoles were cyanated at the 2 position, albeit in low yields. On the basis of experimental studies, a mechanistic pathway of the present cyanation as well as a path leading to the 3-formylindole side product was proposed (Scheme 33).



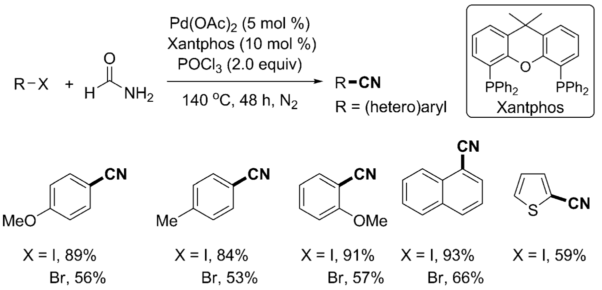
Scheme 32. Cyanation of indoles and benzofurans with DMF as a cyano-group source. MOM = methoxymethyl.



Scheme 33. Proposed mechanism of the Pd-catalyzed cyanation.

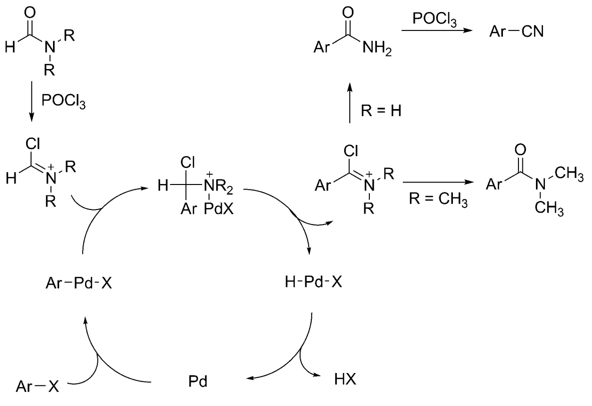
3.4. Formamide

In 2011, Bhanage and co-workers reported the Pd-catalyzed cyanation of (hetero)aryl halides with formamide (Scheme 34).[50] Based on the previously reported aminocarbonylation of aryl halides with DMF,[51] they extended this concept to the cyanation with formamide in the presence of Pd(OAc)$_2$, Xantphos ligand, and POCl$_3$ in formamide at 140 °C for 48 hours. Various aryl iodides and bromides with electron-donating substituents showed high cyanation efficiency.



Scheme 34. Cyanation of (hetero)aryl halides with formamide.

Because the reaction of aryl iodides with DMF instead of formamide gave aminocarbonylated products under the same conditions, it was suggested that cyanation of aryl halides with formamide may generate benzamide as an intermediate that undergoes the sequential dehydration, thus leading to benzonitrile products (Scheme 35).



Scheme 35. Mechanistic proposal for the Pd-catalyzed cyanation with formamide.

4. Conclusion

Until recently, the facile introduction of cyano groups into aromatic compounds was mainly achieved by the transition-metal-catalyzed cyanation of aryl halides using metal-containing cyanide sources. These metal-bound cyanation reagents, such as CuCN, KCN, NaCN, Zn(CN)$_2$, TMSCN, or K$_4$[Fe(CN)$_6$], are toxic and generally produce stoichiometric amounts of metal waste. In addition, the excess amount of cyanide anions that are present under the reaction conditions frequently causes the inactivation of the transition-metal catalyst. To overcome these problems associated with using metal-bound cyano-group sources, a range of nonmetallic cyano-group sources have been introduced in recent years. By using different organic cyano-group sources, cyanation of various substrates, including aryl halides, boronic acids, boronates, indoles, and arenes, has been investigated and afforded the corresponding benzonitriles, as described in this Minireview. Certain advantages of using nonmetallic cyano-group sources to overcome the drawbacks associated with the use of metallic cyanide precursors in the cyanation became apparent. More importantly, the design and synthesis of organic cyano-group precursors are easier and more convenient compared with those of metallic sources. Although further research efforts are needed in order to develop more practical and selective cyanation methods with nonmetallic cyano-group sources, significant progress in this area has been made in recent years.

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