ChemComm

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 2210

C–CN bond formation: an overview of diverse strategies

Sandeep Pimparkar, †[a] Adithyaraj Koodan,†[a] Siddhartha Maiti,[b]
Nesreen S. Ahmed, [c] Mohamed Mokhtar M. Mostafa *[d] and
Debabrata Maiti *[a]

Received 28th November 2020,
Accepted 20th January 2021

DOI: 10.1039/d0cc07783f

rsc.li/chemcomm

Nitrile or cyano compounds are an important part of structural motifs in dyes, agrochemicals, medicinal compounds, and electronic materials. Also, aryl nitrile is an important intermediate in the preparation of numerous compounds *via* transformations such as hydrolysis, hydration, reduction, cycloadditions, and nucleophilic additions. Such methods are beneficial for introducing sensitive functional groups in various positions in the multi-step synthesis of natural products and medicinal compounds. In the past decades, various cyanation methods have been reported in the vast arena of chemistry, which have made several building blocks accessible. Previously reported cyanation reviews, letters, and perspectives are written in parts. Thus, today a comprehensive review that will be able to guide readers through the vast pool of C–CN bond forming reactions *via* different approaches is obligatory. The present feature article depicts the various areas of cyanation methodologies that are based on the metal catalyst used, directed, non-directed, electrochemical, photochemical, asymmetric, and radical based approaches. This feature article will serve as a comprehensive tool to navigate the C–CN (cyanation) reactions across the vast area in synthetic chemistry.

---

[a] *Department of Chemistry, IIT Bombay, Powai, Mumbai 400076, India. E-mail: dmaiti@iitb.ac.in*
[b] *VIT Bhopal University, Bhopal-Indore Highway, Kothrikalan, Sehore, Madhya Pradesh-466114, India*
[c] *Department of Therapeutic Chemistry, National Research Centre, Dokki, Cairo-12622, Egypt*
[d] *Chemistry Department, Faculty of Science, King Abdulaziz University, P.O. Box-80203, Jeddah-21589, Saudi Arabia. E-mail: mmoustafa@kau.edu.sa*

† These authors have contributed equally.

Sandeep Pimparkar

Dr. Sandeep Pimparkar was born and brought up in Nasik (Maharashtra) India. After his MSc in organic chemistry, he joined as a junior research fellow at IISER Pune, India with Dr. M. Jeganmohan. Later, in 2015, he joined Prof. Debabrata Maiti's research group for PhD at IIT Bombay (IITB-Monash Research Academy). During his PhD, he mainly studied the design & discovery of templates for distal C–H activation of aliphatic and aromatics by using transition metal catalysis.

Adithyaraj Koodan

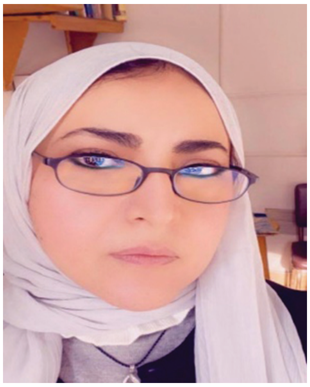
Mr. Adithyaraj Koodan was born and brought up in Kerala, India. He obtained his Integrated MSc in chemistry from Integrated Science Education and Research Centre, Visva-Bharati, India. He did his final year MSc dissertation project under Prof. Debabarata Maiti from Indian Institute of Technology Bombay, India on transition metal catalyzed remote C–H functionalization reactions.

Introduction

Nitrile or cyano (CN) is one of the versatile synthons in synthetic chemistry because of its ability to transform into other functional groups such as carbonyls and amines.[1a–c] Also, the introduction of the nitrile group on a bioactive molecule or another functional molecule can alter its properties.[1d] Cyano group is found as an integral part of natural products, dyes, herbicides, agrochemicals, and pharmaceuticals.[1e,f] Sandmeyer and Rosenmund–von Braun reactions were the most promising methods for the cyanation of arenes at laboratory and industrial scales but these past couple of decades have seen a remarkable development of newer approaches and newer sources of –CN to prepare nitriles from various coupling partners. In general, aryl cyanides are prepared from activated aryl–X coupling partners (where X can be halides or OTf (trifluoromethanesulfonate)) by transition metal catalysis with various cyanation sources such as CuCN, KCN, NaCN, $Zn(CN)_2$, and organic cyanation sources, namely, TMSCN (trimethylsilylcyanide), acetone cyanohydrin, DMF (dimethylformamide), and NCTS (*N*-cyano-*N*-phenyl-*p*-toluenesulfonamide). Not only activated but also un-activated arenes have been cyanated by transition metal catalysis utilizing suitable directing groups, which could also promote cyanation at the distal positions of arenes. The present review depicts all the important types of cyanation for aromatic, aliphatic, and heterocyclic compounds by classifying them in various categories including transition metal-catalyzed transformation of aryl halides, cyanation of directed & non-directed arene/heteroarenes, asymmetric, electro-catalyzed and photocatalyzed cyanation of arenes (Scheme 1).

Siddhartha Maiti

Prof. Dr Siddhartha Maiti was born in India. In 2016 for his PhD at the University of Massachusetts Dartmouth (USA), he studied the development of fluorescent sensor for the bioimaging of iron(II) ions under the supervision of Prof. Maolin Guo. He then studied the amidosulfates-mediated peptide formation under potential early-earth conditions at the Indian Institute of Technology, Bombay with Prof. Samir Maji, and Prof. Debabrata Maiti. He is now appointed as Assistant Professor at Vellore Institute of Technology, Bhopal, India in the Bioengineering department.



Nesreen S. Ahmed

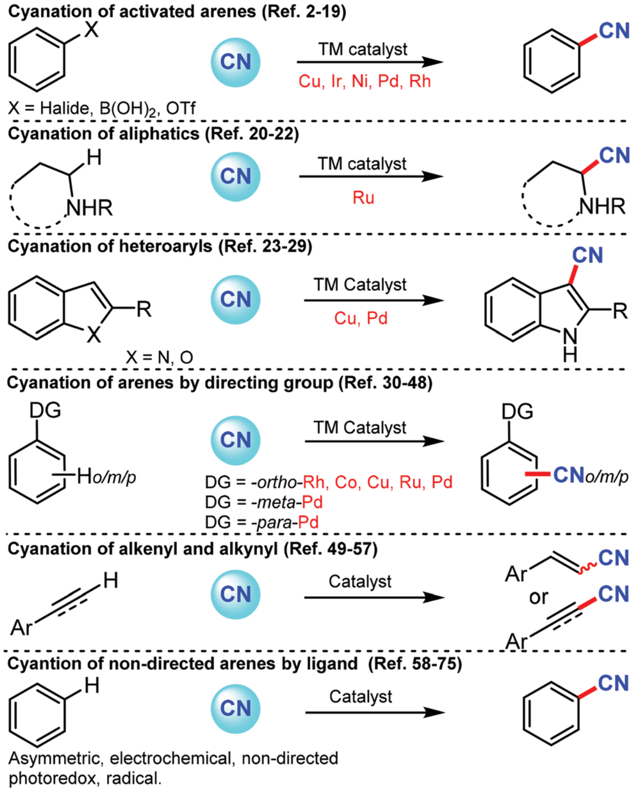
Prof. Dr Nesreen S. Ahmed completed her Master of Science in 1996 from Ain Shams University, Cairo, Egypt and a PhD in 2000 from the same University. She was an assistant Professor of Organic Chemistry at the Department of Therapeutic Chemistry, Pharmaceutical, and Drug Industries Research Division, National Research Center (NRC), Dokki, Cairo, Egypt. She was delegated as Associate Professor (2006–2018) in the Department of Chemistry at the King Abdulaziz University (KAU), Jeddah, Saudi Arabia. Her scientific interest is in medicinal chemistry, heterocyclic compounds, and green chemistry. She is experienced in the preparation, elucidation, and biological tests of new organic compounds.

Mohamed Mokhtar M. Mostafa

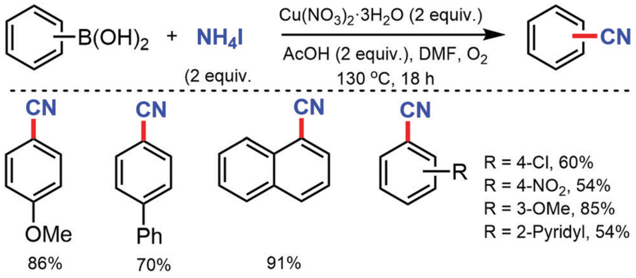
Prof. Dr Mohamed Mokhtar got his Master's degree in 1993 from Zagazig University and PhD in 1997 from Cairo University, Cairo, Egypt. He was a researcher from DAAD, in Karlsruhe, Germany in 1998–1999. He was invited as a research fellow to the Surface Chemistry and Catalysis Department, Ulm University, Ulm, Germany in 2003 and at Erlangen-Nuremberg University (FAU), Germany in 2007. His dual roles at the NRC and the KAU are just the latest in a string of leadership roles he has held in the scientific research field for almost 30 years. His focus is in advanced materials and heterogeneous catalysis.

Debabrata Maiti

Prof. Dr Debabrata Maiti received his PhD from John Hopkins University (USA) in 2008 under the supervision of Prof. Kenneth D. Karlin. After postdoctoral studies at the Massachusetts Institute of Technology (MIT) with Prof. Stephen L. Buchwald (2008–2010), he joined the Department of Chemistry at IIT Bombay in 2011. His research interests are focused on the development of new and sustainable synthetic and catalytic methods, aliphatic & aromatic distal C–H activation, photocatalysis, electrocatalysis, heterocycle synthesis, and lignin valorisation.



Scheme 1 Contextual overview of the present feature article on the different approaches of C–CN bond formation.



Scheme 3 Copper-mediated sequential cyanation of aryl C–B/arene C–H bonds using NH_4I and DMF.

1. Transition metal based cyanation of activated arenes

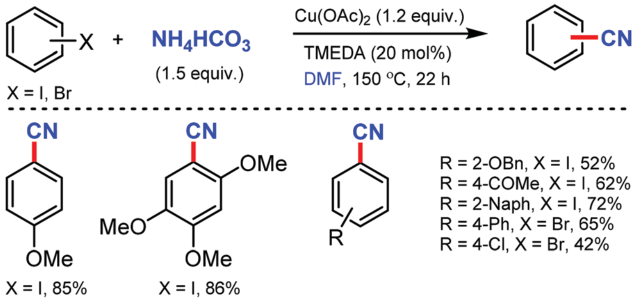
1.1. Copper-catalyzed cyanation of activated arenes

A combination of DMF and NH_4HCO_3 as a safe cyanide source for the copper-mediated cyanation of aryl halides was developed by Cheng and co-workers in 2011.[2] Notably, expensive palladium catalyst or a large excess of ammonia was not required for this transformation (Scheme 2). Aryl iodides with –OMe, benzyloxy, –OAc, and –OH groups could yield the corresponding nitriles. However, the alkyl, alkenyl, and alkynyl iodides did not work for this transformation.

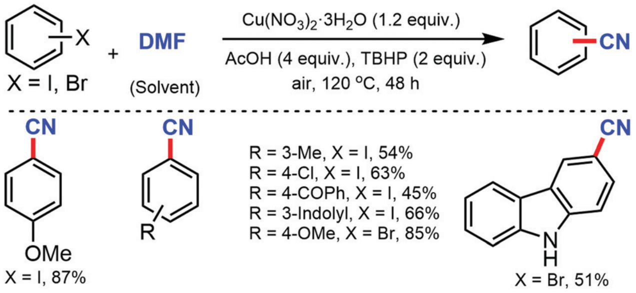
In 2012, Chang and co-workers reported the copper-mediated cyanation of boronic acids, boronate esters, borate salts, and electron-rich arenes under oxidative conditions using ammonium iodide and DMF as the cyanation source.[3] The reaction proceeds *via* a two-step process: initial iodination and subsequent cyanation, where NH_4I plays a dual role in supplying iodide and nitrogen for cyanation, thus being the first example of utilizing both cationic and anionic species of ammonium salts in metal-mediated reactions (Scheme 3). Aryl pinacolboronate and phenylborate salts could also afford the corresponding nitriles along with cyanation of electron-rich arenes such as 1,3,5-trimethoxybenzene and 1,2,4-trimethoxybenzene.

A copper-catalyzed strategy for the cyanation of aryl halides using DMF as a single source of cyanide was developed by Wang and co-workers in 2015 by using a stoichiometric amount of $Cu(NO_3)_2{\cdot}3H_2O$ (Scheme 4).[4] Substrates such as methyl, biphenyl, naphthyl, and pyrenyl iodides were well tolerated under this protocol but aryl iodides with carbonyl and amino resulted in a decreased yield. Aryl bromides with fused structures, such as 1-naphthyl, 1-pyrenyl, 2-naphthalenyl, 9-anthracenyl, and 9-phenathlenyl bromides proceed smoothly to produce the corresponding nitriles in moderate to good yields.

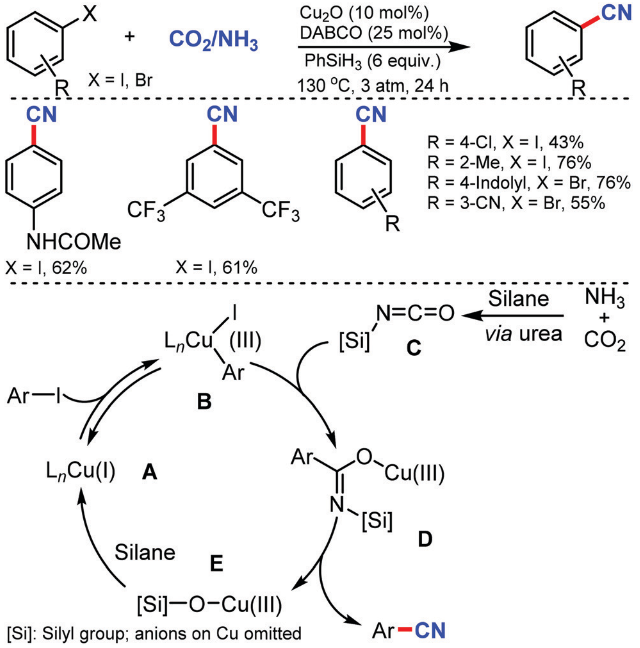
Later, an efficient cyanide-free protocol for the cyanation of aryl halides with CO_2 and NH_3 as sources of cyanation was disclosed by Li and co-workers in 2018 using Cu_2O/DABCO as the catalyst.[5] Substrates bearing *o*-substitution were tolerated better than *meta*- or *para*-substitution on the aryl ring (Scheme 5). A slightly lower yield was observed in the presence of alkyl, chloro, or alkoxy substituents, indicating that the electronic effect of the substituents varies while hydroxyl, ester, amino, cyano, and amide groups were also favorable for this transformation.



Scheme 2 Copper mediated cyanation of aryl halides with the combined cyanide source.



Scheme 4 $Cu(NO_3)_2{\cdot}3H_2O$ mediated cyanation of aryl halides DMF.

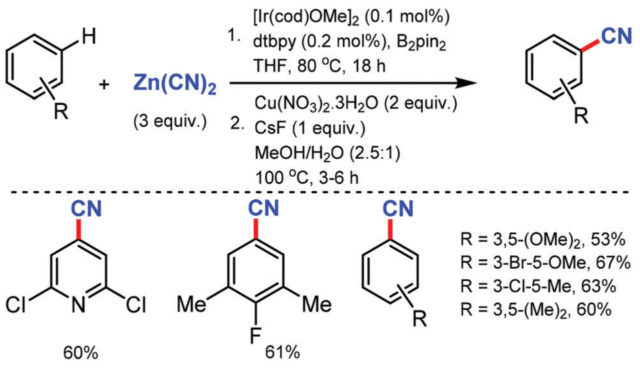


Scheme 5 Cyanide-free catalytic cyanation using CO_2 and NH_3 and the plausible isocyanate mediated cyanation mechanism.

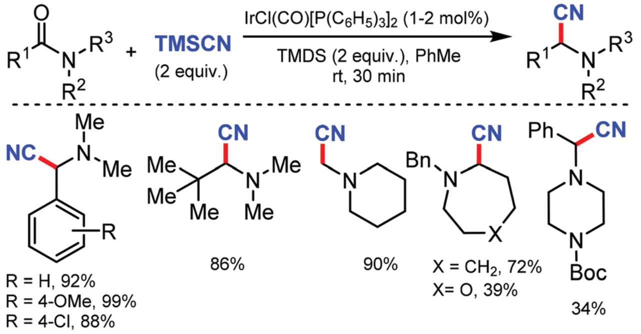
However, in case of activated arenes, mechanistic studies have suggested that the oxidative addition of Cu(I) intermediate **A** to aryl iodides led to the active Cu(III) species **B**. Silyl isocyanate **C** formation was followed by the copper–carbon insertion to generate a transient imidate species **D**, which gives the cyano product *via* a plausible 1,3-silyl *N*-to-*O* migration, whereby the Cu(III) intermediate **E** was released and rapidly reduced by silanes to Cu(I) species. The insertion of isocyanate intermediates into Cu(III)–aryl was crucial for the high chemoselectivity.

1.2. Iridium catalyzed cyanation of activated arenes

In 2010, Hartwig and co-workers first reported the tandem cyanation of arenes by iridium/copper catalytic system for di or tri-substituted arenes/heteroarenes (Scheme 6).[6] The reaction showed tolerance towards alkyl, alkoxy, halides, alkylcarbonyl, aminocarbonyl, alkoxycarbonyl, or protected phenols as well as 2,6-disubstituted pyridines. Also, arylboronic acids with electron-donating or electron-withdrawing groups produced the corresponding benzonitriles in 67–70% yield. The regioselectivity observed in this reaction resulted from the steric effects that controlled the C–H borylation step.



Scheme 6 Copper mediated cyanation *via* Ir-catalyzed borylation.

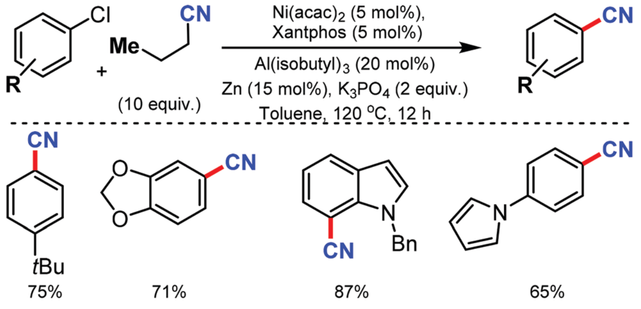


Scheme 7 Iridium-catalyzed reductive Strecker reaction for late-stage amide and lactam cyanation.

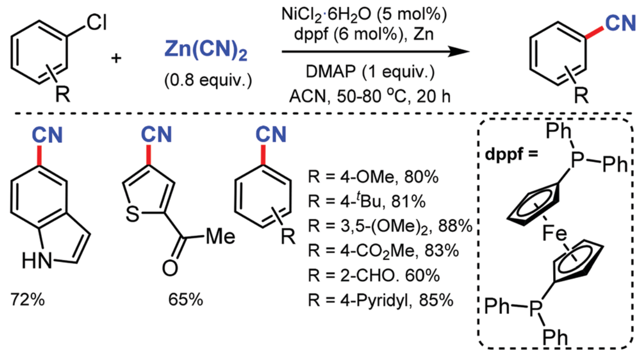
Recently, an efficient route for the synthesis of α-amino nitrile from a wide range of (hetero)aromatic and aliphatic tertiary amides, and *N*-alkyl lactams by exploiting the iridium-catalyzed reductive Strecker reaction was reported by Dixon and co-workers in 2017.[7] The chemo-selective reduction of the amide and lactam by $IrCl(CO)[P(C_6H_5)_3]_2$ (Vaska's complex) in the presence of tetramethyldisiloxane (TMDS) as a reductant to generate a hemiaminal species on the substitution by cyanide using TMSCN was developed (Scheme 7). This protocol was also suitable for furanyl heterocycles, cinnamamides, aliphatic carboxylic acids, diethyl amines, 1-methylpiperidine, and boc-piperazine.

1.3. Nickel-catalyzed cyanation of activated arenes

The merging of transfer hydro-functionalization and cross-coupling was employed for the synthesis of aryl nitriles from a wide range of aryl chlorides and aryl/vinyl triflates by Morandi and co-workers in 2017 using butyronitrile as the cyano source, which prevents catalyst poisoning.[8] Both electron-donating and withdrawing groups tolerated the reaction conditions well (Scheme 8). Naphthyl, 9-phenanthryl chlorides, heterocycles including pyrrolidine, dioxole, carbazole, pyrazole, quinoline, and several medicinally important heterocycles could afford the cyanated products in good yields.



Scheme 8 Nickel-catalyzed cyanation of aryl chlorides.

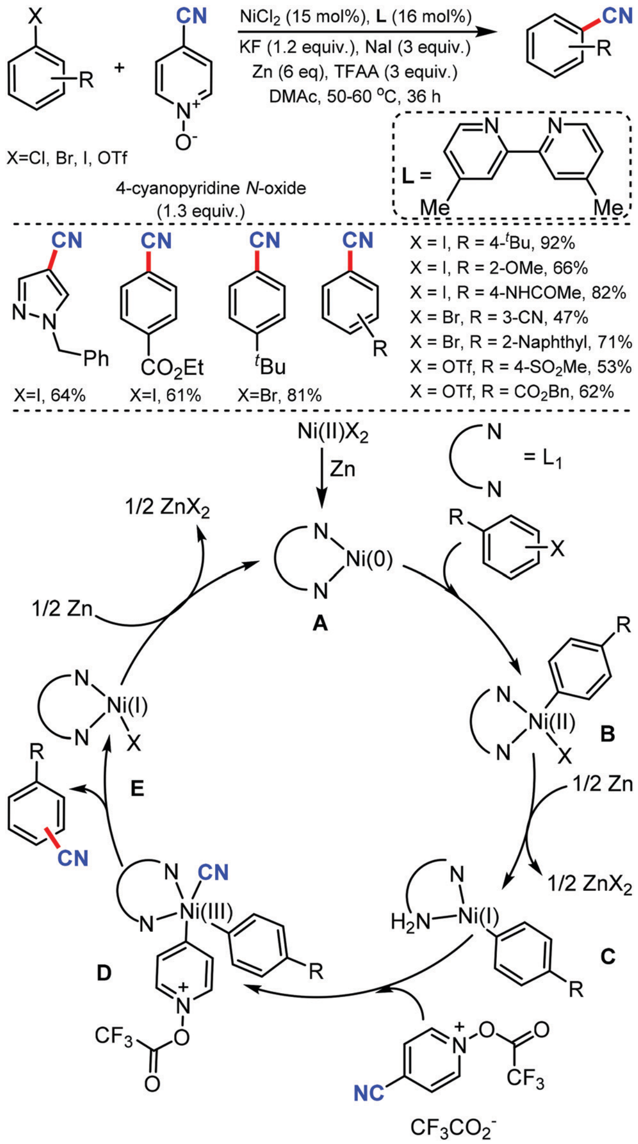


Scheme 9 Nickel-catalyzed cyanation of aryl/heteroaryl chlorides with $Zn(CN)_2$.

Later, Liu and co-workers developed an inexpensive $NiCl_2 \cdot 6H_2O$/dppf(1,1′-bis(diphenylphosphino)ferrocene)/Zn catalytic system for the cyanation of hetero(aryl) chlorides using less toxic $Zn(CN)_2$ as the cyanide source.[9] Employing DMAP as the additive, under mild conditions, various aromatic and heteroaromatic chlorides were well tolerated (Scheme 9). The use of $Zn(CN)_2$ was expected to prevent catalyst de-activation due to its low solubility in most organic solvents. *n*-Bu, *t*-Bu, $TBSOCH_2$, 3,5-dimethoxy, and trimethylsilyl-substituted aryl-chlorides produced the corresponding nitriles in 81–90% yield.

This cyanation protocol was also applicable to several aryl bromides and iodides. The mechanistic studies suggested that the use of DMAP is crucial for the reaction efficiency and the reaction proceeds *via* a Ni(0)/Ni(II) catalytic pathway.

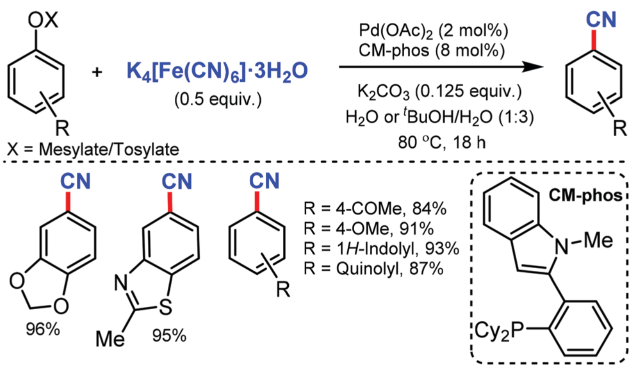
In 2020, Liao and co-workers reported the cyanation of aryl halides using nickel catalysis with inexpensive and non-toxic 4-cyanopyridine-*N*-oxide under mild conditions.[10] A broad spectrum of aryl halides bearing different electron-neutral, donating, and withdrawing groups could afford the cyanated products in moderate to good yields (Scheme 10). This Ni catalytic system, with a little modification, was also exploited for the hydrocyanation of alkynes with good regioselectivity. Diaryl alkynes substrates furnished an excellent *E*/*Z* selectivity while exclusively Markovnikov vinyl nitriles were obtained in case of terminal alkynes. In the plausible mechanism, the pre-catalyst $Ni^{II}X_2$ may first get reduced by zinc to generate the bipyridine ligand-chelated Ni^0 **A**, followed by the oxidative addition of aryl halide generating Ni^{II} complex **B**, which was then reduced by zinc to give aryl Ni^I complex **C**. The subsequent oxidative addition of cyano source with assistance from TFAA resulted in the Ni^{III} species **D**, which then undergoes reductive elimination to yield a cyanation product and the Ni^I complex **E**.



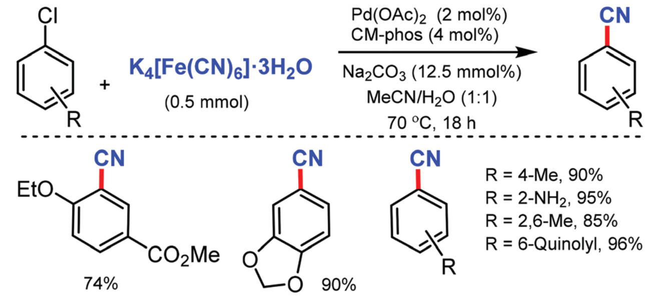
Scheme 10 Nickel-catalyzed cyanation of aryl halides *via* C–CN bond cleavage and the cyano transfer mechanism.

1.4. Palladium-catalyzed cyanation of activated arenes

The development of phenolic derivatives as suitable electrophilic coupling partners for cyanation has made the use of less expensive and stable aryl mesylates or sulfonates as cyanation substrates highly desirable (Scheme 11). In 2010, Kwong and co-workers reported the efficient Pd-catalyzed cyanation of aryl mesylates using an environment friendly solvent such as water or a water/^{t}BuOH solvent mixture under mild reaction conditions.[11]



Scheme 11 Palladium-catalyzed cyanation of aryl mesylates and tosylates.



Scheme 12 Palladium-catalyzed cyanation of aryl chlorides.

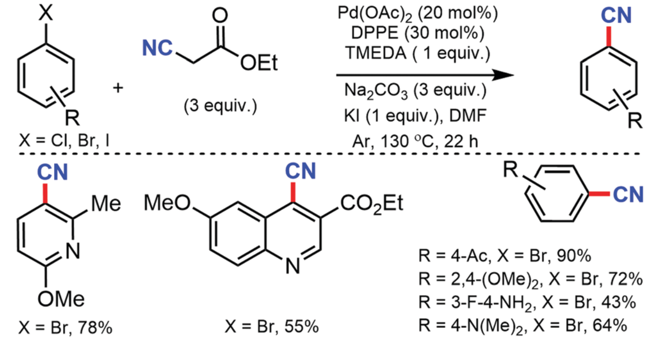
This showed ample functional-group tolerance towards substrates bearing nitrile, ester, keto, aldehyde, amine, and heterocyclic groups to give the cyanated products efficiently.

Later, in 2011, the Pd/CM-phos catalyzed cyanation of aryl chloride was developed by Kwong and co-workers using $K_4[Fe(CN)_6]{\cdot}3H_2O$ as the cyanide source.[12] Various aryl chlorides, bearing different functional groups such as carbonyls, nitrile, and amine, were cyanated. Heterocyclic groups such as benzothiazolyl, quinolyl, and N–H indoles were well tolerated under the reaction conditions to afford the cyanated product in good to excellent yields. Also, sterically hindered aryl chlorides proceeded smoothly under this cyanation method. Fortunately, water was found to be essential as a cosolvent for the reaction (Scheme 12).

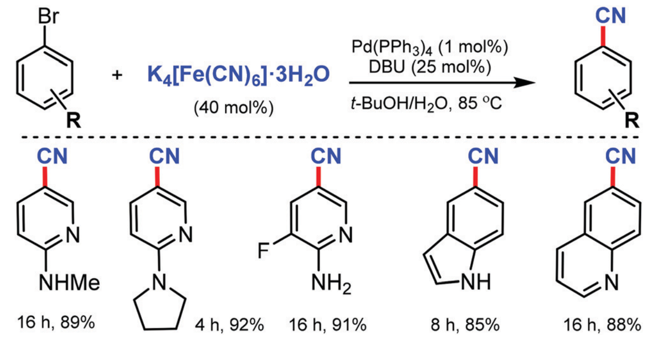
In 2012, Shen and co-workers developed Pd-catalyzed cyanation using inexpensive and user-friendly ethyl cyanoacetate.[13] Different aryl halides with various substituents at the *ortho*-, *meta*-, and *para*-positions could smoothly produce the corresponding nitriles. The reactivity of aryl halides decreased as the bond-dissociation energy of the C–X bonds increased (reactivity: I > Br > Cl). However, the presence of two or more strong electron-withdrawing groups was found to be unfavorable. Also, a relatively high loading of the palladium catalyst was required for this transformation (Scheme 13).

An efficient $Pd(PPh_3)_4$/DBU catalytic system for the cyanation of aryl and heteroaryl bromides using inexpensive and easily handled $K_4[Fe(CN)_6]{\cdot}3H_2O$ was developed by Liu and co-workers in 2012.[14]

The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) enhanced the release of the cyanide ion as a promoter and reduced the inactivation of Pd as the co-catalyst (Scheme 14).



Scheme 13 Pd-Catalyzed cyanation with ethyl cyanoacetate.

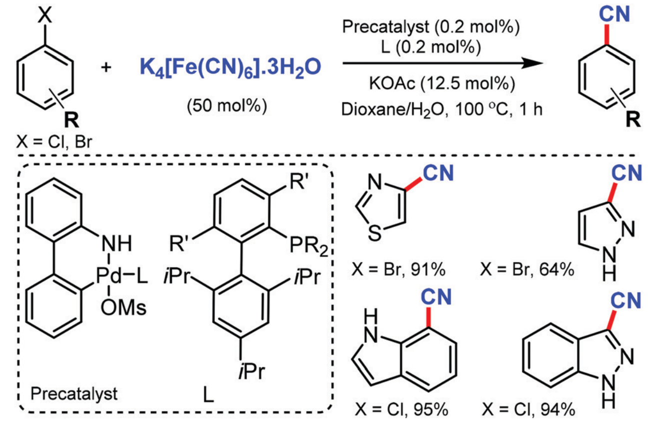


Scheme 14 Pd/DBU mediated cyanation of aryl/heteroaryl bromides.

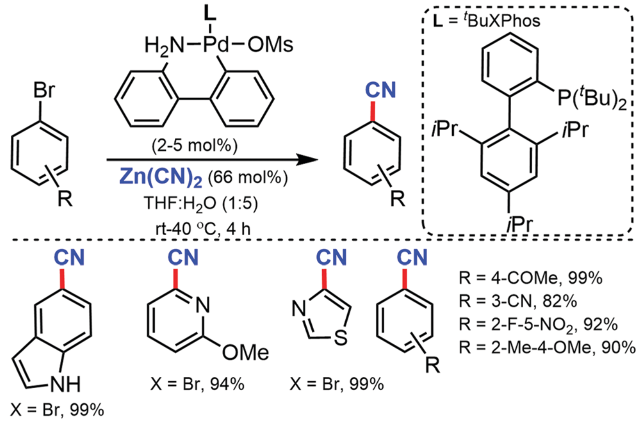
Various bromo-aminopyridines smoothly underwent this reaction protocol, giving corresponding nitriles in good to excellent yields. Substituents such as $-CF_3$, –F, and –Cl were also found to be compatible with this transformation. In addition, different aryl bromides bearing electron-donating groups, such as alkoxy and free amine and electron-withdrawing keto groups at the *meta*- and *para*-positions were also favorable for this reaction to proceed.

Later, in 2013, Buchwald and co-workers reported a convenient Pd-catalyzed protocol for the cyanation of aryl/heterocyclic halides using non-toxic $K_4[Fe(CN)_6]{\cdot}3H_2O$.[15] Electron-donating, electron-withdrawing, and di-*ortho*-substituted aryl chlorides were smoothly cyanated under this approach. Interestingly, substrates bearing free NH/OH groups (primary amides), sulfonamides, anilines, and benzylic alcohols could also afford the cyanated products using less than 1 mol% of Pd (Scheme 15). Furthermore, various heterocycles including indole, thiophenes, thiazole, pyrroles, pyrazoles, and indazoles efficiently transformed their halides into the corresponding nitriles in good to excellent yields (64–99%).

Later, in 2015, a general and efficient room temperature palladium-catalyzed method for the cyanation of (hetero)aryl halides and triflates was developed by Buchwald and co-workers using $Zn(CN)_2$ in aqueous media.[16] A wide range of aryl halides/triflates, five/six-membered heterocycles, and



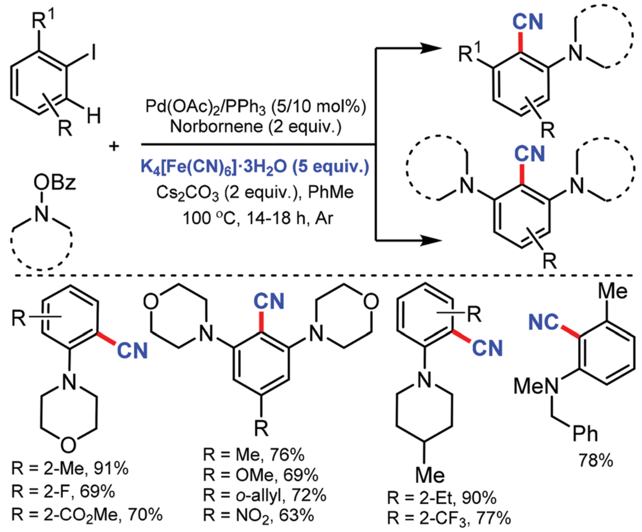
Scheme 15 Palladium-catalyzed cyanation of (hetero)aryl chlorides and bromides.



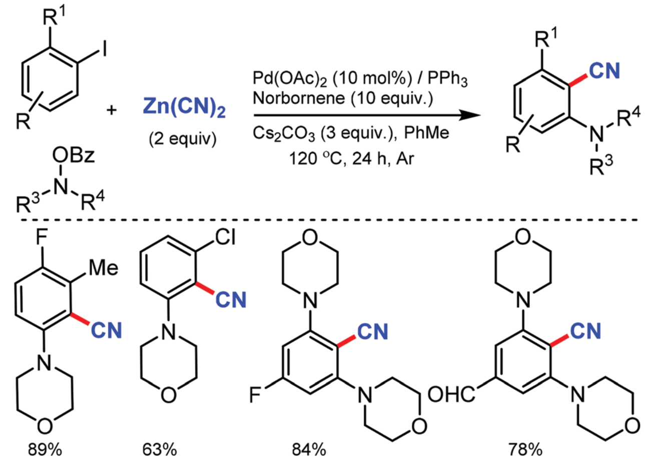
Scheme 16 Cyanation of (hetero)aryl halides and triflates.

natural product derivatives were efficiently cyanated in good to excellent yields (77–99%) (Scheme 16). In addition, an ample scope of heterocycles including indoles, benzothiophene, benzofuran, thiophene, pyrazole, quinoline, and pyridine were readily tolerated under the reaction conditions. Interestingly, the cyanation of natural products derivatives such as estrone, coumarin, and δ-tocopherol triflates could also be carried out efficiently using this method.

The scope of the Catellani reaction by Pd-catalyzed norbornene-mediated *ortho*-C–H substitution of iodoarenes, followed by terminal cross-coupling, was reported for a tandem *ortho*-C–H amination/*ipso*-cyanation by Ranu and co-workers in 2016[17] and Lautens and co-workers[18] at the same time using the user-friendly cyanating agent $K_4Fe(CN)_6{\cdot}3H_2O$ and $Zn(CN)_2$, respectively. Different *ortho*-substituted aryl iodides bearing both electron-donating ($-CH_3$, –Et, $-OCH_3$, $-N(CH_3)_2$, $-OCH_2Ph$) and electron-withdrawing groups (–F, –Cl, $-CO_2CH_3$, $-OCF_3$, $-CF_3$) were smoothly cyanated to produce the corresponding 2-aminobenzonitriles (Scheme 17). However, in the case of *ortho*-unsubstituted iodoarenes, double *ortho*-C–H amination and *ipso*-C–I-cyanation was observed. With $Zn(CN)_2$ also, a broad variety of aryl iodides bearing electron-donating and electron-withdrawing groups were found to be compatible with the reaction conditions and yielded the corresponding nitriles in moderate to good yields (Scheme 18).[18] Substituted *N*-benzoyloxyamines such as secondary and cyclic *N*-benzoyloxyamines were the appropriate nitrogen source for this multicomponent reaction.



Scheme 17 Palladium-catalyzed norbornene mediated tandem *ortho*-C–H amination/*ipso*-cyanation of iodoarenes.



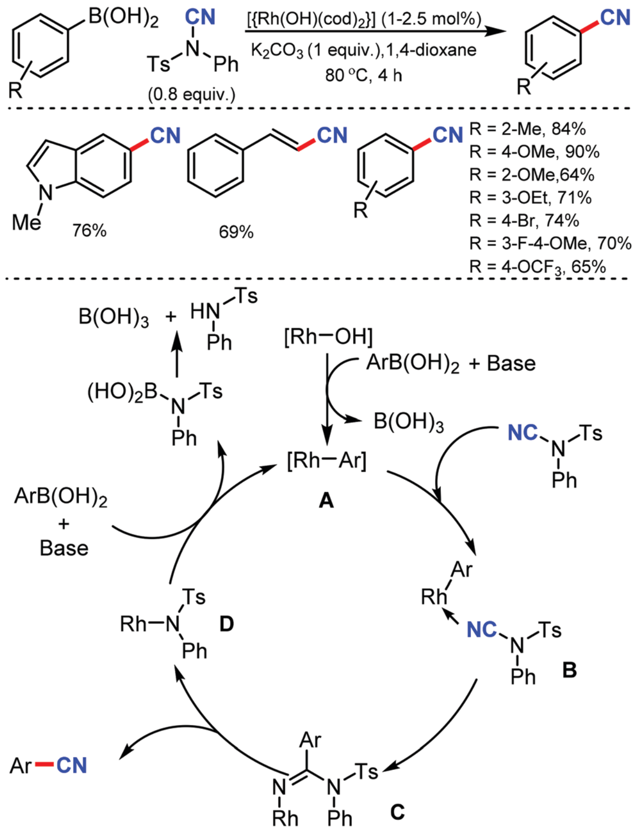
Scheme 18 Norbornene-mediated Pd-catalyzed tandem amination/cyanation.

1.5. Rhodium-catalyzed cyanation of activated arenes

In 2011, Beller and co-workers reported the first Rh-catalyzed cyanation of aryl and alkenyl boronic acids using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as the cyanating agent and with K_2CO_3 in 1,4-dioxane solvent.[19] Sterically demanding as well as non-hindered boronic acids were efficiently transformed into the corresponding nitriles under mild reaction conditions (Scheme 19). Moreover, electronically different and more challenging functionalized aryl boronic acids were also found to be compatible. The reaction is expected to proceed through the transmetalation of the aryl boronic acid with the active rhodium(I) species, which leads to the formation of the aryl–rhodium species **A**, which upon coordination with N–CN reagent forms the intermediate **B**. The transfer of the aryl motif to the nitrile carbon atom generates species **C**; then, the rearrangement of **C** results in the formation of the cyanated product.

2. Transition metal-catalyzed aliphatic cyanation

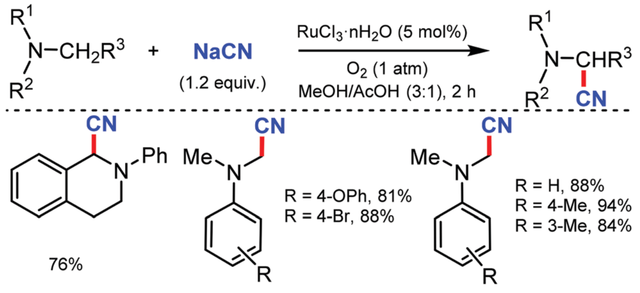
In 2003, Nakae *et al.* reported the ruthenium-catalyzed oxidative cyanation of tertiary amines with NaCN for regioselective cyanation of the substituted *N*,*N*-dimethylanilines with electron-donating or withdrawing groups.[20] Even cyclic amines such as tetrahydroisoquinoline were cyanated by this transformation. In this reaction, the oxo–ruthenium species seem to be formed as an active species to generate the iminium ion



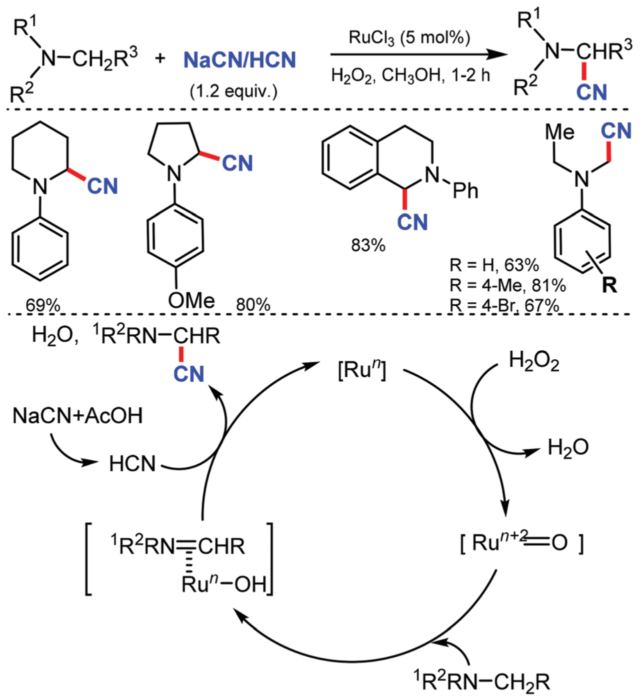
Scheme 19 Rh-Catalyzed cyanation of boronic acids.

intermediate and kinetic studies revealed that electron transfer from amine to ruthenium would take place at the initial step (Scheme 20).

In 2005, Terai *et al.* reported similar results on ruthenium-catalyzed oxidative cyanation with H_2O_2 and NaCN or HCN as the cyanation source for tertiary amines.[21] This was the first attempt for direct C–H activation and C–C bond formation under H_2O_2 oxidative conditions. Both electron-donating/withdrawing substituents reacted well under this condition. In the presence of other alkyl groups, *N*-methyl reacts predominantly along with cyclic amines such as piperidines, pyrrolidines, and tetrahydroisoquinolines to give α-cyanoamines (Scheme 21). While probing the mechanistic analysis, relative rates for the oxidative cyanation of four *para*-substituted *N*,*N*-dimethylanilines with H_2O_2 in the presence of NaCN was found to be R^2 = 0.998 (determined by ^{1}H NMR). The ρ-value of −3.61 indicates the presence of cationic intermediate in the rate determining step. Moreover, intramolecular and intermolecular deuterium isotope effect was found to be 4.1 and 3.7, respectively. These data suggested that low-valent Ru(II) undergoes reaction with H_2O_2 to give the oxo–ruthenium species [Ru^{n+2}=O], which produces the iminium ion intermediate by electron and hydrogen transfer, followed by nucleophilic attack by HCN to give the corresponding α-cyanated product and water and the Ru^{II} species, which completes the catalytic cycle.



Scheme 20 $RuCl_3 \cdot nH_2O$-Catalyzed cyanation of tertiary amines.

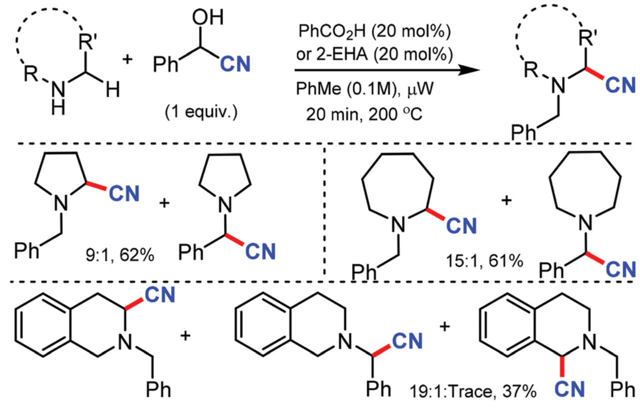


Scheme 21 $RuCl_3$-Mediated cyanation of tertiary amines with H_2O_2.

In 2012, Seidel's group reported the redox-neutral α-cyanation of secondary cyclic amines in the presence of benzoic acid as the catalyst under microwave irradiation.[22] The reaction could convert pyrrolidines and benzaldehyde in presence of TMSCN to give α-aminonitrile in 9 : 1 in 61% yield (Scheme 22). Other cyclic amine such as piperidine and azapane could give α-aminonitriles in moderate yields in the presence of 20 mol% of 2-ethylhexanoic acid (2-EHA) as the catalyst.

3. Cyanation of heterocycles by various cyanation sources

The copper-catalyzed regioselective cyanation of aromatic heterocycles was developed by Daugulis and co-workers in 2010 using NaCN as the cyanide source.[23] Several heterocycles including benzoxazole, benzothiazole, benzimidazole, caffeine, and triazoles were cyanated in reasonable to good yields (Scheme 23). Notably, pyridine derivatives with electron-withdrawing (fluorine) or electron-donating (methoxy) substituents were also tolerated under these reaction conditions.



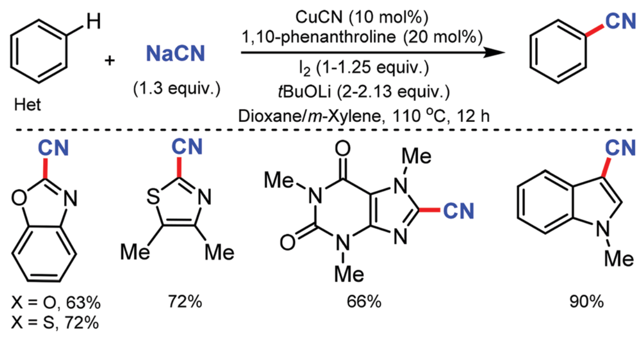
Scheme 22 Redox neutral α-cyanation of cyclic amine.

Similarly, in 2010, Wang and co-workers disclosed palladium-catalyzed C–H cyanation of indoles using less toxic and easily available $K_4[Fe(CN)_6]$. *N*-Methylindole with electron-donating substituents underwent the reaction without difficulty (Scheme 24). 2-Substituted *N*-alkyl- and *N*-arylindoles afforded cyanation in high yields but *N*-acetyl, *N*-phenylsulfonyl, or *N*-Boc substituents did not. *N*-Substituted indoles were compatible, albeit with less product yield.[24]

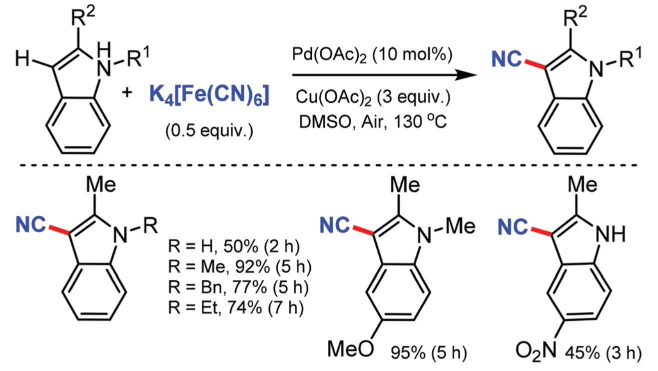
Jiao and co-workers, in 2011, reported the cyanation of indoles and benzofurans using DMF as the cyano reagent and solvent.[25] Electron-donating or electron-withdrawing substituents on 2-aryl indole were tolerated under the reaction conditions. 2 and 3-phenylbenzofuran could also be cyanated in moderate yields. Mechanistic studies indicated that both nitrogen and carbon of the CN group were provided by DMF (Scheme 25).

Later, a synthetic route to cyanoindoles/pyrroles using a Lewis acid catalyzed protocol was developed by Wang and co-workers in 2011.[26] Benign, bench-stable electrophilic cyanating agent NCTS was employed along with $BF_3 \cdot OEt_2$ as the catalyst under mild reaction conditions (Scheme 26) to C-3 cyanate with various indole and pyrrole substrates.

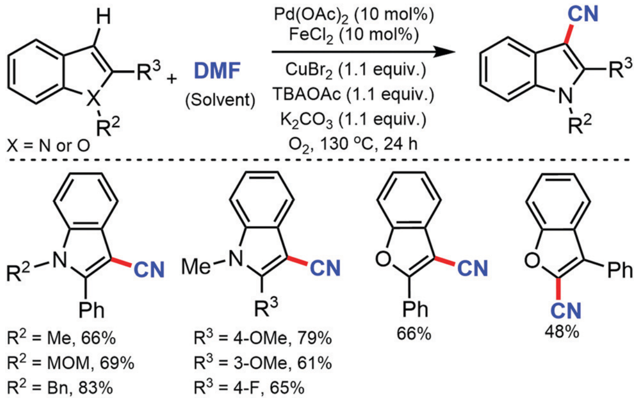
Interestingly, indole with or without substitution at the C-2 position afforded the cyanated indoles in excellent yields by avoiding the formation of the homocoupling by-products observed with similar Pd catalyzed methods.



Scheme 23 Copper-catalyzed cyanation of heterocycles.



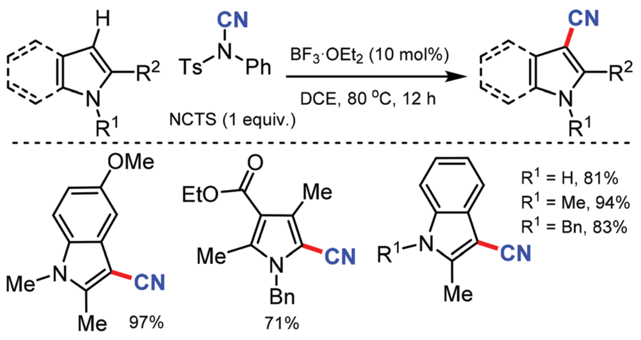
Scheme 24 Palladium-catalyzed direct cyanation of indoles.



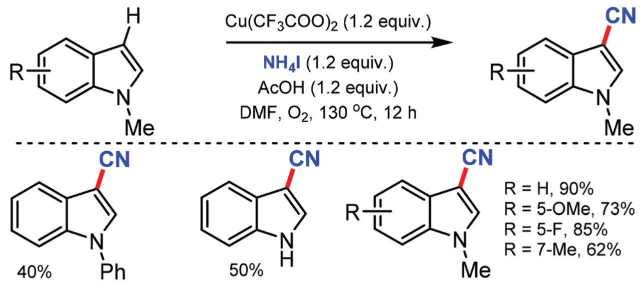
Scheme 25 Pd-Catalyzed cyanation of heteroarenes using DMF.

The combination of NH_4I and DMF as the CN source for the copper-catalyzed regioselective cyanation of indoles was reported by Chang and co-workers in 2012.[27] Various substituted indole such as *N*-Ph and *N*-Bn were cyanated at the C-3 position selectively. The *N*-carbonyl group substituted indoles were accompanied by decarbonylation, leading to the formation of 3-cyano-1*H*-indole (Scheme 27). Mechanistic studies indicated that the reaction proceeds through electrophilic iodination, followed by cyanation.

Two different methods to synthesize hetero(aryl)nitriles under Pd catalysis using *t*-butyl isocyanide as the CN source



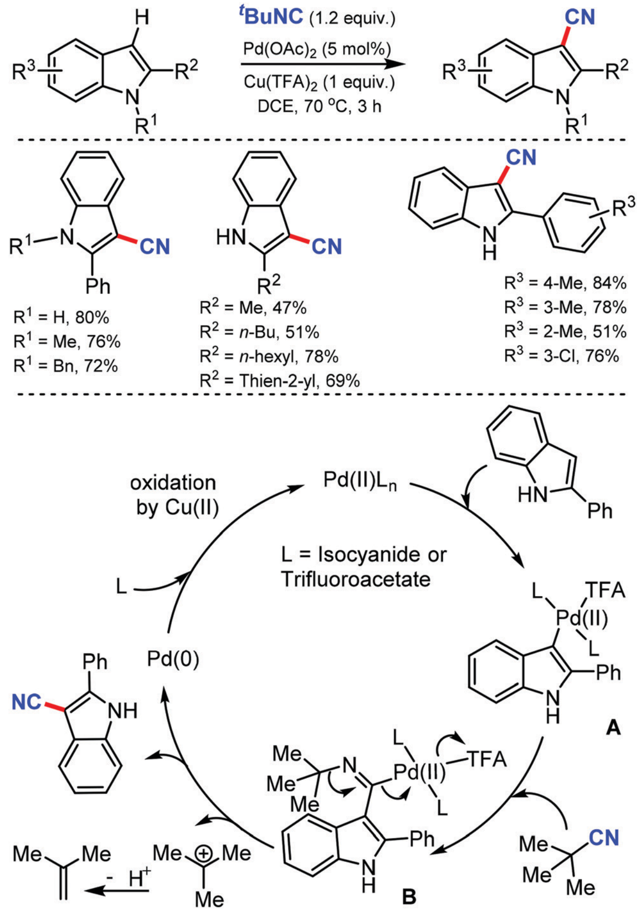
Scheme 26 Lewis acid catalyzed cyanation of indoles and pyrroles.



Scheme 27 Copper-mediated regioselective cyanation of indoles.

was developed by Xu and co-workers in 2012[28] and again by Zhu[29] at the same time. Both these C–H cyanation reactions were suitable to cyanate a wide range of indoles, pyrroles, and aromatic rings with high regioselectivity (Scheme 28).

Due to the direct electrophilic palladation at C-3 indole, C-3-palladated intermediate forms, which leads to C-3 cyanated indoles. Furthermore, *N*-substituted pyrroles, arylpyridines, and arylpyrimidines were also compatible with this palladium catalytic system, producing the corresponding nitriles regioselectively. Zhu's method used a stoichiometric oxidant, the trifluoroacetate counter-ion. Various electron-rich 2-alkyl(aryl)indoles, and electron-poor 2-arylpyridine cyanated as well. Indoles with electron-deficient groups either at the C-5 position or on the 2-phenyl ring demanded an additional requirement of PivOH as the additive. The high electrophilicity of Pd(II) and the stability of the tertiary carbon were beneficial in breaking the C–N bond, which led to the formation of cyanated products (Scheme 28). The mechanistic studies indicated that the electrophilic palladation of Pd(II) on C-3 of the indole forms the σ-indolylpalladium(II) intermediate **A**. The subsequent migratory insertion of isocyanide generates the key imidoyl palladium(II) intermediate **B**, in which the loosely-coordinated trifluoroacetate makes the palladium center more electrophilic. The high electrophilicity of Pd(II) and the stability of the tertiary carbocation are crucial for the cleavage of the C–N bond, leading to the cyanation product.

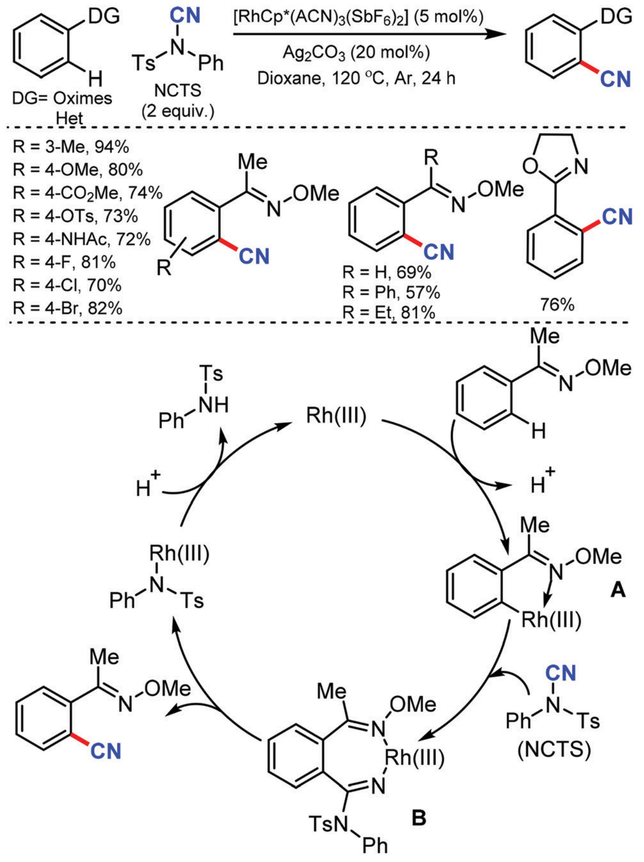


Scheme 28 Palladium-catalyzed cyanation by *tert*-BuNC and the reaction mechanism.

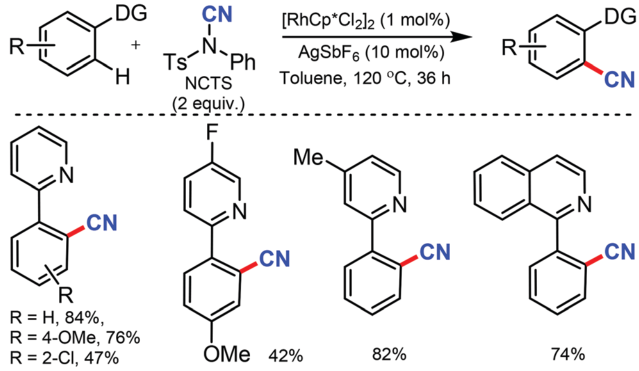
4. Directing group approach for C–H cyanation

4.1. *ortho*-C–H cyanation

4.1.1. Rhodium-catalyzed *ortho*-cyanation. In 2013, Fu *et al.* developed the redox neutral Rh-catalyzed directed C–H cyanation of arenes using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS).[30] Both electron-poor and electron-rich substituents, halides, OTs, cyclic/acyclic oximes, furan, thiophene, pyrrole, and indole afforded a wide range of cyanation (Scheme 29). Kinetic isotope



Scheme 29 Rh-Catalyzed *ortho*-cyanation of oximes with a plausible mechanism.



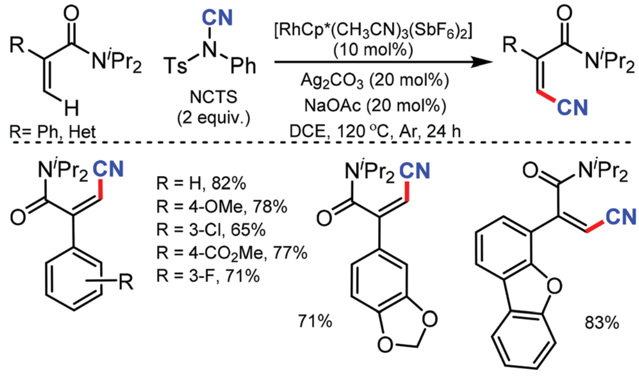
Scheme 30 Rh-Catalyzed cyanation for heterocycles.

effect (KIE) experiments suggested that a five-membered rhodacycle intermediate **A** was formed through a C–H activation step during the reaction. NCTS then coordinates with Rh(III) in **I**, followed by the insertion of the C–N moiety into the C–Rh(III) bond, which leads to the formation of **B**.

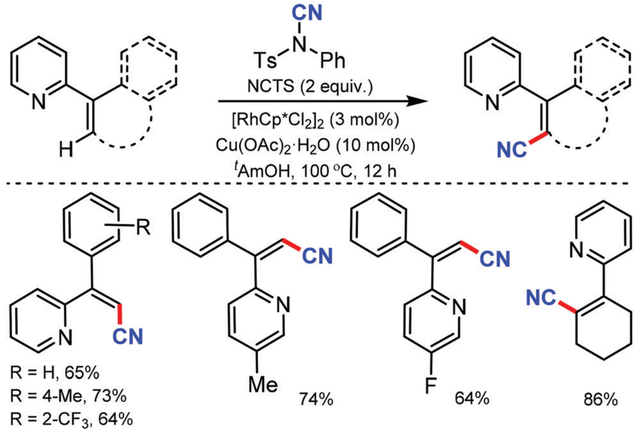
Lastly, the product was formed by the elimination of a tosylaniline-coordinated Rh(III) complex from **B**.

Similarly, the chelation-assisted rhodium-catalyzed cyanation of C–H bonds using NCTS was reported by Anbarasan and co-workers, which yielded various benzonitriles in good to excellent yield.[31] Chelating groups such as pyridine, isoquinoline, benzoquinoline, pyrazine, and pyrimidine were employed in this strategy with low catalyst loading and catalytic additives (Scheme 30). Electron-withdrawing, electron-donating, and sterically-hindered substituted phenyl substrates were also found to be tolerable. Substrates with substitution on the pyridine ring and steric factors played a crucial role in determining the feasibility of the reaction.

In 2015, Fu and co-workers reported the synthesis of alkenyl nitriles by Rh(III)-catalyzed cyanation of vinylic C–H bonds employing NCTS.[32] The combination of NaOAc and Ag_2CO_3 as additives considerably accelerated the reaction and arenes with both electron-withdrawing and electron-donating groups were cyanated successfully (Scheme 31). Pharmaceutically prominent fluorinated $-CF_3$, $-OCF_3$, and synthetically important heterocycles such as furan and dibenzofuran derivatives were also cyanated effectively under the optimized conditions.



Scheme 31 Rh-Mediated C–H cyanation of vinylic amides.



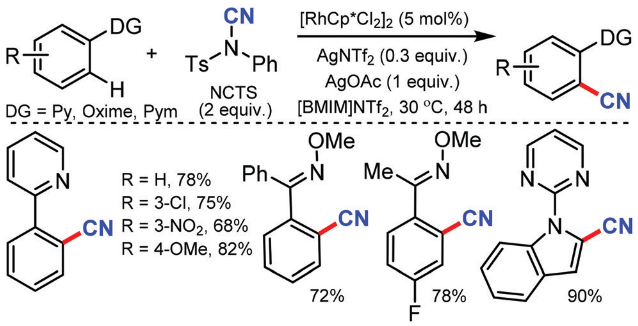
Scheme 32 Rh-Catalyzed cyanation of alkenes.

Many of the typical synthetic routes to acrylonitrile derivatives suffer from limited substrate scope and/or poor stereoselectivity. In 2015, Anbarasan and co-workers reported an efficient and selective rhodium-catalyzed cyanation of alkenes by chelation assistance using the readily available NCTS.[33] Electron-donating groups (–OMe, –SMe) substituted and sterically-hindered *ortho*-substituted aryl groups possessing acrylonitriles underwent this reaction smoothly (Scheme 32). Nevertheless, strongly electron-withdrawing and electron-chelating nitro and acetyl-substituted aryl containing alkenes were found to be incompatible for the desired transformation.

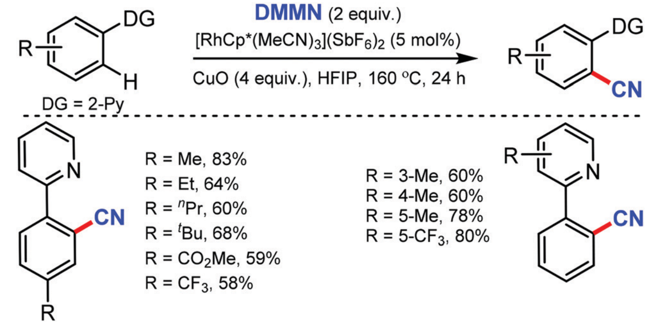
Less toxic and highly stable ionic liquids (ILs) have been used as recyclable reaction media in organic synthesis in recent times. Wu and co-workers developed rhodium-catalyzed C–H bond cyanation using 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[BMIM]NTf_2$), an ionic liquid, as the recyclable medium.[34]

2-Phenylpyridine derivatives and aryl ketoneoxime ether derivatives were successfully cyanated through this protocol near room temperature. Both electron-donating and electron-withdrawing groups were found to be suitable for the cyanation of 2-phenyl pyridine, pyrazole, and triazole scaffolds (Scheme 33). Notably, the kinetic experiments indicate that C–H bond cleavage is the rate-determining step in this transformation.

In 2019, dimethylmalononitrile (DMMN), an easily available and less toxic organic cyanating reagent, was employed for the rhodium-catalyzed aromatic C–H bond cyanation by Bao and



Scheme 33 Rh-Catalyzed cyanation of heterocycles.

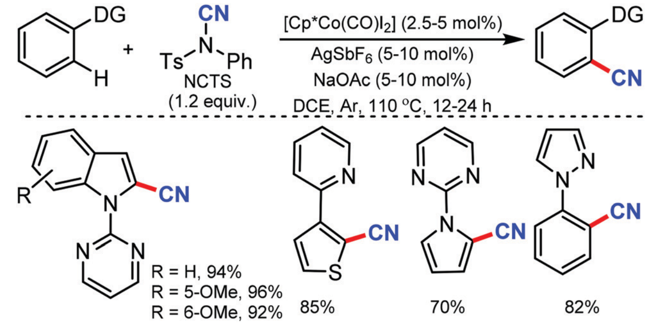


Scheme 34 Rh-Catalyzed cyanation by dimethylmalononitrile.

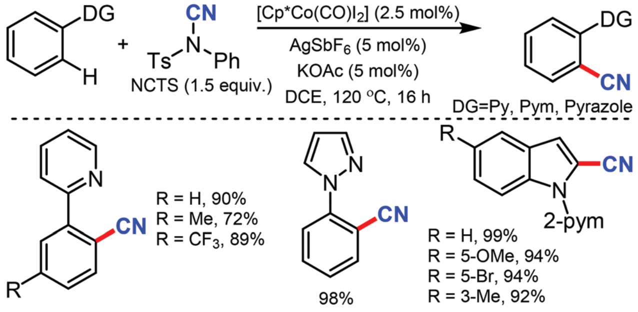
co-workers.[35] Pyridine, quinoline, pyrimidine, and pyrazole as DG could afford the cyanated products with the use of copper oxide as a promotor (Scheme 34). Moderate to satisfactory yields of products were obtained from the reactions of substrates bearing substituted pyridine, irrespective of their electronic properties. Heterocycles such as quinoline, pyrimidine, and pyrazole could also afford the cyanated products.

4.1.2. Cobalt-catalyzed *ortho*-cyanation. The direct cyanation of indole at the C-2 position has been challenging and seminal in organic synthesis. Using a bench-stable complex [Cp*Co(CO)I_2] as the catalyst, Glorius and co-workers, in 2014, reported cobalt-catalyzed cyanation as a route to (hetero)aryl/alkenyl nitriles with high regio- and mono-selectivity using NCTS as the cyanating agent in the presence of catalytic amounts of $AgSbF_6$ and NaOAc.[36] The C-2 cyanation of *N*-(2-pyrimidinyl)indole with functional groups such as methoxy/halides were tolerated efficiently to give the corresponding products. Importantly, this method could cyanate not only (hetero)-arenes but also olefins such as 2-(prop-1-en-2-yl)pyridine (Scheme 35).

Ackermann and co-workers utilised *in situ* generated cationic cobalt complex as an efficient catalyst for C–H cyanation using NCTS as the CN source.[37] Diverse electrophilic groups such as esters or ketones yielded the desired products with notable chemoselectivity (Scheme 36). Pyridines (py), pyrimidine (pym), pyrazole, pyrrole and thiophene could be employed as the directing groups (DG) using this protocol. Mechanistic probing for kinetic studies suggested that C–H metalation is not the rate-determining step.

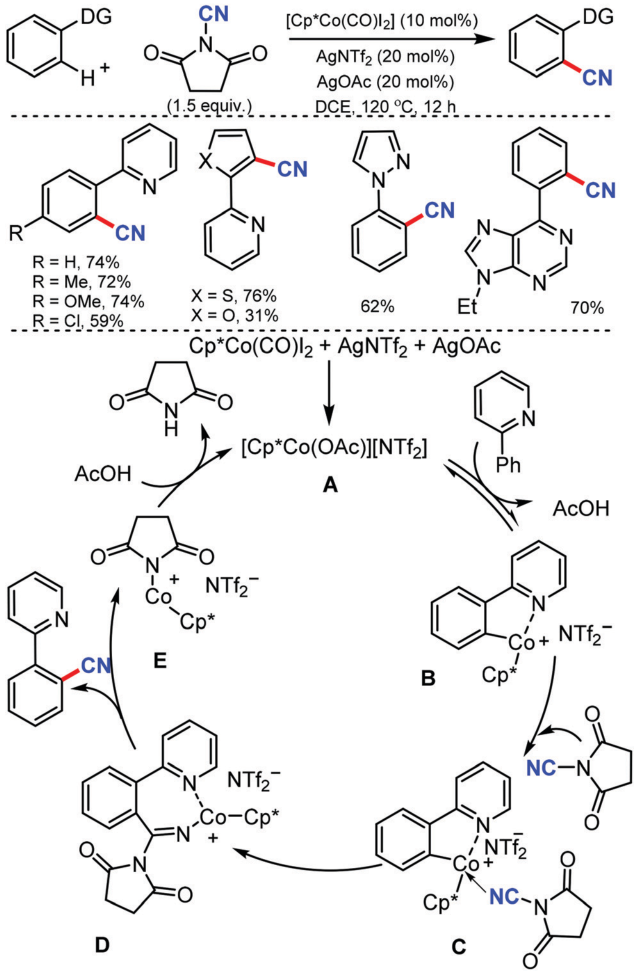


Scheme 35 Cobalt-mediated cyanation of indole and heterocycles.

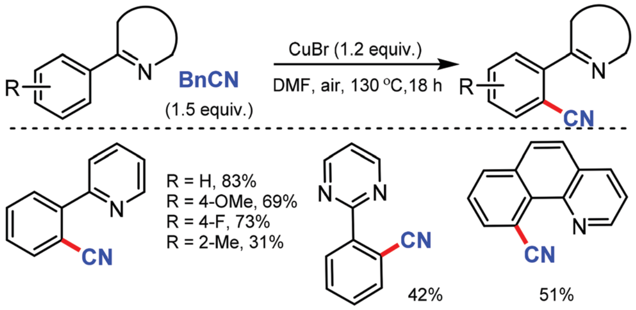


Scheme 36 Cobalt-mediated cyanation of 2-phenylpyridines and indoles.

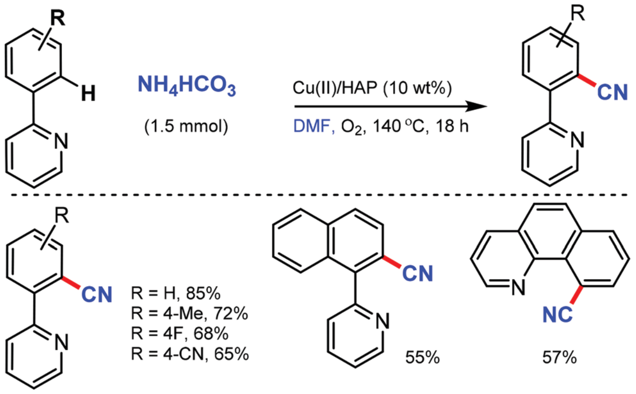
N-Cyanosuccinimide, an easily available and bench-stable electrophilic cyanating reagent, was employed for the cobalt mediated C–H cyanation of arenes and heteroarenes by Chang and co-workers in 2015.[38] In general, electron-donating groups, hydroxyl-protecting groups such acetate, silyl, methoxymethyl, *p*-methoxybenzyl (PMB) halides, heterocycles such as pyrazole, pyrimidine, thiophenyl, furanyl, pyrrolyl, and 6-arylpurines could also be cyanated efficiently (Scheme 37).



Scheme 37 Cobalt-catalyzed cyanation of (hetero)arenes.



Scheme 38 Cu-Catalyzed cyanation by BnCN.



Scheme 39 Cu-Mediated cyanation by NH_4HCO_3 and DMF.

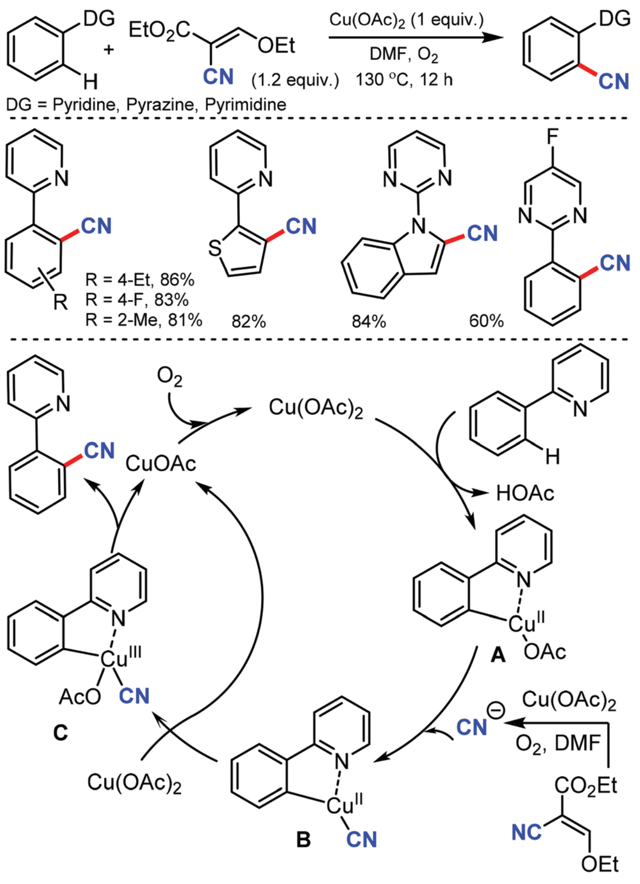
Mechanical studies suggest that C–H bond cleavage may not be involved in the rate-limiting step and the reaction may proceed through a key imido intermediate. The cationic Co(III) species **A** is generated *in situ* from $Cp^*Co(CO)I_2$ and $AgNTf_2$ in the presence of AgOAc reacts reversibly with 2-phenylpyridine to form a cobaltacycle **B**. The cyanating reagent coordinates to the cobalt center of **B** and then the migratory insertion of cyano (CN) into the metallacycle would lead to a key imido intermediate **D**.

The cyanated product is liberated from **D**. Kinetic experiments suggested that the C–H activation step could be reversible but might not be involved in the rate-limiting step.

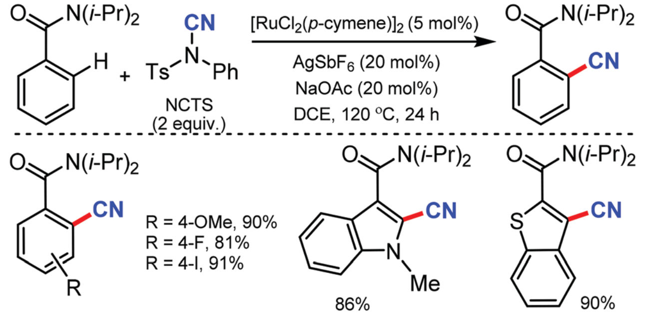
4.1.3. Copper-catalyzed *ortho*-cyanation. The copper-catalyzed cyanation of arenes using benzyl nitrile as the cyanide anion surrogate was reported by Wang and co-workers in 2012.[39] The use of substituted benzyl cyanide resulted in low yield and lack of selectivity. However, when directing groups such as pyrimidine, pyrazole, and 3-methyl-pyrazole were employed, relatively low yield of the desired products was obtained. Kinetic studies suggest that Cu(I) is responsible for the oxidation of benzyl cyanide, while the *in situ* generated Cu(II) is responsible for the cyanation of 2-phenylpyridine (Scheme 38).

Venugopal and co-workers reported hydroxyapatite [HAP: $Ca_5(PO_4)_3(OH)$]-supported Cu catalyst as an efficient and reusable heterogeneous catalyst for the cyanation of arenes with the combination of NH_4HCO_3 and DMF as the CN source.[40] The surface basicity and Cu metal surface area of the catalysts were crucial for this cyanation reaction up to five catalytic cycles, which showed consistent activity and selectivity (Scheme 39). Interestingly, pyridine, isoquinolines, quinoline, and benzo[*h*]quinoline could act as the directing groups, delivering the corresponding aryl nitriles in good yields.

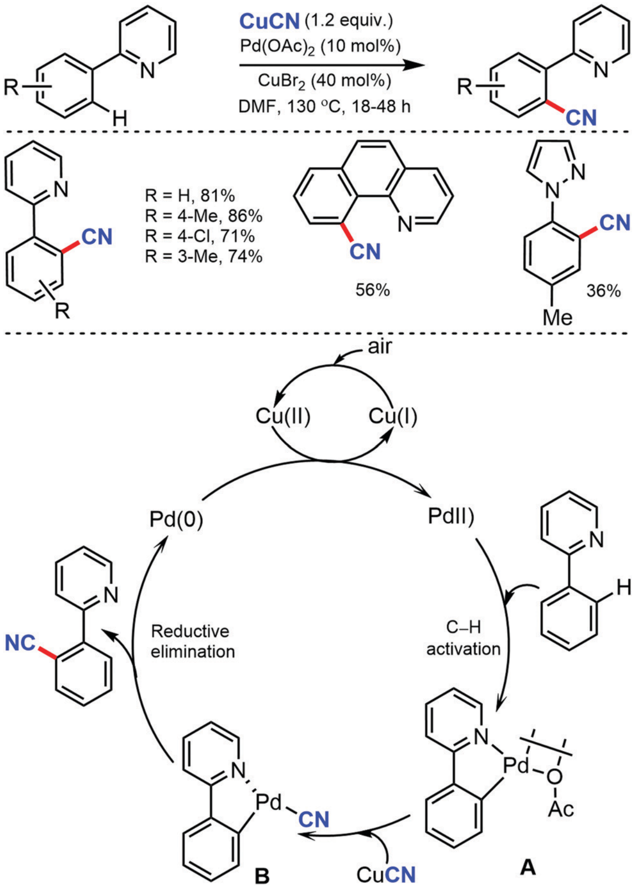
Later, an efficient method for the synthesis of (hetero)aryl nitriles mediated by copper was developed by Jiang and co-workers in 2017 using non-toxic and easily available ethyl (ethoxymethylene)cyanoacetate as the cyanide source with oxygen as the oxidant.[41] 2-Arylpyridines bearing either electron-donating or electron-withdrawing groups at the *para*-position of the aryl ring underwent the reaction smoothly, giving mono-cyanated products in moderate to high yields (Scheme 40). The *ortho*- and *meta*-substituted substrates could also afford the less hindered *ortho*-cyanated products regioselectively. For this transformation, kinetic studies suggested that C–H bond cleavage might be involved in the rate limiting step. The initial coordination of the nitrogen atom of the substrate to $Cu(OAc)_2$ and the subsequent irreversible cyclocupration give the Cu(II) species **A**, which would undergo coordination exchange with the *in situ* generated cyanide anion to form the intermediate **B**. After disproportionation with another equivalent of $Cu(OAc)_2$, intermediate **B** is then oxidized to the Cu(III) species **C**. Subsequently, the reductive elimination of **C** yields the cyanated product along with CuOAc.



Scheme 40 Cu-Catalyzed cyanation of 2-phenylpyridines with the plausible reaction mechanism.



Scheme 41 Ruthenium-catalyzed *ortho* C–H cyanation of amides.



Scheme 42 Palladium-catalyzed *ortho*-cyanation of arenes.

4.1.4. Ruthenium-catalyzed *ortho*-cyanation. A facile ruthenium(II)-catalyzed direct cyanation of weakly coordinating amides was developed by Ackermann and co-workers in 2014, using NCTS as the cyanating reagent (Scheme 41).[42] The method tolerated a range of electrophilic groups, such as ester, halides heteroaromatics such as thiophenes, furanes, benzothiophenes, benzofuranes, and indoles, which were smoothly cyanated both at the C-2 and C-3 positions with excellent yield and regioselectivity. Electrophilic-type activation mode of the cationic ruthenium species was revealed from the intermolecular competition experiments between differently substituted amides. Mechanistic studies support a reversible C–H metalation mechanism by a cationic ruthenium(II) complex.

4.1.5. Palladium-catalyzed *ortho*-cyanation. Cheng and co-workers reported a chelation-assisted palladium-catalyzed *ortho*-cyanation of aromatics without strong bases or expensive ligands.[43] Substrates bearing methoxy, chloro, fluoro, vinyl, and cyanogen groups were able to afford the corresponding nitriles smoothly (Scheme 42). Also, benzo[*h*]quinoline and pyrazole acted as the directing group for this cyanation reaction, even though the yield was low.

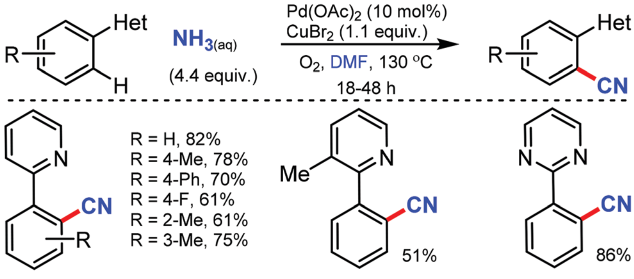
In the proposed catalytic cycle, the cyclopalladated intermediate **A** is formed through the chelate-directed C–H activation of 2-phenylpyridine. Subsequent ligand exchange of CN$^-$ affords the Pd(II) species **B**, which undergoes the carbon–carbon bond forming reductive elimination to deliver the product and Pd(0), which on oxidation by Cu(II) and/or air, regenerates Pd(II).

Combining DMF and NH$_3$ as the effective CN source for the palladium-catalyzed C–H cyanation was revealed by Chang and co-workers in 2010.[44] Intriguingly, the carbon source of "CN" was provided by the dimethylamino moiety rather than the formyl group of DMF. However, the electron-deficient groups resulted in decreased product yields. Notably, substrates such as 1-phenylisoquinoline and benzo[*h*]quinoline also proceeded smoothly (Scheme 43).

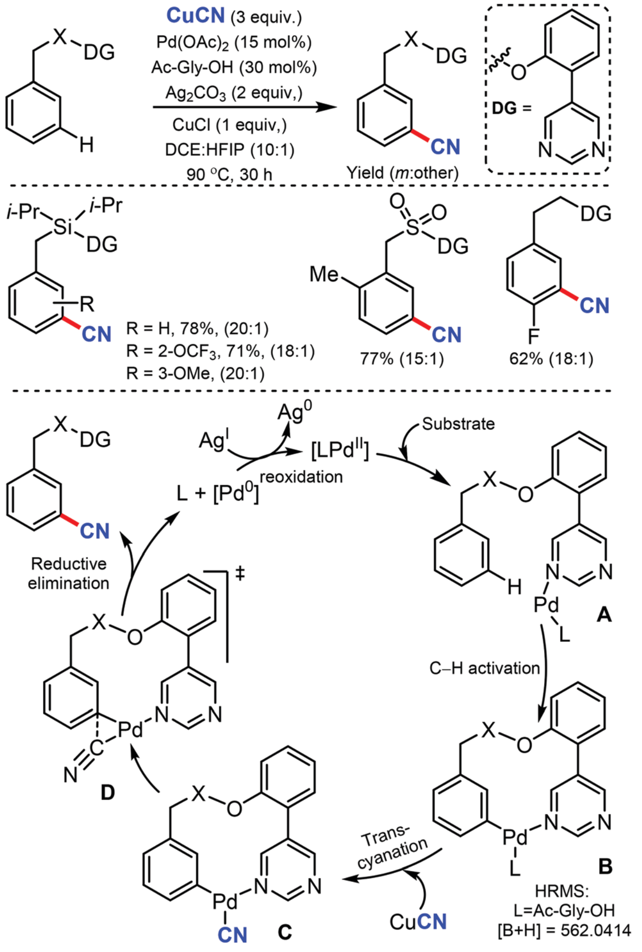
4.2. *meta*-C–H cyanation by the *meta*-directing template

In 2017, Maiti and co-workers disclosed the palladium-catalyzed *meta*-C–H cyanation of arenes by the removable pyrimidine-based directing group and CuCN.[45] H-bonding interaction with pyrimidine and HFIP is hypothesized to decrease the basicity of the DG and synergistically increases the π-acidity of the palladium center. Electron-rich, electron-poor, and sterically-encumbered *para*-substituted benzylsilane, benzylsulfonates, benzylphosphonates, phenethylsulfonates, and phenethyl ether derivatives could afford the mono-cyanated products with high yield and selectively (Scheme 44).

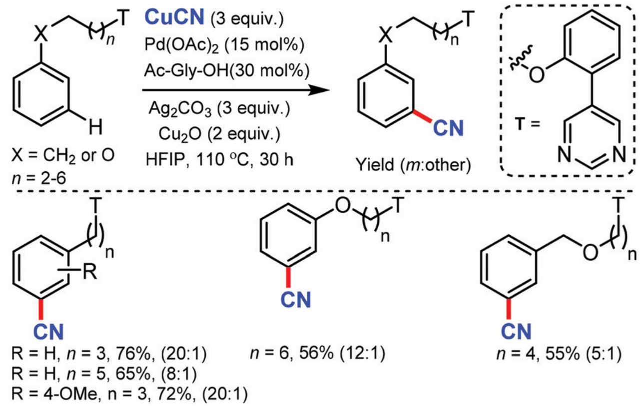
The detailed NMR study by varying the amount of 1,1,1,3,3,3-hexafluoro-propan-2-ol (HFIP) in the presence of *meta*-substrate in CDCl$_3$ revealed that hydrogen bonding is present in between the pyrimidine-directing group (DG) and HFIP and the kinetic isotope effect (KIE) experiment reported k_H/k_D = 1.25 and the intermolecular competition experiment P_H/P_D was found to be 1.15. In the probable catalytic cycle, first, the pyrimidine directing group coordinates with the mono-



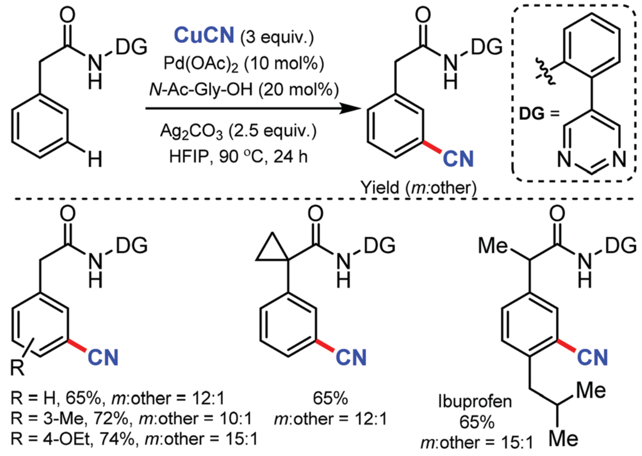
Scheme 43 Palladium-catalyzed cyanation of aryl by NH$_3$ and DMF.



Scheme 44 Remote *meta* C–H cyanation of arenes.



Scheme 45 Palladium-catalyzed *meta*-C–H cyanation of arenes.



Scheme 46 Palladium-catalyzed *meta*-C–H cyanation of amides.

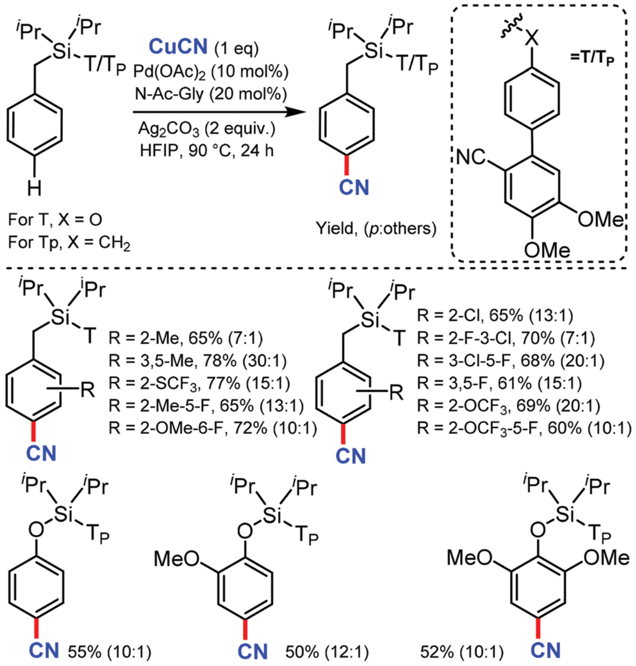
protected amino acid (MPAA)-ligated palladium catalyst (**A**) and the close proximity activates the *meta*-C–H bond (most probably *via* concerted metallation–deprotonation) to afford the macrocyclic transition state **B**. The ligand exchange of CN^- between copper(I) cyanide and cyclopalladated intermediate forms **C**. The reductive elimination from **C** *via* the complex transition state **D** is presumed to provide the desired cyanation product.

Later, the same group developed the *meta*-C–H cyanation of arenes containing long alkyl chains using an ether-tethered, conformationally flexible, pyrimidine-based directing group using CuCN.[46] Various arene/phenols scaffolds with chains ranging from propyl to octyl were selectively functionalized to afford the *meta*-cyanated product (Scheme 45). Electron-donating, electron-withdrawing, and sterically encumbered α-methyl propylbenzene were also tolerated. Along with cyanation, alkylation, olefination, and acetoxylation were also facile under the same reaction condition. The control experiments indicated that the pyrimidine-based template has a crucial role in the formation of the macrocyclic transition state for palladium-catalyzed C–H bond activation.

Again in 2020, Maiti and co-workers reported the palladium-catalyzed *meta*-C–H cyanation of amides with the assistance of a pyrimidine-based directing group and CuCN under mild reaction conditions.[47] Differently substituted phenylacetamides were selectively cyanated using this strategy. Notably, the cyanation of Ibuprofen could also be afforded with good yield and excellent *meta*-selectivity. Other than cyanation, diverse remote *meta*-C–H functionalizations of arenes such as allylation, alkylation, alkynylation, and deuteration were well executed under these reaction conditions (Scheme 46).

4.3. *para*-C–H cyanation by the *para*-directing template

Recently in 2020, Maiti's group reported a new method for the distal *para*-selective C–H cyanation of toluenes and phenols by using nitrile-based *para*-directing template using $Pd(OAc)_2$ & monoprotected amino acid (MPAA) as ligand, Ag_2CO_3 as base and CuCN as the cyano source (Scheme 47).[48] Groups such as CF_3, OCF_3, OMe, or Me on the same ring gave the *para*-cyanation product in good yield and with high *para*-selectivity. The higher *para* selectivity for this reaction was due to the design of the directing group, which has two methoxy group (Scheme 48), which forms hydrogen bonding with 1,1,1,2,2,2-hexafluoropropan-2-ol (HFIP). The reaction proceed *via* C–H activation, which is not the rate determining step of the reaction (probed by experimental and computational studies), followed by CN

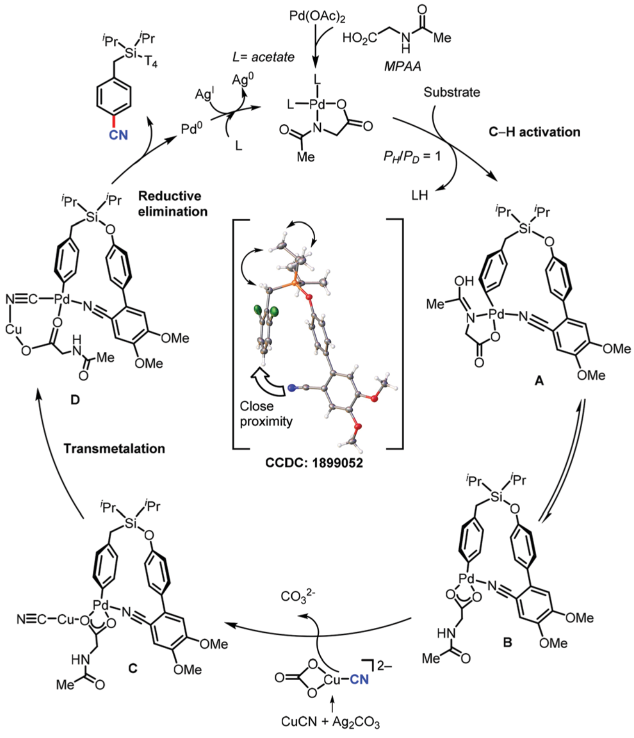


Scheme 47 *para*-Selective cyanation by *para*-directing templates.

coordination assisted by Cu and subsequent reductive elimination gives the *para*-cyanated product.

This method is superior due to the iterative multi-functionalization and post synthetic modifications.

To understand the mechanism for *para*-cyanation, a detailed study using density functional theory (DFT) was carried out. Unlike other *para*-functionalizations reported earlier, mono-*N*-protected amino acid (MPAA) ligand promotes *para*-C–H activation *via* the concerted metalation deprotonation (CMD) pathway. The *N*-acyl group of MPAA ligand acts as the base to form **A.** Intermediate **A** then tautomerizes into a more stable palladacycle **B** with the carboxylic group bound in the κ^2 fashion to the Pd center. Density function theory (DFT) computations for a series of possible CuCN complexes with anions showed that $CuCN(CO_3)^{2-}$ is the most stable species. Later, CuCN coordinates to the carboxylic group of palladacycle **B** to form intermediate **C.** The resulting palladacycle **D** smoothly undergoes C–C reductive elimination to form the cyanation product (Scheme 48).



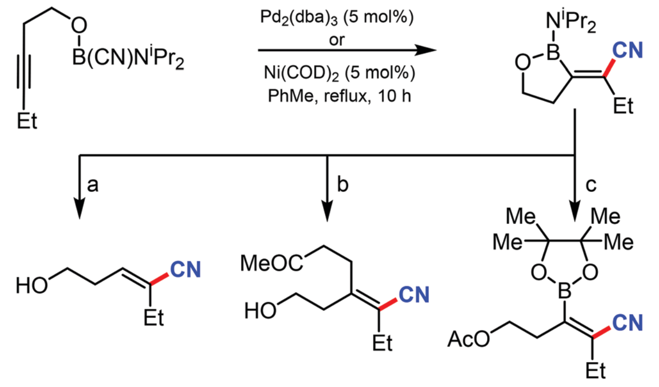
Scheme 48 Plausible mechanism for *para*-C–H cyanation.

Also, C–H activation was found to be reversible, which was consistent with the experimental observation. The partial solubility of CuCN was very crucial for this reactivity. Due to the favorable interaction with ^{t}BuOH ($\Delta G = -7.3$ kcal mol^{-1}), CuCN is soluble in ^{t}BuOH with a relatively high –CN concentration. This increases the possibility of catalyst deactivation, leading to a low yield with ^{t}BuOH as the solvent. In contrast, the interaction of CuCN with HFIP is thermodynamically neutral ($\Delta G = 0.2$ kcal mol^{-1}), which provided an optimum cyanide concentration for the reactivity rather than catalyst deactivation.

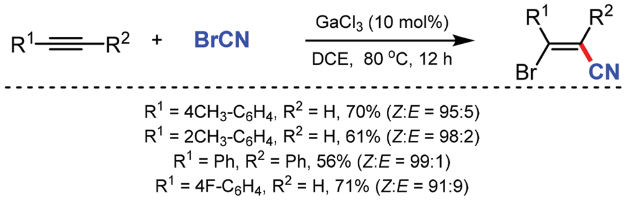
5. Alkenyl and alkynyl C–H cyanation

In 2003, Suginome's group reported $Pd_2(dba)_3$ and $Ni(COD)_2$ catalyzed intramolecular cyanoboration of alkynes. In this transformation, terminal and internal alkynes with various substituted groups reacted well to yield the cyanoboration complexes. This complex, when subjected to various synthetic procedures, yielded multi-substituted cyanoalkenyl products (Scheme 49).[49]

The gallium-catalyzed bromocyanation of alkynes with cyanogen bromide was developed by Ohe and coworkers in 2011, which opened up a novel route to synthesize (*Z*)-β-bromoacrylonitriles regio- and stereoselectively.[50] Several arylacetylenes having aromatic rings gave bromocyanated products with high regioselectivity while some internal aliphatic or alicyclic alkynes gave complex



Scheme 49 Pd/Ni-catalyzed cyanoboration of alkynes. (a) Rh(acac)(COD)/dppb (3 mol%), H_2O, dioxane, 50 °C (b) methyl vinyl ketone (1 equiv.), Rh(acac)(COD)/dppp (3 mol%), MeOH, dioxane, 50 °C (c) pinacol (1.2 equiv.), Ac_2O (1.2 equiv.), THF, 40 °C.



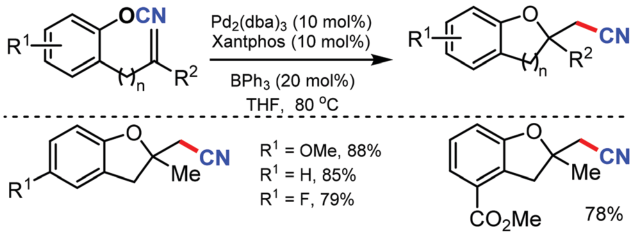
Scheme 50 Gallium-catalyzed bromocyanation of alkynes with cyanogen bromide.

mixtures (Scheme 50). NMR studies indicated the probability of formation of a complex between BrCN and $GaCl_3$ during the reaction.

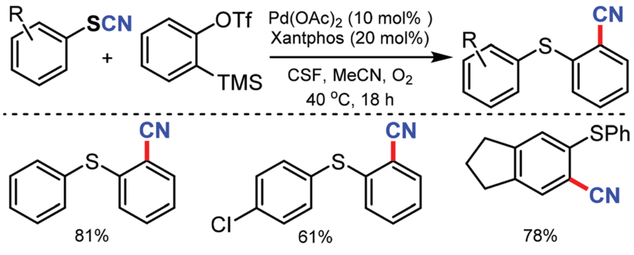
An excellent strategy for the intramolecular oxycyanation of alkenes was reported by Nakao and coworkers in 2012.[51] Under palladium/BPh_3 catalysis, the cleavage of O–CN bonds and the subsequent insertion of double bonds was carried out. Using this method, the simultaneous incorporation of a tetra-substituted carbon and cyano group through O–CN bond activation was accomplished, which gave access to different substituted dihydrobenzofurans with high regioselectivity (Scheme 51).

An easy access to various 1,2-thiobenzonitriles under mild reaction conditions and palladium catalysis was put forward by Werz and coworkers in 2015.[52] Palladium mediated activation of carbon–sulfur bonds helps in aryne insertion into aryl thiocyanates to make the new C–SAr and C–CN bond simultaneously. Employing an oxygen atmosphere could reasonably increase the yields and was helpful in minimizing the side reactions (Scheme 52).

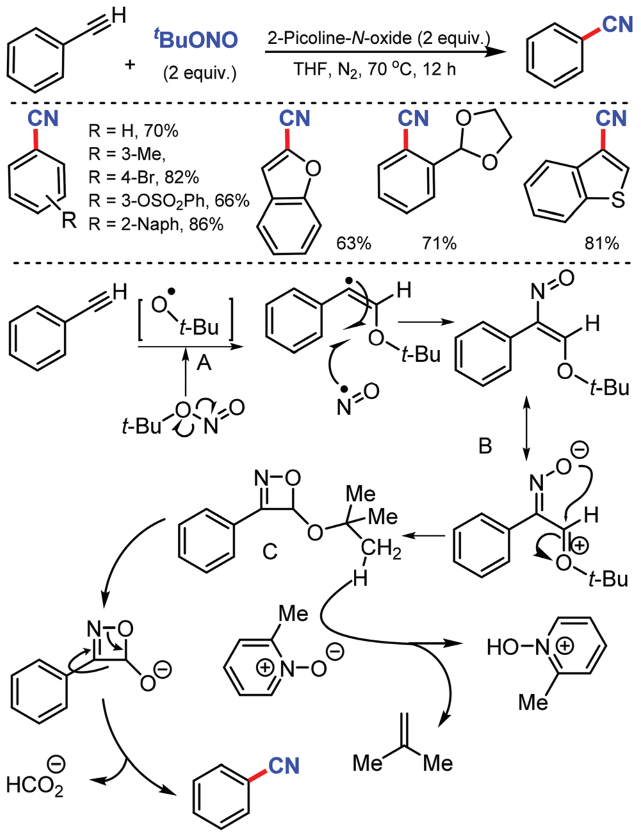
In 2016, Maiti and co-workers reported an efficient strategy for the synthesis of a wide range of aryl nitriles by incorporating a metal-free cyanation of terminal alkynes by *tert*-butyl nitrite (^{t}BuONO) under mild reaction conditions[53] (Scheme 53). Phenylacetylenes bearing electron-rich groups as well as phenanthrene and pyrene acetylenes could afford the desired product in good to excellent yields. Functional groups such as 4-OMe, 2-Me-4-OMe, 4-pentoxy, 4-Br, esters, amides, and ketones were well tolerated.



Scheme 51 Intramolecular oxycyanation of alkenes by cooperative Pd/BPh_3 catalysis.



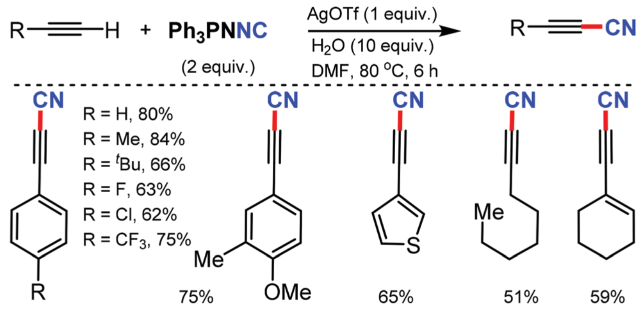
Scheme 52 Synthesis of 1,2-thiobenzonitriles through the activation of aryl thiocyanates, followed by aryne insertion.



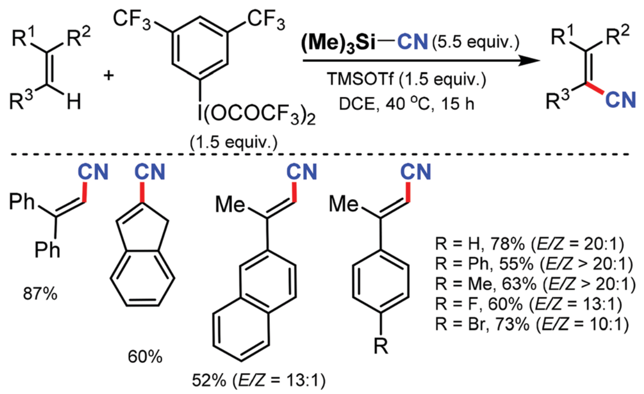
Scheme 53 Synthesis of aryl nitriles from phenylalkynes and the radical induced mechanism.

However, the internal alkynes and aliphatic alkynes were not suitable substrates for this cyanation method. Based on the kinetic studies, a plausible mechanism was proposed, in which *tert*-butyloxy and nitroso radical were formed by the *in situ* homolysis of *tert*-butyl nitrite. The alkyne forms a phenyl-substituted vinyl radical **A** by reacting with the *tert*-butyloxy radical. The subsequent cyclization of **B** then provides the strained four-membered intermediate **C** with the elimination of formic acid, leading to the formation of benzonitrile. Similarly, silver-mediated direct cyanation of terminal alkynes was developed by Bi and co-workers in 2017, employing non-toxic and facile *N*-isocyanoiminotriphenylphosphorane (NIITP) as the cyanating agent (Scheme 54).[54]

A metal-free approach for the direct cyanation of alkenes using TMSCN and [bis(trifluoroacetoxy)iodo]arene was reported by Studer and co-workers in 2018.[55] Under mild reaction conditions, various 1,1-disubstituted, 1,2-disubstituted, and trisubstituted alkenes could be cyanated in moderate to good yields with high diastereoselectivity (Scheme 55). Notably, the selectivity was found to reduce as the size of the α-alkyl substituent increased.



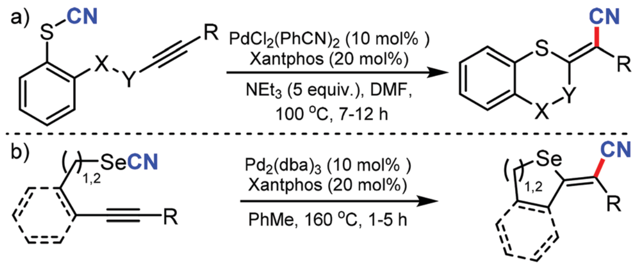
Scheme 54 Silver-mediated C–H cyanation of terminal alkynes with NIITP.



Scheme 55 Metal-free direct C–H cyanation of alkenes.

Mechanistic studies suggest that the electrophilic activation of alkene by the cyano iodine(III) species generated *in situ* from the [bis(trifluoroacetoxy)iodo]arene reagent is involved in this transformation.

Recently, the realm of cyano-functionalization was further explored by Werz and coworkers by palladium catalysis and was utilized for the cyanosulfenylation[56] and cyanoselenylation[57] of internal alkynes independently in 2020 (Scheme 56). Both aromatic and aliphatic thiocyanates underwent the *syn*-1,2-cyanosulfenylation of internal alkynes and could access the tetra-substituted double bonds with sulphur and cyano in adjacent positions. The reaction could tolerate the addition of aromatic and aliphatic thiocyanates in an intra- and intermolecular fashion. Under similar reaction conditions, cyanoselenylation was accomplished, which gave novel access to the intra- and intermolecular synthesis of selenium-substituted acyclic and heterocyclic acrylonitrile derivatives with the assistance of palladium catalysis and with high functional group tolerance. X-ray studies indicate the occurrence of short non-covalent chalcogen–chalcogen (Se···O) interaction.



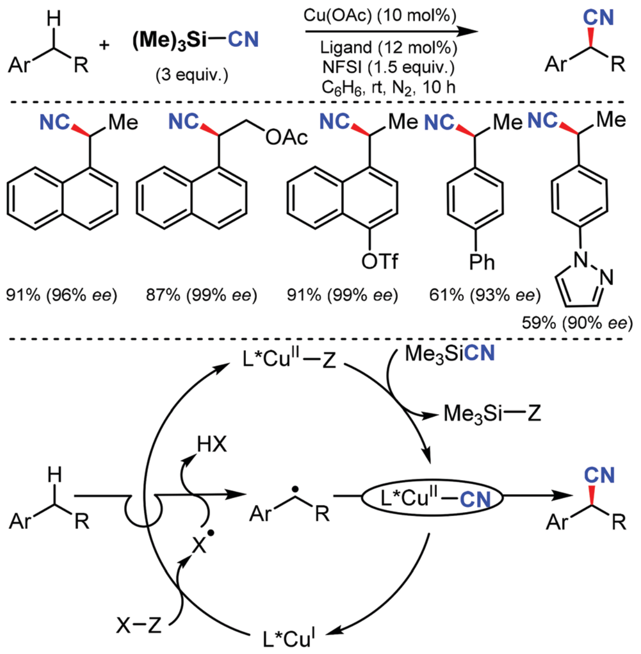
Scheme 56 Palladium-catalyzed cyanosulfenylation (a) and cyanoselenylation (b) of internal alkynes.

6. Asymmetric C–H cyanation

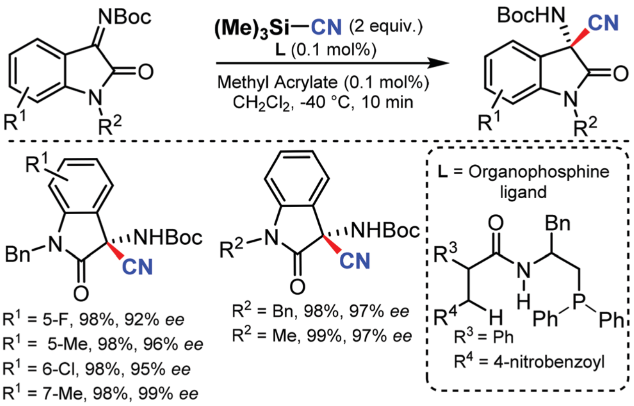
An efficient enantioselective cyanation of benzylic C–H bonds assisted by the copper catalyzed radical pathway was illustrated by Liu and co-workers in 2016.[58] Various alkyl naphthalenes, alkyl arenes, and heterocycle containing alkyl arenes were tolerated under this protocol (Scheme 57). The mechanistic studies suggested that hydrogen-atom abstraction provides an achiral benzylic radical that undergoes asymmetric C(sp^3)–CN bond formation upon reaction with a chiral copper catalyst. The proposed mechanism suggests that the ethylbenzene-derived radical reacts with Cu^{II} in an (L)Cu^{II}(CN)$_2$ species to afford the benzyl-Cu^{III} species. Subsequent C(sp^3)–CN reductive elimination generates the benzylic nitrile product.

In 2016, Zhao and co-workers developed a chiral dipeptide-derived multifunctional organophosphine-based dual-reagent catalytic system for the asymmetric cyanation of ketoimines derived from isatins.[59] Importantly, a zwitterion intermediate, which is generated *in situ* by mixing a chiral multifunctional organophosphine with methyl acrylate, functions as an efficient Lewis-base catalyst in this transformation (Scheme 58).

The broad substrate scope of ketoimines derived from isatins and azomethine aldimines was asymmetrically cyanated in excellent yield and enantioselectivity with very low catalyst



Scheme 57 Enantioselective cyanation of benzylic C–H bonds.



Scheme 58 Asymmetric cyanation of ketoimines.

loading; the kinetic resolution of racemic 3-substituted azomethine imines was also carried out.

7. Electro-catalyzed C–H cyanation

Using 9-azabicyclononane *N*-oxyl (ABNO) as the catalytic mediator, the electrochemical α-cyanation of secondary piperidines was developed by Stahl and co-workers in 2018.[60] The cyanation of the heterocycle adjacent to nitrogen without requiring protection or substitution of the N–H bond was accomplished through this strategy by using TMSCN as the source of cyanide nucleophile. Employing ABNO as a hydride-transfer mediator helps the reaction to proceed at low electrode potentials and is compatible with a wide range of functional groups. The reaction mechanism involved the electrochemical oxidation of ABNO, which produces the corresponding oxoammonium species that promotes the dehydrogenation of the secondary piperidine to the cyclic imine, followed by the addition of cyanide (Scheme 59).

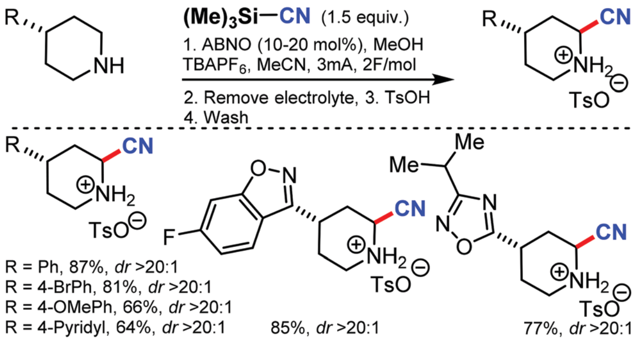
8. Non-directed C–H cyanation of unactivated arenes

Ohe and co-workers reported simple direct cyanation of aromatic and heteroaromatic C–H bonds under gallium catalysis using cyanogen bromide (BrCN) as the CN source.[61] Electron-donating groups substituted arenes and polycyclic aromatic compounds such as anthracene and pyrene were tolerated well in moderate to high yields. The scope of this protocol was also applicable to several substituted heterocycles such as pyrrole, furan, thiophene, indole, and benzofuran (Scheme 60).

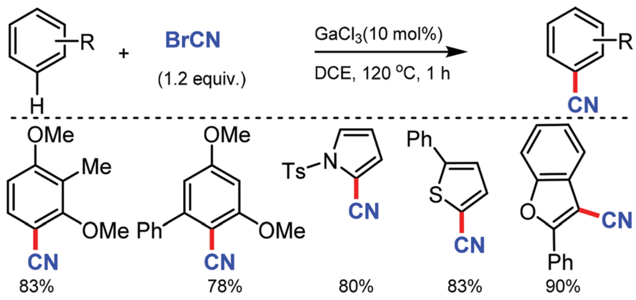
An efficient approach for the direct conversion of methyl arenes into aromatic nitriles using $Pd(OAc)_2$ and *N*-hydroxyphthalimide (NHPI) as the catalysts was developed by Wang and co-workers in 2013.[62] This ammoxidation method utilizes *tert*-butyl nitrite as the nitrogen source and oxidant under mild reaction conditions. Interestingly, multi-substituted toluene or oxidative sensitive groups such as Bpin were also compatible with this protocol. The scope of this reaction was also applicable for several polycyclic and heteroaromatic compounds efficiently. Mechanistic studies indicated that the reaction involves the formation of aldoxime as the key intermediate (Scheme 61).

Using 3,5-di(trifluoromethyl)phenyl(cyano)iodonium triflate (DFCT) as the cyanation agent, Wang and co-workers developed the oxidative cyanation of arenes catalyzed by Fe(II).[63] Various electron-rich benzene derivatives were smoothly cyanated, with the regioselectivity governed by both electronic and steric effects of the substituents (Scheme 62). In case of heteroaromatic substrates, an additional requirement of 2,6-di-*tert*-butylpyridine was necessary for the reaction to proceed. The steric effects of the substituents played a crucial role in determining the selectivity of the reaction.

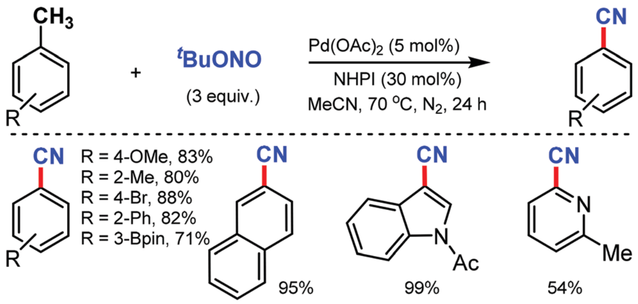
The reaction mechanism involves a single-electron transfer pathway (SET), in which a highly reactive radical species **A** is initially produced. SET from the radical species **A** to the arene



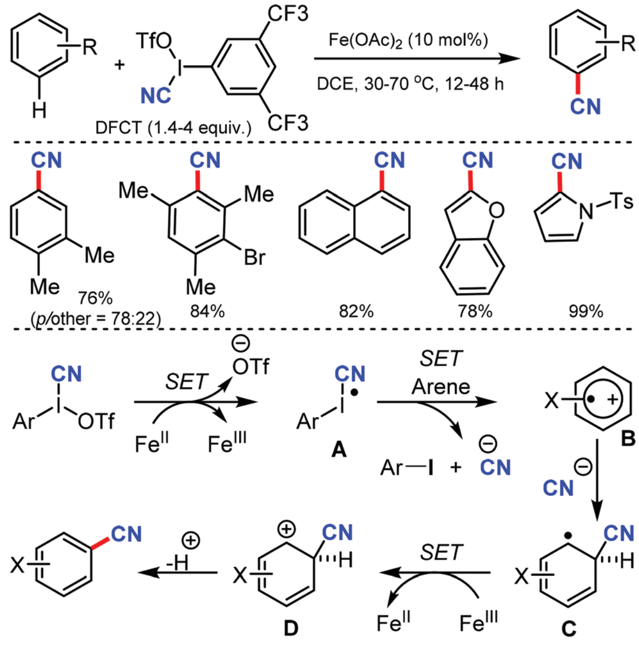
Scheme 59 Electrochemical ABNO-mediated α-cyanation of secondary piperidines.



Scheme 60 Gallium-catalyzed electrophilic cyanation of arenes.



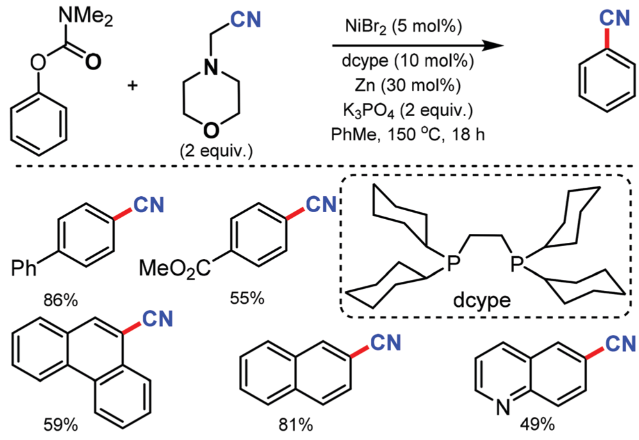
Scheme 61 Palladium(II)-catalyzed direct conversion of methyl arenes into aromatic nitriles.



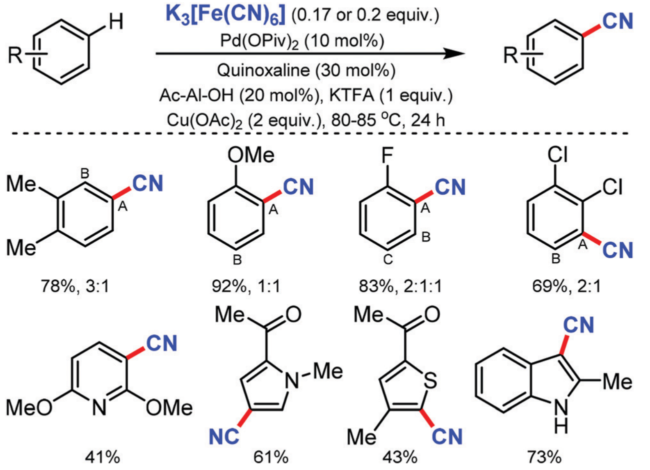
Scheme 62 Iron(II)-catalyzed direct cyanation of arenes with DFCT.

substrate affords intermediate **B**; nucleophilic addition of cyanide ion to **B** then generates a radical intermediate **C**. In the final step, cation intermediate **D** is formed, the deprotonation of which affords the cyanated product.

Phenol derivatives are generally inexpensive and readily available chemicals in organic synthesis. An environmentally benign protocol for the cyanation of phenol derivatives was disclosed by Yamaguchi and co-workers in 2016 with the help of a nickel-based catalytic system consisting of a unique diphosphine ligand such as dcype (1,2-bis(dicyclohexylphosphino)ethane) or dcypt (3,4-bis-(dicyclohexylphosphino)thiophene) and aminoacetonitrile as the metal-free cyanating agent.[64] Various aryl carbamates such as biphenyl, naphthyl, polycyclic, quinoline, carbazole, flavone, estrone, and tyrosine derivatives carbamates could afford the cyanated products in moderate to good yields (Scheme 63). Fortunately, this nickel catalytic system was applicable to tosylates, mesylates, triflates, sulfamates, phosphates as well as enol derivatives and provided the corresponding cyanated products in good yields.



Scheme 63 Aryl carbamates' cyanation with aminoacetonitrile.



Scheme 64 Pd-Catalyzed non-directed C–H cyanation.

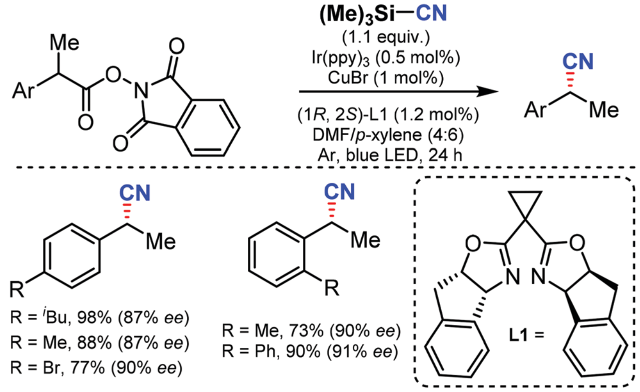
Ritter and co-workers in 2019[65] described an expedient approach for benzonitrile derivatives by the non-directed method with $K_3Fe(CN)_6$ as the CN source. With broad substrate scope and functional-group tolerance, this protocol could easily afford the direct cyanation of several marketed small-molecule drugs, common pharmacophores, and organic dyes even though low regioselectivity was observed (Scheme 64).

Notably, pyridine, thiophene, pyrrole, indoles as well as functional groups including sulfonamides, esters, amides, unprotected hydroxyl groups, and ketones were compatible with the reaction conditions. Both monoprotected amino acids (MPAA) and quinoxaline played a crucial role in accessing the catalyst active sufficiently for C–H metalation.

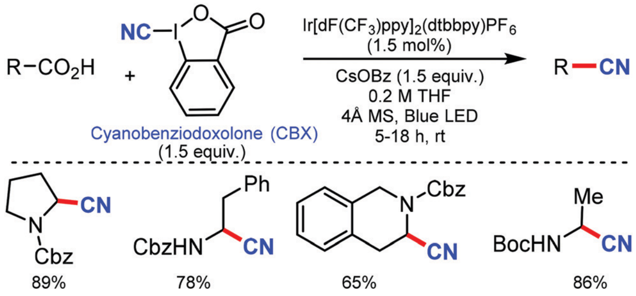
9. Photocatalysis approaches for C–H cyanation

In 2017, Liu and co-workers reported an enantioselective decarboxylative cyanation by combining photoredox and copper catalysis using TMSCN as the CN source to give the alkyl nitriles.[66] A broad range of NHP esters derived from simple carboxylic acids could afford the anticipated products in good yields and excellent enantioselectivities with high functional group tolerance. Mechanistic studies suggested that both benzylic radicals and reactive chiral copper(II) species were generated from the photocatalytic cycle (Scheme 65).

Later, in 2017, a similar approach for decarboxylative cyanation was developed by Waser and co-workers in 2017.[67] A variety of natural and non-natural α-amino, several dipeptides, drug precursors, and α-oxy acids were cyanated smoothly using an iridium photoredox catalyst. Notably, different protecting groups, such as –Cbz, –Boc, and –Fmoc were tolerated for this transformation. It was proposed that single electron transfer (SET) to form the iminium intermediate, followed by cyanide addition, was involved in the reaction mechanism (Scheme 66).



Scheme 65 Enantioselective decarboxylative cyanation by cooperative photoredox and copper catalysis.

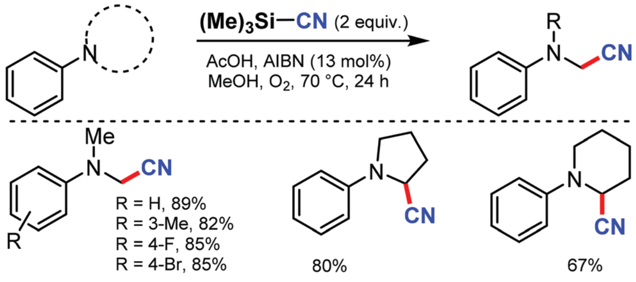


Scheme 66 Decarboxylative cyanation of carboxylic acids.

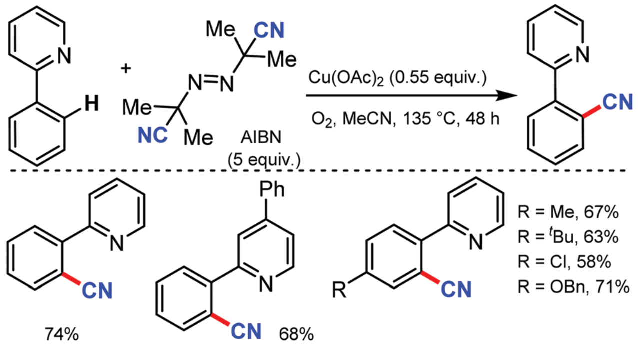
10. Radical mediated cyanation

In 2008, Porta and co-workers reported a method for the synthesis of β-hydroxynitriles by the cross coupling of stabilized radicals and the α-cyanoisopropyl radical.[68] In this transformation, Ti(IV) chelates and promotes homolytic C–C cleavage and enhances the captodative effect. This allowed the application of the well-known Ingold–Fischer effect to a wider range of stabilized carbon-centered radicals.

Later, a metal-free aerobic oxidative cyanation of tertiary amines to R-aminonitriles using a catalytic amount of azobisisobutyronitrile (AIBN) was disclosed by Yan and co-workers in 2012.[69] Several substituted *N*,*N*-dimethylanilines, with electron-donating or -withdrawing groups, could afford the corresponding cyanated products in excellent yields (Scheme 67). The reaction proceeds through the formation of highly reactive iminium ion intermediates.



Scheme 67 AIBN initiated oxidative cyanation of tertiary amines.

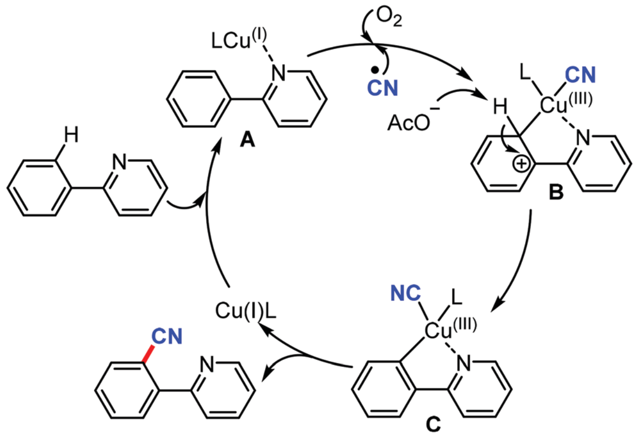


Scheme 68 Copper-mediated direct aryl C–H cyanation with AIBN.

Employing AIBN as a free radical CN source, a direct aryl C–H cyanation method was disclosed by Han and co-workers under Cu catalysis in 2013.[70] Various 2-aryl pyridines with electron-donating and -withdrawing groups at the aryl ring gave the corresponding nitriles in moderate to good yields. Several substrates with substitution at the pyridyl ring were also tolerated. In general, electron-rich substrates gave better yield than electron-deficient substrates (Scheme 68). A CN free radical mechanism was involved in this reaction.

The proposed mechanism involves the *in situ* generation of active catalytic species Cu(I)L by the reduction of Cu(II) with AIBN. The coordination of Cu(I)L with the substrate forms complex **A**. The subsequent oxidation of **B** with the assistance of the CN radical and O_2 yields the high-valent Cu(III) complex **C** *via* **B** through electrophilic Cu(III) promoted de-aromatization and re-aromatization. Later, the reductive elimination of **C** produces the cyanated product (Scheme 69).

In 2014, Wang and co-workers developed a cost-effective copper catalyzed direct cyanoalkyarylation with AIBN to give the substituted oxyindoles. The thermal decomposition of AIBN released the free 2-cyanoprop-2-yl radical, which mediated the reaction by the single electron transfer (SET) process.[71] On a



Scheme 69 Proposed mechanism for radical mediated cyanation of tertiary amines.

similar note, Tang *et al.* reported Cu-DTBP (di-*tert*-butyl peroxide) mediated synthesis of oxyindoles.[72] This method could also tolerate different substituted AIBN derivatives. Inter and intramolecular KIE (Kinetic Isotope Effect) of 1 and 1.3 indicated that free radical mechanism is involved. Later, in 2016, Tang and co-workers also reported the aerobic oxidative cyclization of benzamides *via meta*-selective C–H *tert*-alkylation using AIBN. This gave rapid access to 7-*tert*-alkylated isoquinolinediones.[73] A radical scavenger such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) could suppress the cyclization indicating the radical-mediated mechanism. These methods does not form direct C–CN bonds but involve nitrile/cyano functionalization.

In 2017, Li and co-workers used AIBN with Cu-catalyst for the [2+2+2] annulation of 1,*n*-enynes for the synthesis of 7,8-dihydrophenanthridine-6,9(5*H*,6*aH*)-diones and fluorenes. Enynes with *N*-Bn, *N*-Ts, or free NH were well tolerated in this reaction. Unlike previous methods, this reaction also proceeds *via* radical mediated mechanism. First, it forms the corresponding nitriles, which upon subsequent hydration and annulation, forms diones and fluorenes.[74] Recently, Chen's group also described the one-pot construction of benzofuran-2(3*H*)-one *via* the radical cascade of *para*-quinone methides with AIBN/H_2O. This method offered an elusive and efficient route to cyano-containing benzofurans as well as 2,3-dialkylating benzofurans. Late-stage functionalizations by non-polar C(aryl)–C(*t*-butyl) bond cleavage *via* Cu catalysis provided an interesting synthetic transformation of *para*-quinone methides.[75]

11. Conclusion

Undoubtedly, the cyano/nitrile group is a versatile synthetic intermediate owing to its capability to get smoothly transformed into various functional groups such as acids, ketone, amine, aldehyde, and N-heterocycles. Thus, cyanation has become a topic of wide significance in organic/material/medicinal synthesis and has been exploited for the synthesis of various structurally complex molecules. Until a decade ago, the facile introduction of cyano group was achieved by transition metal-catalyzed cyanation of aryl halides. However, since then, approaches developed by various research groups across the globe in recent years showed the diversity of synthetic routes and budding capabilities to discover new routes to make the CN bond. Furthermore, in the near future, the merger of different approaches in one pot for tandem functionalization to synthesize novel motifs, which will serve in agrochemical, pharmaceutical, and fine chemical industries, is highly conceivable. However, more importantly, the design and synthesis of novel organo-cyano reactions in the area of distal C–H activation of aliphatic and aromatic compounds is yet to be achieved.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research activity is supported by SERB (CRG/2018/003951) India. SP thanks IITB-Monash Research Academy for PhD fellowship (IMURA0414).

Notes and references

1 (*a*) A. J. Fatiadi, in *Preparation and Synthetic Applications of Cyano Compounds*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1983, vol. 2, pp. 1057–1303; (*b*) J. S. Miller and J. L. Manson, *Acc. Chem. Res.*, 2001, **34**, 563; (*c*) F. F. Fleming and Q. Wang, *Chem. Rev.*, 2003, **103**, 2035; (*d*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902; (*e*) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049; (*f*) M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300.
2 G. Zhang, X. Ren, J. Chen, M. Hu and J. Cheng, *Org. Lett.*, 2011, **13**, 5004.
3 J. Kim, J. Choi, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528.
4 L. Zhang, P. Lu and Y. Wang, *Chem. Commun.*, 2015, **51**, 2840.
5 H. Wang, Y. Dong, C. Zheng, C. A. Sandoval, X. Wang, M. Makha and Y. Li, *Chem*, 2018, **4**, 2883.
6 C. W. Liskey, X. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 11389.
7 Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2017, **56**, 3655.
8 P. Yu and B. Morandi, *Angew. Chem., Int. Ed.*, 2017, **56**, 15693.
9 X. Zhang, A. Xia, H. Chen and Y. Liu, *Org. Lett.*, 2017, **19**, 2118.
10 H. Chen, S. Sun, Y. A. Liu and X. Liao, *ACS Catal.*, 2020, **10**, 1397.
11 P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2010, **49**, 8918.
12 P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 648.
13 S. Zheng, C. Yu and Z. Shen, *Org. Lett.*, 2012, **14**, 3644.
14 D. Zhang, H. Sun, L. Zhang, Y. Zhou, C. Li, H. Jiang, K. Chen and H. Liu, *Chem. Commun.*, 2012, **48**, 2909.
15 T. D. Senecal, W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 10035.
16 D. T. Cohen and S. L. Buchwald, *Org. Lett.*, 2015, **17**, 202.
17 B. Majhi and B. C. Ranu, *Org. Lett.*, 2016, **18**, 4162.
18 B. Luo, J.-M. Gao and M. Lautens, *Org. Lett.*, 2016, **18**, 4166.
19 P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519.
20 S.-I. Murahashi, N. Naruyoshi, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312.
21 S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931.
22 L. Ma, W. Chen and D. Seidel, *J. Am. Chem. Soc.*, 2012, **134**, 15305.
23 H.-Q. Do and O. Daugulis, *Org. Lett.*, 2010, **12**, 2517.
24 G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052.
25 S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.
26 Y. Yang, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 5608.
27 J. Kim, H. Kim and S. Chang, *Org. Lett.*, 2012, **14**, 3924.
28 S. Xu, X. Huang, X. Hong and B. Xu, *Org. Lett.*, 2012, **14**, 4614.
29 J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang and Q. Zhu, *Org. Lett.*, 2012, **14**, 4966.
30 T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 10630.
31 M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2013, **15**, 4960.
32 W. Su, T.-J. Gong, B. Xiao and Y. Fu, *Chem. Commun.*, 2015, **51**, 11848.
33 M. Chaitanya and P. Anbarasan, *Org. Lett.*, 2015, **17**, 3766.
34 S. Lv, Y. Li, T. Yao, X. Yu, C. Zhang, L. Hai and Y. Wu, *Org. Lett.*, 2018, **20**, 4994.
35 H. Li, S. Zhang, X. Yu, X. Feng, Y. Yamamoto and M. Bao, *Chem. Commun.*, 2019, **55**, 1209.
36 D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722.
37 J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 3435.
38 A. B. Pawar and S. Chang, *Org. Lett.*, 2015, **17**, 660.

39 J. Jin, Q. Wen, P. Lu and Y. Wang, *Chem. Commun.*, 2012, **48**, 9933.
40 B. Venu, B. Vishali, G. Naresh, V. V. Kumar, M. Sudhakar, R. Kishore, J. Beltramini, M. Konarova and A. Venugopal, *Catal. Sci. Technol.*, 2016, **6**, 8055.
41 C. Qi, X. Hu and H. Jiang, *Chem. Commun.*, 2017, **53**, 7994.
42 W. Liu and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1878.
43 X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 4716.
44 J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272.
45 S. Bag, R. Jayarajan, U. Dutta, R. Chowdhury, R. Mondal and D. Maiti, *Angew. Chem., Int. Ed.*, 2017, **56**, 12538.
46 R. Jayarajan, J. Das, S. Bag, R. Chowdhury and D. Maiti, *Angew. Chem., Int. Ed.*, 2018, **57**, 7659.
47 A. Gholap, S. Bag, S. Pradhan, A. R. Kapdi and D. Maiti, *ACS Catal.*, 2020, **10**, 5347.
48 S. Pimparkar, T. Bhattacharya, A. Maji, A. Saha, R. Jayarajan, U. Dutta, G. Lu, D. W. Lupton and D. Maiti, *Chem. – Eur. J.*, 2020, **26**, 11558.
49 A. Yamamoto, M. Murakami and M. Suginome, *J. Am. Chem. Soc.*, 2003, **125**, 6358.
50 M. Murai, R. Hatano, S. Kitabata and K. Ohe, *Chem. Commun.*, 2011, **47**, 2375.
51 D. C. Koester, M. Kobayashi, D. B. Werz and Y. Nakao, *J. Am. Chem. Soc.*, 2012, **134**, 6544.
52 M. Pawliczek, L. K. B. Garve and D. B. Werz, *Org. Lett.*, 2015, **17**, 1716.
53 U. Dutta, D. W. Lupton and D. Maiti, *Org. Lett.*, 2016, **18**, 860.
54 H. Wang, P. Mi, W. Zhao, R. Kumar and X. Bi, *Org. Lett.*, 2017, **19**, 5613.
55 X. Wang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 11792.
56 M. Bürger, M. N. Loch, P. G. Jones and D. B. Werz, *Chem. Sci.*, 2020, **11**, 1912.
57 M. Bürger, S. H. Röttger, M. N. Loch, P. G. Jones and D. B. Werz, *Org. Lett.*, 2020, **22**, 5025.
58 W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, *Science*, 2016, **353**, 1014.
59 H.-Y. Wang, C.-W. Zheng, Z. Chai, J.-X. Zhang and G. Zhao, *Nat. Commun.*, 2016, **7**, 12720.
60 A. J. J. Lennox, S. L. Goes, M. P. Webster, H. F. Koolman, S. W. Djuric and S. S. Stahl, *J. Am. Chem. Soc.*, 2018, **140**, 11227.
61 K. Okamoto, M. Watanabe, M. Murai, R. Hatanoa and K. Ohe, *Chem. Commun.*, 2012, **48**, 3127.
62 Z. Shu, Y. Ye, Y. Deng, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 10573.
63 Z. Shu, W. Ji, X. Wang, Y. Zhou, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 2186.
64 R. Takise, K. Itami and J. Yamaguchi, *Org. Lett.*, 2016, **18**, 4428.
65 D. Zhao, P. Xu and T. Ritter, *Chem*, 2019, **5**, 97.
66 D. Wang, N. Zhu, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 15632.
67 F. L. Vaillant, M. D. Wodrich and J. Waser, *Chem. Sci.*, 2017, **8**, 1790.
68 R. Spaccini, N. Pastori, A. Clerici, C. Punta and O. Porta, *J. Am. Chem. Soc.*, 2008, **130**, 18018.
69 L. Liu, Z. Wang, X. Fu and C.-H. Yan, *Org. Lett.*, 2012, **14**, 5692.
70 H. Xu, P.-T. Liu, Y.-H. Li and F.-S. Han, *Org. Lett.*, 2013, **15**, 3354.
71 W. Wei, J. Wen, D. Yang, M. Guo, L. Tian, J. You and H. Wang, *RSC Adv.*, 2014, **4**, 48535.
72 D. Zhou, Z.-H. Li, J. Li, S.-H. Li, M.-W. Wang, X.-L. Luo, G.-L. Ding, R.-L. Sheng, M.-J. Fu and S. Tang, *Eur. J. Org. Chem.*, 2015, 1606.
73 Y.-L. Deng, J. Li, W.-X. Wang, Y.-C. Wang, Z.-Z. Li, L. Yuan, S.-L. Chen, R.-L. Sheng and S. Tang, *Chem. Commun.*, 2016, **52**, 4470.
74 B. Liu, C.-Y. Wang, M. Hu, R.-J. Song, F. Chen and J.-H. Li, *Chem. Commun.*, 2017, **53**, 1265.
75 J. Yu, H.-X. Sheng, S.-W. Wang, Z.-H. Xu, S. Tang and S.-L. Chen, *Chem. Commun.*, 2019, **55**, 4578.