NJC

ROYAL SOCIETY OF CHEMISTRY

PERSPECTIVE

View Article Online
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Cite this: *New J. Chem.*, 2020, **44**, 17177

Recent advances in C–CN and C–H bond activation of green nitrile (MeCN) for organo-complexation, cyanation and cyanomethylation†

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Received 21st April 2020,
Accepted 13th September 2020

DOI: 10.1039/d0nj01996h

rsc.li/njc

The use of green and inexpensive organic nitrile (MeCN) as a cyano and cyano-methyl source for organo-complexation, cyanation, and cyanomethylation is reviewed. In recent decade, a lot of developments have been made to realize the possibility of using a green cyanide source (MeCN) for cyanation, and this CN source has been used as, for example, a slow dosage cyanide source that could solve the problem of using metal cyanides ($K_4[Fe(CN)_6]$, $Zn(CN)_2$, KCN, CuCN, NaCN), which (1) tend to cause rapid deactivation of the catalyst and (2) are notoriously toxic, producing highly toxic HCN gas in reactions. In view of these problems, here we attempted to discuss new catalyst systems to achieve the cyanation of various aromatic hydrocarbons, such as aryl halides, aryl boronic acids, aryl carboxylic acids, indoles, diazoarenes, aryl alkynes, aryl sulfonamides, and directing group substituted arenes, under variety of reaction parameters. Moreover, acetonitrile is used as the carbon pro-nucleophile in C–C bond formation, which involves complications usually associated with the catalyst active mode or its resting state. This review demonstrates a set of innovations for practical usage *via* direct complexation, cyanation and cyanomethylation methodologies.

1. Introduction and importance

Nitriles are a unique class of compounds and have various applications in natural products, pharmaceuticals, agrochemicals, dyes, and herbicides (Scheme 1).[1,2] Moreover, the "CN" group can be used as a precursor which can further be transformed into various functional groups, such as amines, amidines, amides, aldehydes, carboxylic acids, and tetrazoles (Scheme S1, ESI†).[3a] In recent decades, significant progress has been achieved in the transition metal catalyzed synthesis of benzonitriles.[3b–d,4] Notably, the cyanation of aryl (pseudo)halides, activated arenes, and arenes with directing groups has been elegantly developed. In most cases, metal cyanides are often used as the cyanating reagents. A significant problem is the cyanation at a high temperature and the high affinity of the cyanide ion for the transition metal,

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0nj01996h

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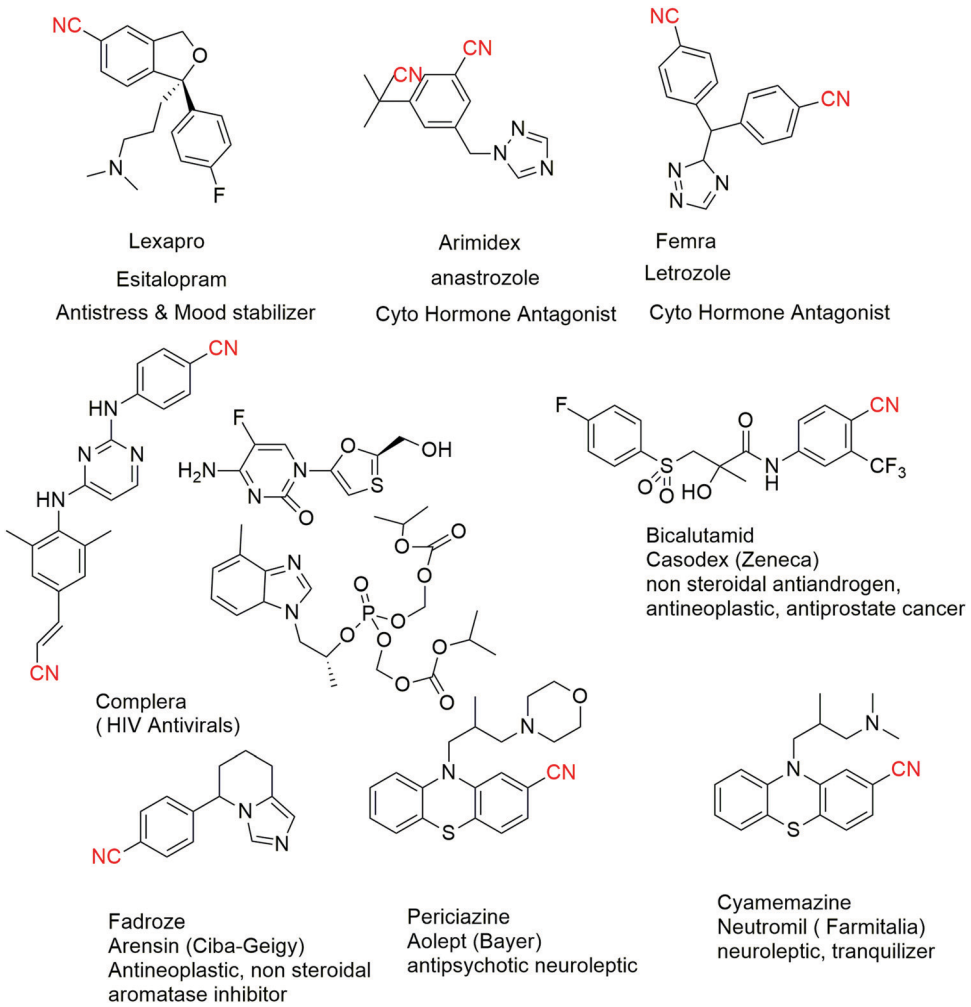

Scheme 1 Biologically active aromatic compounds with a cyano structural unit.

which often results in a rapid deactivation of the catalyst (Scheme S2, ESI†). Moreover, most of the cyano sources, in particular NaCN,[5–11] KCN,[12–19] CuCN,[20] $Zn(CN)_2$[21–32] and TMSCN[33,34] are notoriously toxic. Recently, the investigation of combined cyano sources as an alternative strategy, such as ammonium salts in combination with DMF, DMSO and C–CN activation, has attracted considerable attention.[35–44]

As we mentioned, acetonitrile is a common solvent that shows weak coordination to metal centers and is typically inert in transition metal-catalyzed coupling reactions owing to a high CH_3CN bond dissociation energy (133 kcal mol^{-1}), relative to that of alkane C–C bonds (*ca.* 83 kcal mol^{-1}). At the same time, due to its high pK_a value [pK_a (CH_3CN) = 31.3 in DMSO], it is relatively difficult to use as a pronucleophile. Consequently, the catalytic activation of an acetonitrile C–CN bond as well as the Csp^3–H bond activation of acetonitrile by transition metals has rarely been explored in past decades. Recently, the fast growth regarding acetonitrile being used as a CN source and cyanomethylation reagent has attracted much attention from chemists. Keeping in view the fact, due to the higher pK_a value of the intermediate carbonium ion, a strong base needs to be used, which is incompatible for base susceptible substrates.

Moreover, activated nitriles are being used, such as malononitriles, α-cyano esters and α-sulfonyl nitriles, to overcome this issue.[45] However, acetonitrile consists of various modes of direct activation using basic medium (Scheme 2). In general,

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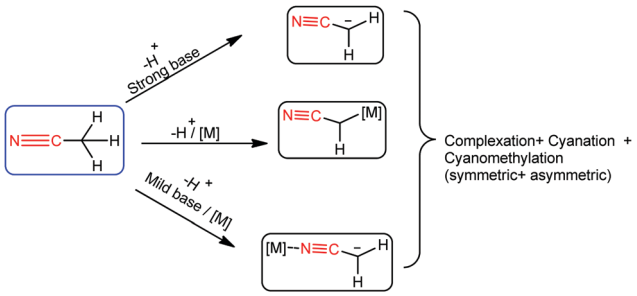


Scheme 2 The direct activation modes of acetonitrile.

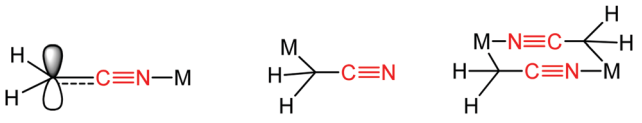


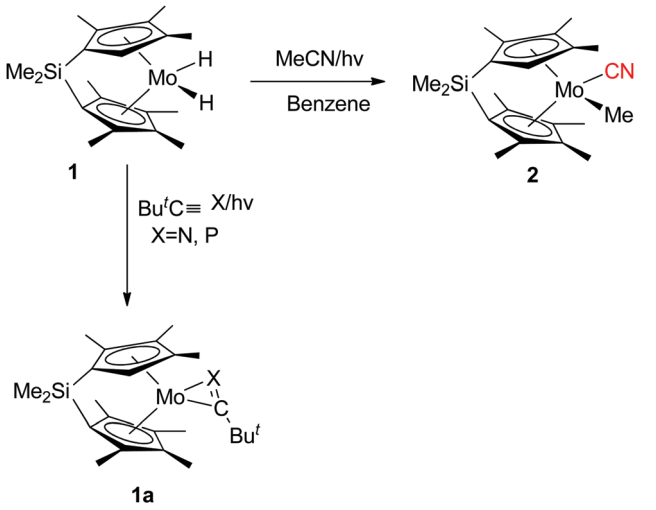
Fig. 1 Metalated acetonitrile.

its reactivity depends upon the catalytic generation of metalated acetonitrile/nitrile and cyanomethyl radicals. As far as its reaction mechanism is concerned, the C–C bond activation of acetonitrile is a promising pathway towards C–CN bond construction through a coordinative cyanating process. This activation accomplished complexes through the formation of η^1- or η^2 cyanide intermediates, due to the higher affinity of metals such as Mo, Ni and Rh for carbon atoms. It provides three kinds of Metalation; C-metalation, N-metalation, and μ^2-N,C metalation of acetonitrile (Fig. 1).

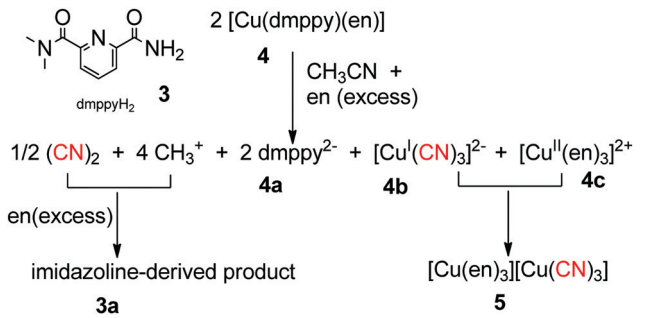
1.2. Metal complex synthesis *via* the C–CN activation of acetonitrile

As we mentioned, acetonitrile is used as a versatile source for the synthesis of organometallic complexes through C–CN bond cleavage could be an immense development in organometallic chemistry. In 1999, Churchill first synthesized Mo–Si complexes, where the dimethylsilane ansa-bridge promotes intermolecular C–H and C–C bond activation with the permethylmolybdenocene $[Me_2Si(C_5Me_4)_2]MoH_2$ complex by reaction with a mixture of benzene and acetonitrile.[46] Moreover, the reaction proceeds by photolysis of the $[Me_2Si(C_5Me_4)_2]MoH_2$ substrate with C_2H_4 molecules to give rise to a vinyl hydride $[Me_2Si(C_5Me_4)_2]$-$Mo(CHCH_2)H$ complex. Finally, the $[Me_2Si(C_5Me_4)_2]Mo(CN)(Me)$ complex is formed by ultraviolet radical cleavage of the Me–CN bond (Scheme 3).

In 2001, Marlin and co-workers reported a simple $[Cu(en)_3]$-$[Cu(CN)_3]$ complex by heterolytic cleavage of CH_3CN into the CN anion and CH_3 cation.[47] The reaction was relatively new for Cu^{II} species, although the reactivity ensures that CH_3CN cleavage is a well-known route for synthesis of Cu complexes. The reactivity of the [Cu(dmppy)(en)] complex toward CH_3CN was higher due to the basic nature of the $[dmppy]^{2-}$ ligand. The application of this methodology demonstrated the regeneration of $dmppyH_2$, methylated imidazoline and the [Cu(dmppy)(en)] intermediates in the synthesis of the $[Cu(en)_3][Cu(CN)_3]$ complex (Scheme 4). The geometry of [Cu(dmppy)(en)] confirms that the $dmppy_2$ ligand coordinates to the Cu(II) ion in the basal plane geometry system with a distorted square pyramidal form and the en ligand lodged the remaining two sites of the Cu(II) species. The reaction of [Cu(dmppy)(en)] with acetonitrile and the en ligand usually slows due to its low solubility under the given reaction parameters.



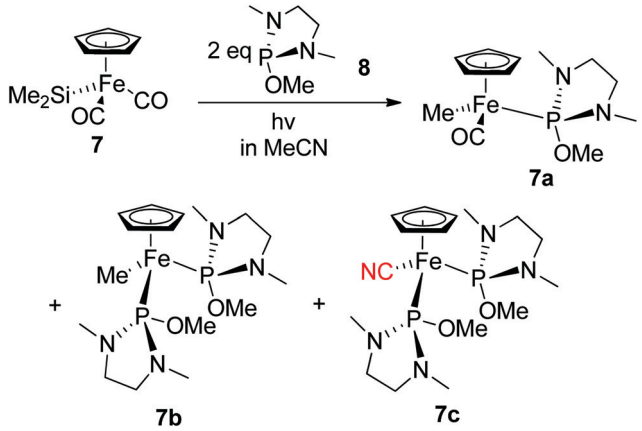
Scheme 3 Molybdenocene complex formation with MeCN.



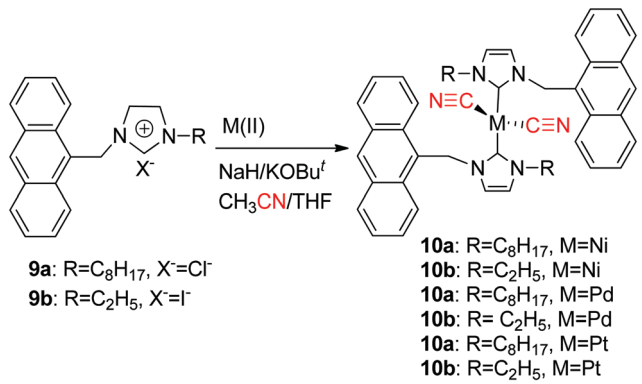
Scheme 4 $[Cu(en)_3][Cu(CN)_3]$ complex formation using the CN of acetonitrile.

In 2004, Nakazawa and co-workers offered a silyl iron-cyanide complex using a $Cp(CO)_2Fe(SiMe_2)$ substrate and $P(NMeCH_2)_2(OMe)$ as the ligand, and acetonitrile to afford $Cp(CO)L_2FeMe$, CpL_2FeMe, and CpL_2Fe–(CN) through C–C bond cleavage of acetonitrile (Scheme 5).[48] Moreover, a mechanistic study shows that oxidative addition is not a feasible step due to the high energy barrier in the activation process (activation energy of 14.8 kcal mol^{-1}). $Cp(CO)Fe(SiMe_2)$ coordination with acetonitrile is a more favorable step and rearrangement of the CN functional group inside the complex leads to the substitution of CN with an Me_2Si group in the Fe complex due to the very lower energy barrier (4 kcal mol^{-1}). Furthermore, they proposed and proved, in a ZPE and isotopic labelling study, that the methyl and cyanide functional groups coordinate with the metal complex which comes from the acetonitrile.

In 2004, Liu reported a new advancement in the C–C cleavage of acetonitrile by NaH and $KOBu^t$ in the presence of metal(II) catalysts.[49] The geometry of the metal(II) center seems to be square planar with a *trans* configuration of the ligand and



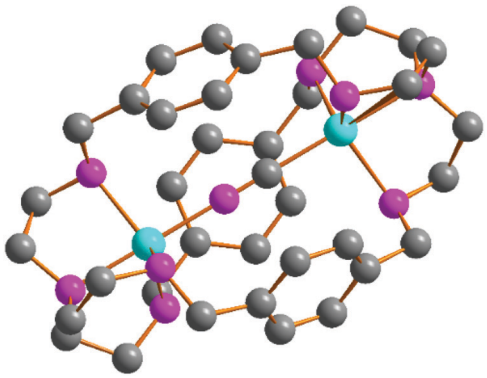
Scheme 5 $CpL_2Fe-(CN)$ complex formation using MeCN.



Scheme 6 $[(Carbene)_2M^{II}(CN)_2]$ complex formation with MeCN.

CN unit in various types of metal complexes (Scheme 6). According to the proposed pathway, the CN moiety and N-heterocyclic carbene generated *in situ* reacted with the (1-(9-anthracenylmethyl)-3-octylimidazoliumhalide) substrate and afforded $[(carbene)_2M(II)(CN)_2]$ complexes. However, the activation of C–C bonds by transition metal (TM) complexes in a homogeneous medium remains a challenge in the field of organometallic chemistry.

Moreover, a new way of acetonitrile cleavage with a binuclear copper(II) cryptate was reported for the first time by Lu in

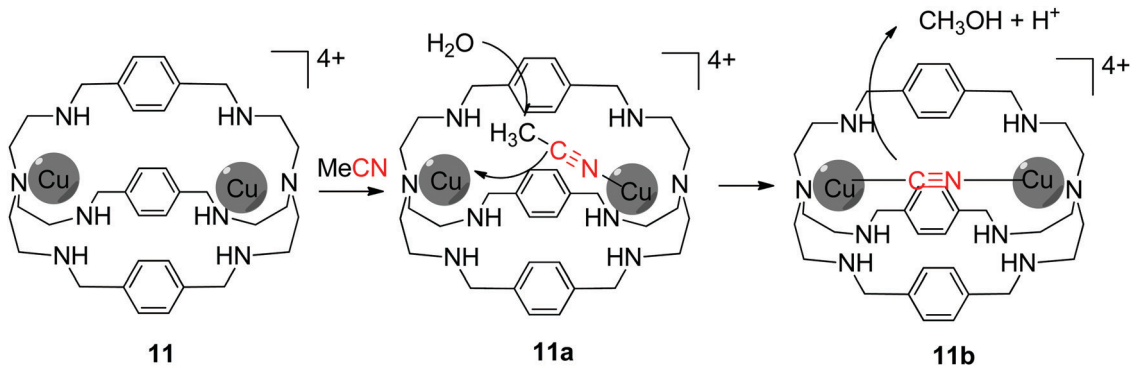


Scheme 8 The single crystal structure of the binuclear Cu(II) cyanide cryptate [LnCu(II)CN] complex.

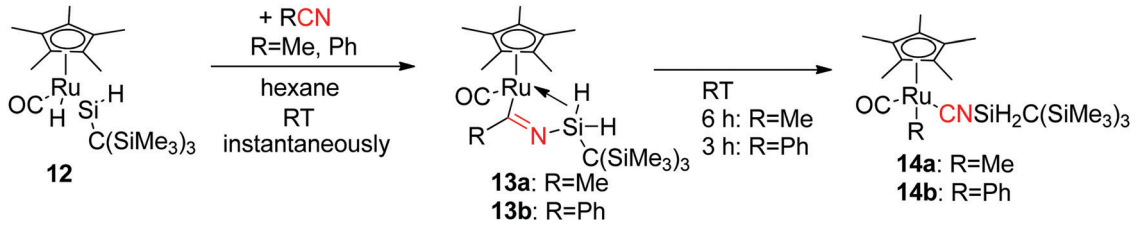
2004.[50] In general, binuclear copper(II) cryptate bridged with a CN moiety and the electron pair of the nitrogen of the CN group interacted with binuclear Copper(II), and the 2nd Cu bonded with the pi-orbital of the Sp-hybridized carbon of acetonitrile. The probability of C–C cleavage would increase due to electronic flow from the acetonitrile carbon to the Cu(II) complex intermediate and resulted in a stable bridged complex [LnCu(II)CN] by the release of methanol (Schemes 7 and 8). However, the rate of bond cleavage is very slow as compared with that of benzocyanide C–CN cleavage, when the benzocyanide molecule is treated with a ruthenium complex or a Cu(II) complex under same parameters.

In order to further elaborate the scope of cleavage of the C–CN bond of acetonitrile, silylisocyanide complexes [Cp*(CO)-(R)Ru{$CNSiH_2C(SiMe_3)_3$}] through the C–CN bond activation of acetonitrile using rhodium and iron silyl complexes was reported by Ochiaivia in 2007 (Scheme 9).[51]

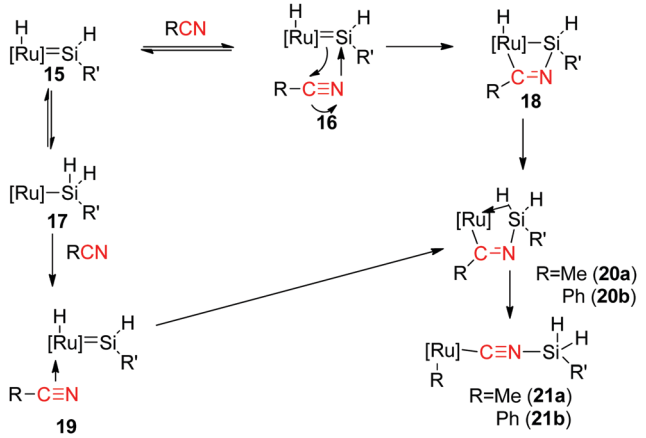
In this process, the reaction proceeded *via* 1,2-H migration and afforded the 16ē silyl complex **17**. Moreover, the RCN silyl ligand migration of nitrogen and η^2-coordination of the Si–H bond occurred to form intermediate **18** (Scheme 10). Similarly, another pathway started from the coordination of a RCN molecule and silylene silicon to create intermediate **19** (Scheme 10). Gratifyingly, [2+2] cycloaddition gave the four membered metal-based intermediate **18**, which followed partial reductive elimination and formed intermediate **20** (Scheme 10).



Scheme 7 Binuclear Cu(II) cyanide complex formation using MeCN.

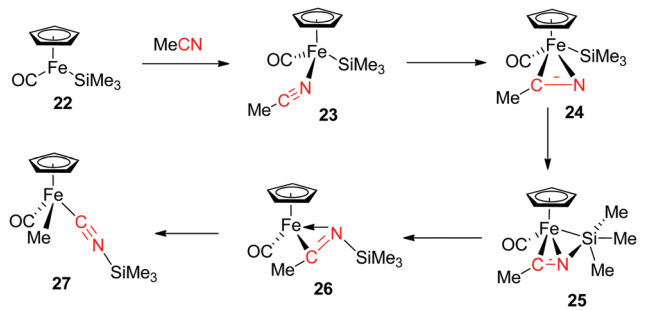


Scheme 9 Hydrido(hydrosilylene)Ru complexation with the CN of acetonitrile.



Scheme 10 Mechanism for hydrido(hydrosilylene)ruthenium complexation with the CN of acetonitrile.

Finally, decomplexation of the η^2-Si–H bond from intermediate **20** and intramolecular oxidative addition of the C–C bond leads to the required complex **21** (Scheme 10). Nakazawa and co-workers conducted a new catalytic cyanation *via* C–C activation of acetonitrile and arene moieties.[71] However, this newly developed protocol is favorable for a wide range of aryl nitriles and acetonitrile substrates for the construction of Si–CN bonds in presence of the $Cp(CO)_2FeMe$ complex with a higher TON. During this reaction, CO was released from the $Cp(CO)_2FeMe$ complex by reaction with Me_3SiH which led to the $Cp(CO)_2FeMe(H)(Me_3Si)$ complex (Scheme 11). Moreover, $Cp(CO)_2Fe(Me_3Si)$ was formed by the successive reductive elimination of methane from the $Cp(CO)_2FeMe(H)(Me_3Si)$ complex (Scheme 11). Finally, the insertion of acetonitrile formed the $Cp(CO)Fe(Me)(\eta^1\text{-}CNSiMe_3)$ complex *via* the intermediate adduct $Cp(CO)Fe(SiMe_3)(\eta^2\text{-}NCMe)$ (Scheme 11).



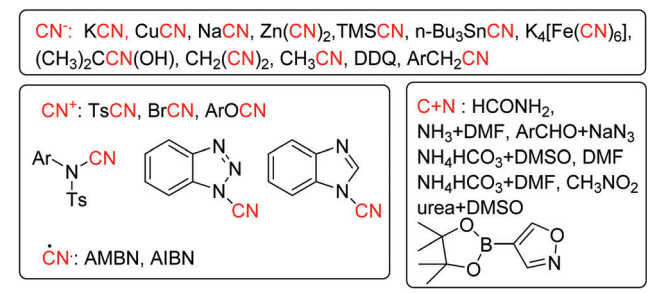
Scheme 11 Fe-catalyzed cyanation for Si–CN bond construction.

1.3. Metal/non-metal catalyzed cyanation *via* the C–CN bond activation of acetonitrile

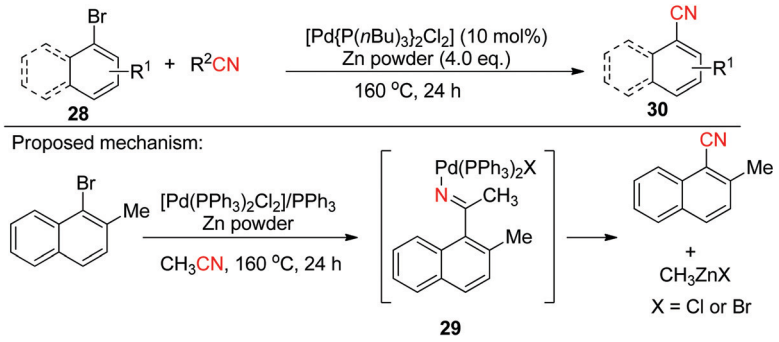
As we know, acetonitrile, a common solvent, can coordinate with the metal center in transition metal-catalyzed reactions. However, the cleavage of the acetonitrile C–CN bond is difficult. It could solve the problem of the fast release of cyanide anions, such as acetocyanohydrin and metal cyanide. In recent years, the use of acetonitrile as a CN source has attracted the attention of a large number of chemists (Scheme 12).[52–69] In 1998, Cheng and co-workers first reported the palladium-catalyzed cyanation of aryl halides with alkyl nitriles as the CN sources and solvent as well.[70] Moreover, various alkyl nitriles, such as propionitrile, *n*-butyronitrile and benzylnitrile, could be used as the cyanide source for Pd-catalyzed cyanation to form the benzonitrile derivatives. However, the yield of the reaction depends upon the amount of phosphine ligand and zinc powder in the reaction system.

In mechanistic studies, the authors concluded that the cyanation might occur through palladium–imine intermediate **29**, followed by cleavage of the C–C bond to form a nitrile product. In addition, they observed alkylzinchalide species (RZnX) formed as a side product in the system. This observation demonstrated that the acetonitrile could be used as a new cyano source. However, there are two limitations: the use of an excess of zinc powder and the requirement of *ortho* substituents in the substrates (Scheme 13).

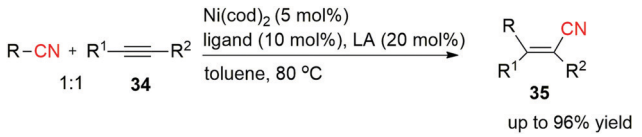
The mechanism involves firstly oxidative insertion of the ArX into Pd complex **32**, followed by RCN into the Pd intermediate **33** (Scheme S3, ESI†). Further, reductive elimination affords the aryl nitrile and regenerates the Pd(0) active species. Here, the authors suggested that the Zn performed a dual role; firstly, Zn complex reacts as ZnX_3 and polarizes the Pd-sphere bond and resulting $[Ar\text{–}PdL_2\text{–}CN]$ coordination. Secondly, it participates in the reductive elimination step to capture the C–CN bond and also give the $RZnX_2$ species (Scheme S3, ESI†).



Scheme 12 Various CN sources used for cyanation.



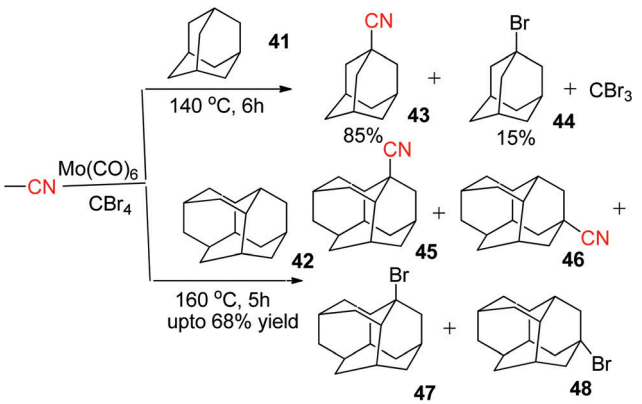
Scheme 13 The Pd-catalyzed cyanation of aryl halides with acetonitrile.



Scheme 14 The Ni-catalyzed cyanation of alkyne with acetonitrile.

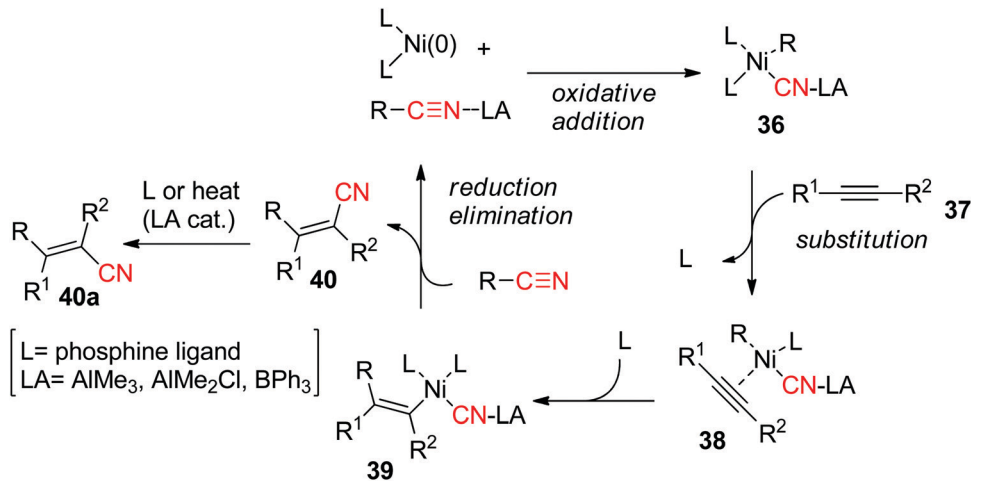
In 2007, Nakao demonstrated the role of the Ni/LA catalyst system for C–C bond activation in the carbocyanation of alkynes.[72] Moreover, this system was extensively investigated, not only for arenes, but also for alkenyl and alkyl substrates (Scheme 14).

A mechanistic study showed that the Lewis acid plays a crucial role in the C–CN bond activation of acetonitrile. Moreover, an electron rich nickel-center would be generated by the coordination of an electron rich ligand which was responsible for the C–CN bond cleavage. In the next steps, alkyne coordination, insertion and reductive elimination gave the *cis* product influenced by a steric effect due to the bulkier R alkyl or aryl group while *trans* isomerization depended on the ligand, temperature and other variable reaction parameters (Scheme 15). In 2008, Khusnutdinov and co-worker reported cyanation by employing a 20 mol% $Mo(CO)_6$ catalyst at a high temperature using diamantane and adamantane substrates with acetonitrile (Scheme 16).[73] In 2012, Li and co-workers reported a copper-catalyzed oxidative cyanation

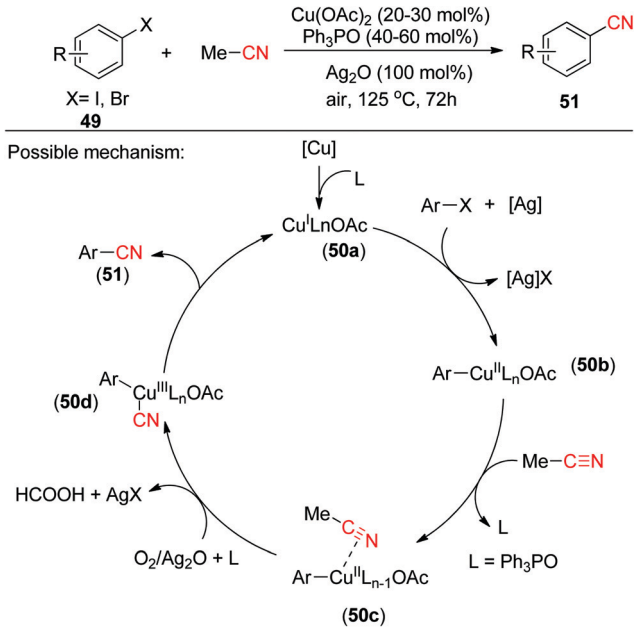


Scheme 16 The Mo-catalyzed cyanation of diamantane and adamantane with MeCN.

of aryl halides using acetonitrile as the cyano source.[74] In this case, silver oxide combined with oxygen to act as a combined oxidant. In this system, a series of aryl iodides converted into aryl nitriles in moderate to good yields. By increasing the loading of the Cu-catalyst and ligand, the rate of conversion could increase for the cyanation of aryl iodide/bromide substrates. However, the mechanism of the C–CN bond cleavage of acetonitrile is still unclear (Scheme 17).



Scheme 15 Mechanism for the Ni-catalyzed cyanation of alkynes with acetonitrile.

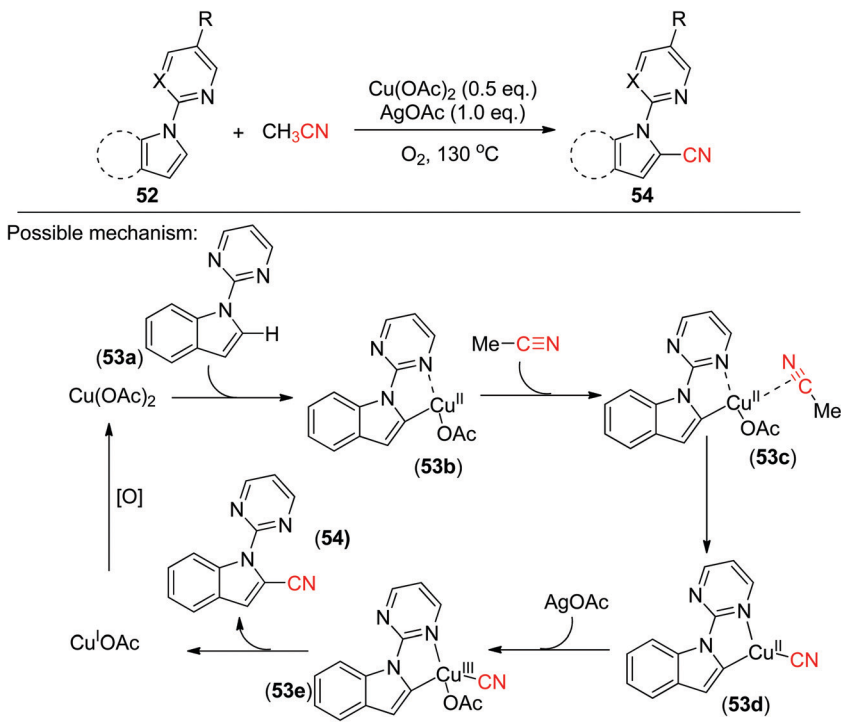


Scheme 17 The Cu-catalyzed cyanation of aryl halides with MeCN.

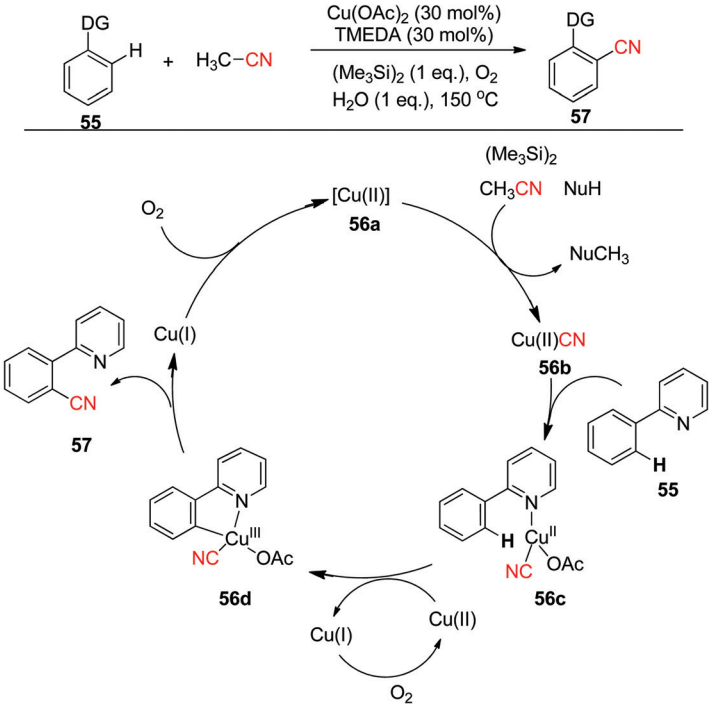
In 2013, Zhu and co-workers reported the Cu-catalyzed cyanation of indoles at the 2-position by using acetonitrile as a CN source and silver salt as an oxidant (Schemes 18 and 20).[75] This Cu-mediated C_2-cyanation of indoles with acetonitrile underwent C–H and C–C bond activation. The installation of the pyrimidyl group as a directing group (DG) on the indole nitrogen atom was key for this C_2 selectivity, which provided an alternative route to form indole-2-carbonitriles (Scheme 18). In 2013, our research group made progress in this field and reported the copper-catalyzed cyanation of arenes and indoles *via* C–H bond activation with acetonitrile (Scheme 19).[76] In this study, the use of one equivalent hexamethyldisilane [$(Me_3Si)_2$] played a mediatory role for the cleavage of the acetonitrile C–CN bond. Moreover, when *N*-pyrimidine attached to the aryl ring it could form 2-cyanophenylpyridine in a high yield under the standard conditions (Scheme 19).

In addition, various alkyl nitriles, such as primary, secondary and tertiary nitriles, could be used as cyano sources. In mechanistic studies of the C–CN bond cleavage, we proposed the SN_2-type C–CN bond cleavage pathway where the η^2-coordinated imine with Cu species was attacked by a nucleophile in order to achieve C–CN cleavage and produce $Cu^{II}CN$ species (**56b**) (Scheme 19). Thereafter, $Cu^{II}CN$ coordinated with 2-phenylpyridine. This intermediate underwent C–H bond activation and another molecule of Cu^{II} acted as an oxidant to generate an aryl Cu^{III} intermediate (**56d**) (Scheme 19).

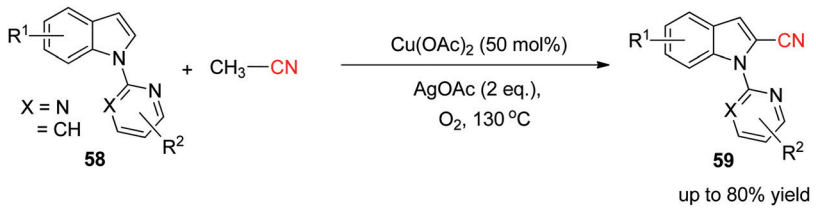
Nitrile product (**57**) could be formed in a reductive elimination step of the aryl Cu^{III} intermediate (**56d**) and regeneration of the Cu^{I} species, which could be re-oxidized with oxygen to produce Cu^{II} for the next cycle (Scheme 19). In 2015, Li and co-workers reported the Pd-catalyzed cyanation of aryl tetrafluoroborate diazonium with acetonitrile as a CN source and solvent as well (Scheme 21).[77] This reaction converted an aryl tetrafluoroborate diazonium salt into a benzonitrile by using 10 mol% of a palladium chloride catalyst and 5 mol% to 1 equivalent of silver oxide at 55 °C under an open system. Moreover, in this Sandmeyer reaction, electron-donating substituents in the aryl substrates easily converted into the



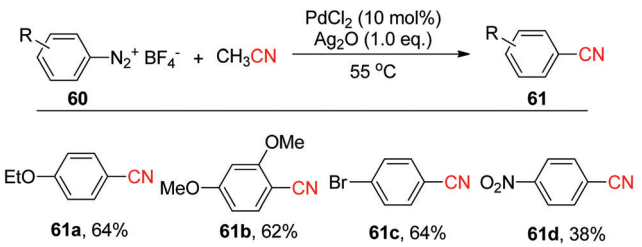
Scheme 18 The Cu-catalyzed cyanation of indoles with MeCN.



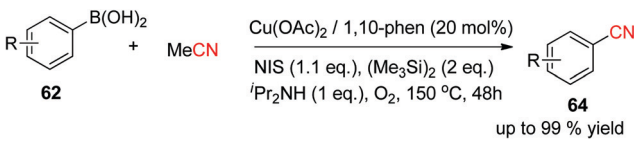
Scheme 19 The Cu-catalyzed cyanation of arenes with MeCN.



Scheme 20 The Cu-catalyzed cyanation of indoles with MeCN.



Scheme 21 Pd-catalyzed Sandmeyer cyanation with acetonitrile.

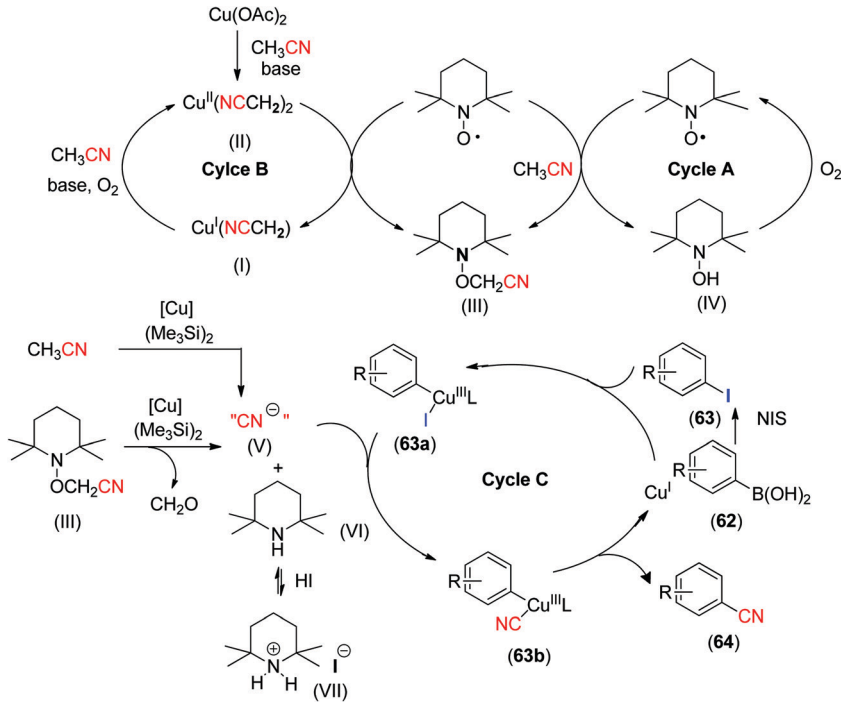


Scheme 22 The Cu-catalyzed cyanation of boronic acid with acetonitrile.

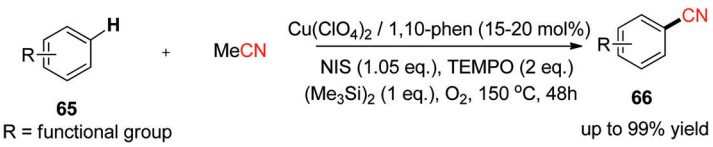
corresponding nitriles, while substrates with electron-withdrawing groups were not that compatible in this system. The proposed possible mechanism of C–CN bond cleavage is still unclear. However, the authors mentioned that Ag_2O was used as an oxidant and a C–CN bond activator as well.

In 2015, our group reported Cu-catalyzed cyanation of aryl boronic acids or arylboronic esters with acetonitrile (Scheme 22).[78] By the screening of oxidants, a new Cu/TEMPO/NIS system was discovered, which efficiently promoted the activation of the C–CN bond of acetonitrile and played a key role in C–C bond construction. Moreover, both electron-poor and electron-rich boronic acids were tolerated well. According to our findings, sequential iodination/cyanation progressed in one pot. In addition, TEMPO exhibited a dual role in this reaction: (1) the generation of the active cyanating agent $TEMPOCH_2CN$; (2) as an oxidant in this catalytic cyanation. Importantly, iodination and cyanation could be achieved by the same Cu catalyst in one pot (Scheme 23). Moreover, in the same year, we reported copper-catalyzed cyanation of simple aromatic compounds by using acetonitrile as the cyano source (Scheme 24).[79] The cyanation of simple arenes without a directing group (DG) has been established *via* a sequential iodination/cyanation process.

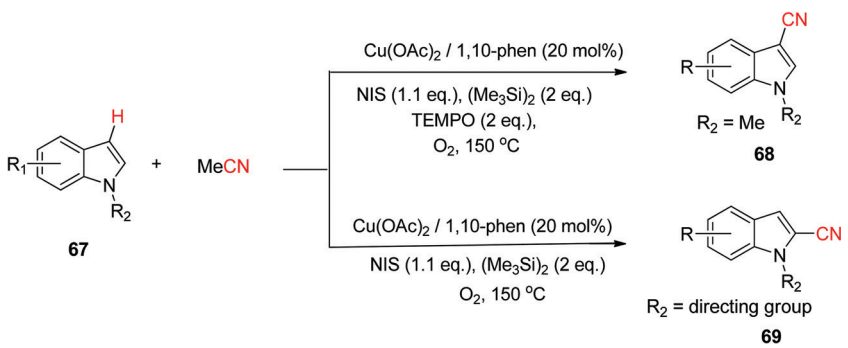
Similarly, our group reported a new way for the selective cyanation of indoles with a Cu-catalyst by using acetonitrile as the solvent and CN source (Scheme 25).[76,80] Interestingly, the selective C–H bond activation of indoles at the 2-position or



Scheme 23 The Cu-catalyzed cyanation of boronic acid with MeCN.



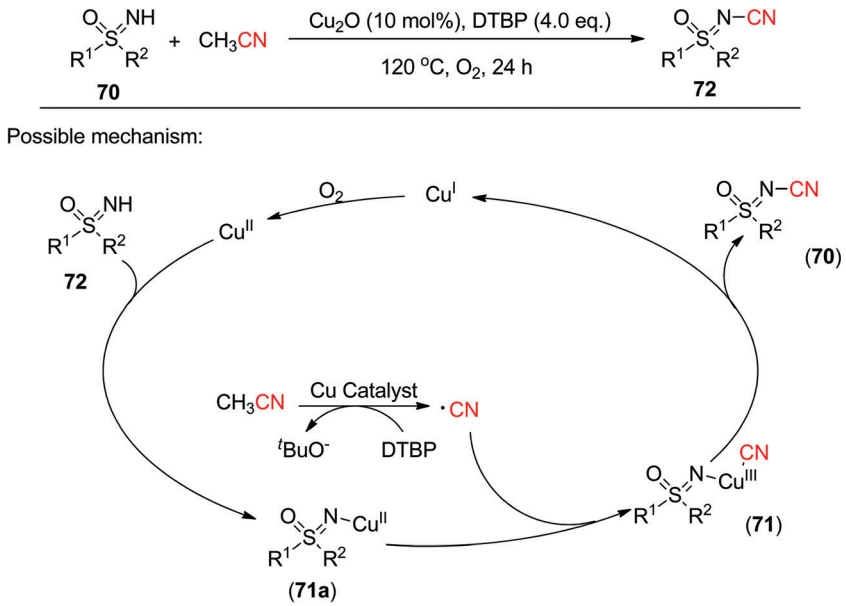
Scheme 24 The Cu-catalyzed cyanation of simple arenes with MeCN.



Scheme 25 The Cu-catalyzed cyanation of 2- or 3-cyanoindoles with MeCN.

3-position was achieved under controllable conditions. The Cu/$(Me_3Si)_2$/TEMPO system showed an efficient activity for the cyanation of the indole C–H bond at the 3-position and provided the corresponding 3-cyanoindoles in good yields. On the other hand, indoles bearing a directing group at the N atom gave the corresponding 2-cyanoindoles in good yields. A series of functional groups, such as Cl, F, Me, NO_2, CHO and OMe were tolerated well.

In 2015, Shao group reported the copper catalyzed *N*-cyanation of sulfonamide with acetonitrile as a CN source and solvent (Scheme 26).[81] In this process, Cu_2O acted as a catalyst and DTBP as an oxidant to furnish *N*-cyanated sulfonamide compound (**70**). In addition, diphenyl sulfonamides, alkyl phenyl sulfonamides, aryl imines and hydrazines could give the corresponding *N*-cyano products under standard conditions. In the mechanistic studies, when TEMPO and BHT (2,6-di-*tert*-butyl-4-methylphenol) were added into reaction, the corresponding cyanated products could not be produced. This experiment indicated that the reaction proceeded through a radical pathway. In their proposed catalytic cycle, Cu^I was oxidized into Cu^{II} by O_2, and then Cu^{II} reacted with

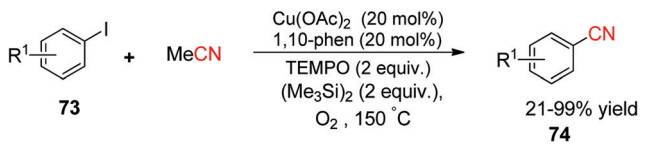


Scheme 26 Cu-catalyzed sulfonamide *N*-cyanation with MeCN.

sulfonamide to form N–Cu^{II} species (**71a**) (Scheme 26). At the same time, the cleavage of acetonitrile produced a cyano radical in the presence of a catalytic amount of copper oxide and DTBP (di-*tert*-butyl peroxide). The generated cyano radical reacted with the N–Cu^{II} species (**71a**) to form the N–Cu^{III}–CN species (**71**) (Scheme 26). The target nitrile product formed in the reductive elimination step and regeneration of the Cu^{I} species. This reaction provided a new way to the C–CN bond cleavage of acetonitrile.

In 2017, our group developed a copper-catalyzed cyanation of aryl iodides (Ar–I) by using acetonitrile as a slow dosage "CN" source with a Cu(cat.)/Si/TEMPO system.[82] This system enabled the cyanation of aryl iodides to provide aromatic nitriles bearing a wide range of substrates (Scheme 27). Similarly, our group also expanded the acylcyanation of an alkyne catalyzed Cu complex with acetonitrile as a slow dosage cyanide source (Scheme 28).[83] Our group elaborated the 5-*exo* and 6-*endo* heterocycloalkenyl cyanation methods with a high selectivity and good yields by using an iodination/cyanation strategy. In addition, a series of (*E*)-3-(1-cyano-1-phenylmethylene)benzoquinone and 3-phenyl-4-cyanoisocoumarins derivatives were synthesized with a Cu-catalyst (Scheme 28). A proposed reaction mechanism for the formation of 5-*exo* or 6-*endo* cyclized nitriles is shown in Scheme 28.

In 2017, Morandi *et al.* reported the cyanation of aryl chlorides, internal alkenes and terminal alkenes with alkyl nitriles, such as butyronitrile, as the CN source through a cross coupling *retro*-hydrocyanation process. Notably, this cyanation reaction was



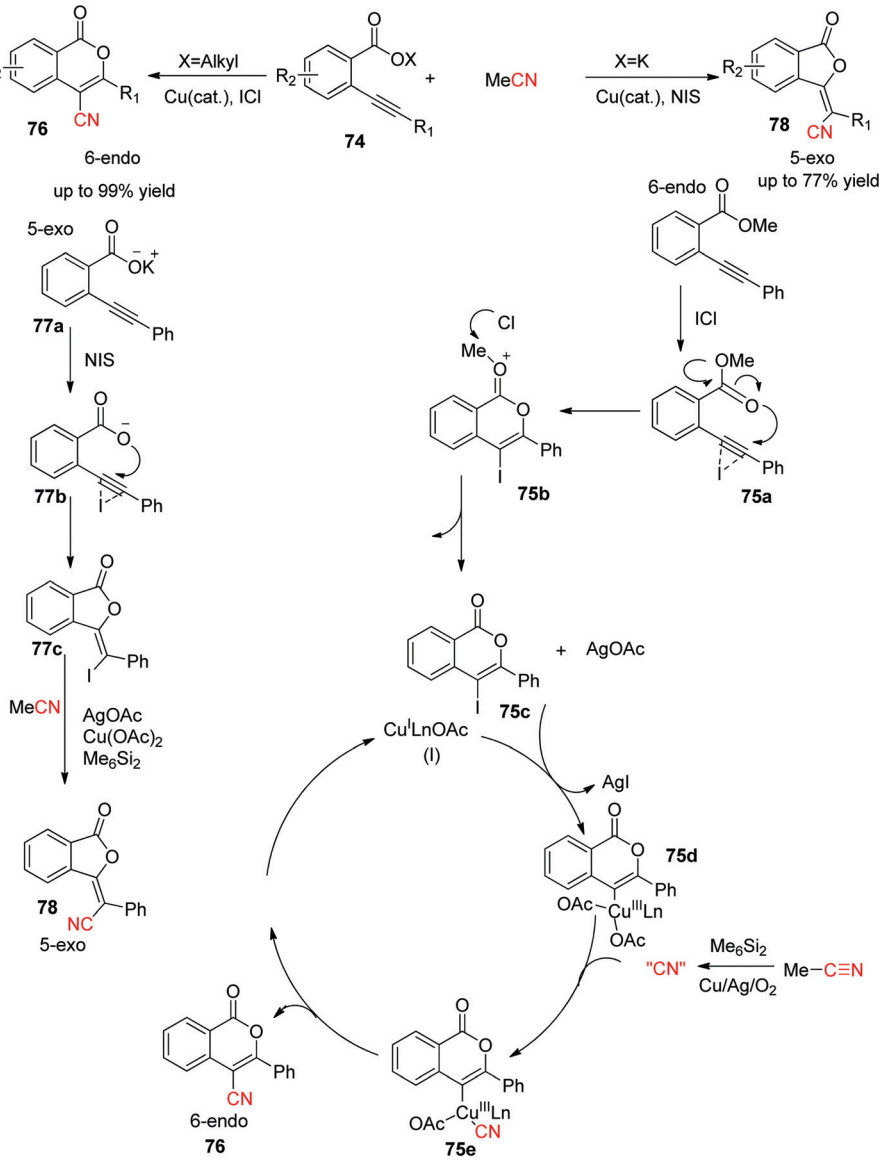
Scheme 27 The Cu-catalyzed cyanation of aryliodides with MeCN.

suitable only for aryl chlorides and formed the alkene as a by-product (Scheme 29).[84] Moreover, our group also designed a copper-catalyzed C–H bond functionalization and cyclization by using a removable bidentate auxiliary, 2-(methylthio)anilide, as the directing group (DG), where inexpensive and green acetonitrile was used as the cyano source and solvent as well (Scheme 30).[85] In 2019, Kuzushi and co-workers reported the Ni-catalyzed cyanation of aryl halides (halide = Br, Cl) by using silanes as the reductant and activator of acetonitrile C–CN bond cleavage (Scheme 31).[86] In this reaction, Ni complex ($[Ni(CH_3CN)_6](BF_4)_2$/1,10-phenanthroline) and 2.5 equivalent of organosilicon (Si-Me_4-DHP) exhibited a good reactivity, while the substrate scope was limited to aryl bromides. The authors also proposed the mechanism for this system shown in Scheme 31.

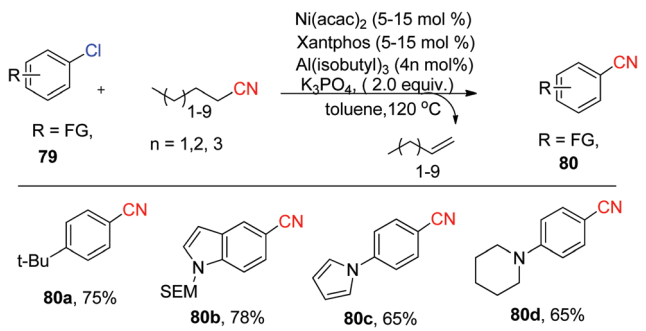
1.4. Metal/non-metal catalyzed cyanomethylation *via* the Csp^3–H bond activation of acetonitrile

The acetonitrile moiety is found as a structural motif in natural product and drugs.[87] Cyanomethylation is also a synthetically useful process due to the easy conversion of nitrile into other functional groups.[88] During the last few decades, a many advancements in the catalytic generation of carbon nucleophiles of acetonitriles have been reported for a wide variety of reactions. In 1985, Masui reported the cyanomethylation of 2,2,6,6 tetramethylpipyridine and its 4-oxo derivatives with acetonitrile through NH^+ and cyanomethyl radical by cross coupling reactions leading to 2,2,6,6 tetramethylpipyridine *N*-acetonitrile products (Scheme 32).[89]

In 1990, Sonawane and co-workers reported the cyanomethylation of cycloalkane through radical C–H acetonitrile cleavage by photo-induced decomposition of H_2O_2 (Scheme 33).[90] In 1996, Yamashita reported an interesting proto-induced cyanomethylation by an inert solvent (MeCN) for various arenes by a keto-photo catalyzed system.[91] The addition of photo-generated radical cations from *t*-$BuNH_2$ to the MeCN through the release



Scheme 28 The Cu-catalyzed acylcyanation of alkynes with MeCN.

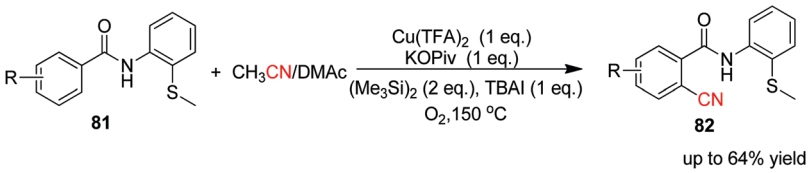


Scheme 29 Ni-catalyzed cyanation with butyronitrile.

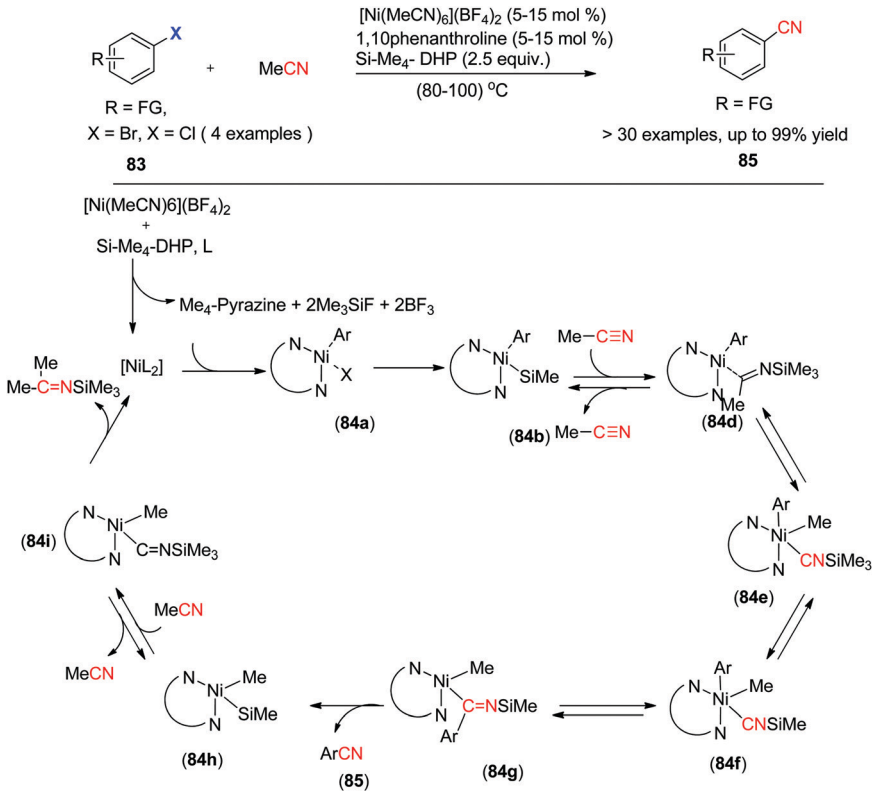
of radical protons (Scheme 34). However, this Ar_2CO-photosensitization in the presence *t*-$BuNH_2$ led to a medium yield of product (Scheme 34). During same decade, Michida and co-workers reported the electrochemical reduction of phenazine by O_2 and cyanomethylation by acetonitrile *via* a radical pathway.[92] However, radicals may not be produced by hydrogen peroxide due the higher redox potential of acetonitrile, the first hydroxide radical of hydrogen peroxide produced by UV radiation, further resulting in the generation of acetonitrile radical (Scheme 35).

In 1999, Kisanga reported a base-catalyzed system for the synthesis of β-hydroxy nitriles by using a combination of Lewis acids (LA), proazaphosphatrane and magnesium sulfate for the activation of the carbonyl carbon at room temperature, which led to good to excellent yields (79–99%) (Scheme 36).[93]

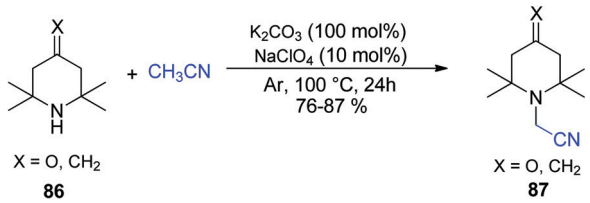
In 2013, Yang and co-workers reported the Pd-catalyzed C–H activation of an acetonitrile solvent for the cyanomethylation of ketone to 3,3-cyanomethyl-hydroxy-2-oxindole derivatives with relatively higher catalyst loadings (10 mol%) (Scheme 37).[94] In 2013, Yoshida reported the use of a Pd/TiO_2 hybrid photo-catalyst to promote the cyanomethyl radical in the cyanomethylation of arenes.[95] The cyanomethyl radical was used as the driving species



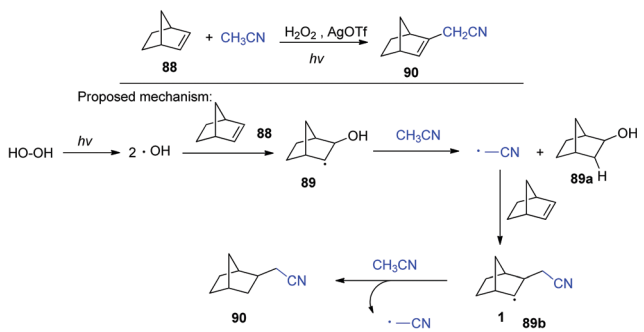
Scheme 30 The Cu-catalyzed cyanation of 2-(methylthio)phthalimide with acetonitrile.



Scheme 31 The Ni-catalyzed cyanation of arylhalides with MeCN.



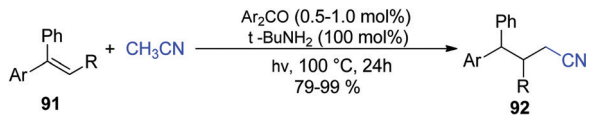
Scheme 32 The cyanomethylation of tetramethylpipyridine with acetonitrile.



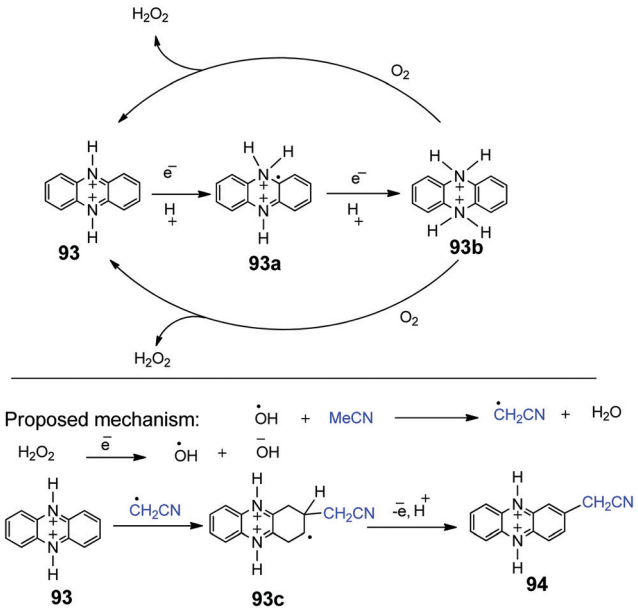
Scheme 33 The cyanomethylation of cycloalkene with acetonitrile.

for the cross coupling of arenes and acetonitrile under mild reaction parameters (Scheme 38).

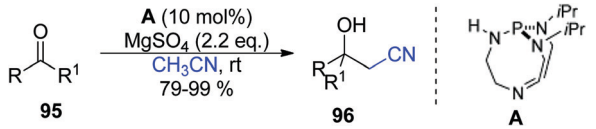
In 2013, Chakraborty reported the cyanomethylation of an aldehyde by acetonitrile in the absence of a base with high turnover numbers (Scheme 39).[96] In this process, the aldehyde was inserted into a carbon bound cyanomethyl radical in a reversible manner. Subsequently, the first C–H activation of acetonitrile formed an intermediate with nickel alkoxide. During this process, nickel alkoxide species overcame the dp–pp repulsion by a thermodynamic driving force. For the Cu oxidative system, our group firstly reported Cu-catalyzed aerobic oxidative coupling (AOC) of aryl alcohols with MeCN to give β-ketonitriles.[97] In this case, the C–C bond construction involved the loss of two radical protons from the carbon of acetonitrile and ketone using a $CuCl_2$ catalyst. The reaction went through mild and ligand free conditions with good to excellent yields (45–93%) (Scheme 40).



Scheme 34 The cyanomethylation of diarylethenes with acetonitrile.

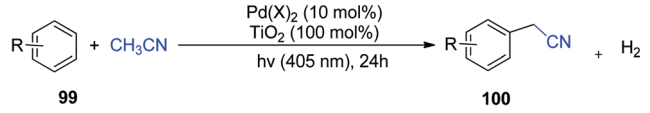


Scheme 35 The cyanomethylation of simple phenazine with acetonitrile.

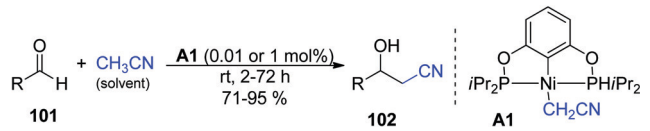


Scheme 36 The cyanomethylation of ketone with acetonitrile.

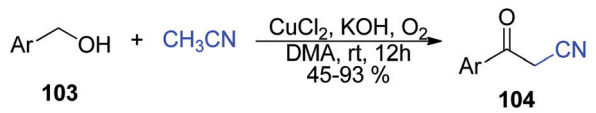
Li and co-workers generated the cyanomethyl radical with DTBP. The methodology applied to an alkene bond and addition/cyclization steps formed oxidole products with mild to excellent yields (52–92%) (Scheme 41).[98] In 2015, an improved version of the Cu-catalyzed cyanoalkylation of allylic alcohols with acetonitrile through 1,2-aryl migration was reported by Bunescu (Scheme 42).[99] The protocol provided an efficient method for the functionalization of a quaternary center containing ketones with alkyl nitrile. Regarding the reaction mechanism, the intermolecular addition of the cyanomethyl radical to alkenes along with the generation of a carbonyl (R_3CO) functionality *via* migration of a vicinal aryl group, it was suggested that 1,2-aryl migration proceeded through a neophyl rearrangement (Scheme 42).



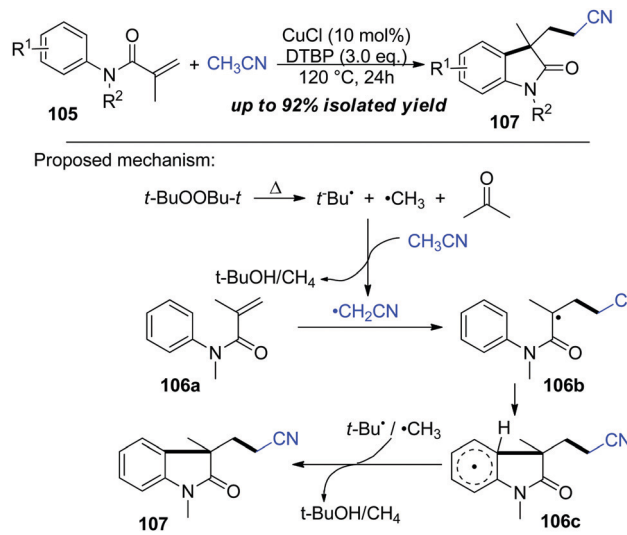
Scheme 38 The Pd/TiO_2 photo-catalyzed cyanomethylation of arenes with acetonitrile.



Scheme 39 The robust Ni-catalyzed cyanomethylation of aldehydes with acetonitrile.

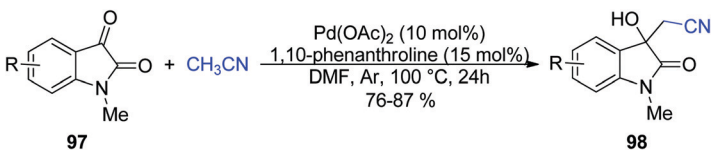


Scheme 40 The Cu-catalyzed cyanomethylation of alcohols with acetonitrile.

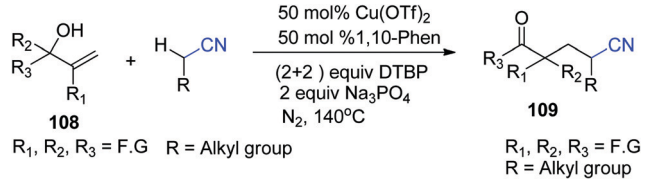


Scheme 41 The Cu-catalyzed cyanomethylation of oxidoles with acetonitrile.

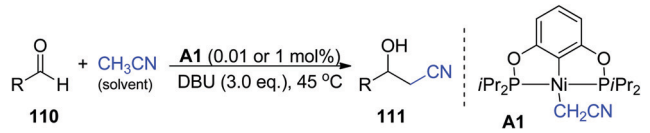
In 2015, Miller *et al.* used acetonitrile for the cyanomethylation of benzaldehyde by Ni-catalysts with aminophosphinite pincer ligands containing diethylamine.[100] Moreover, Ni directly inserted into the C–O bond of benzaldehyde. The catalytic activities of cationic [(NCOP)Ni($NCCH_3$)] and neutral (NCOP)Ni(OBu^t) are unambiguously different in this process. The neutral *t*-butoxide precatalyst is active in the absence of base and leads to



Scheme 37 The Pd-catalyzed cyanation of 3-hydroxy-2-oxindoles with acetonitrile.

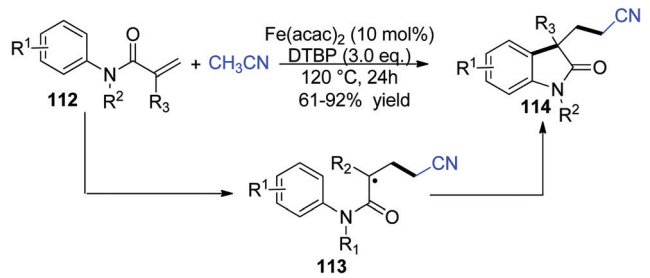


Scheme 42 The Cu-catalyzed cyanoalkylation of allylic alcohols with acetonitrile.



Scheme 43 The Ni-catalyzed cyanomethylation of aldehydes with acetonitrile.

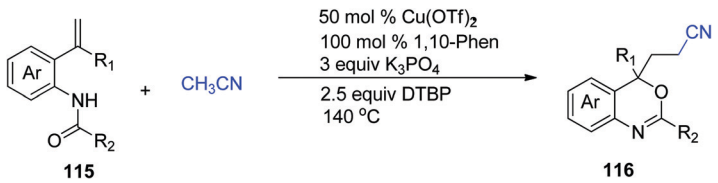
cyanomethylation in good yields *via* a nickel cyanoalkoxide key intermediate complex A1 (Scheme 43). In 2015, Pan reported cyanomethylation of *N*-phenylacrylamides through a free radical mechanism with acetonitrile in the presence of an Fe–metal catalyst.[101] The methodology followed a radical pathway *via* C–H activation of MeCN with a wide range of substrates and excellent productivity (61–84%) (Scheme 44). In same way, C(sp^3)–H



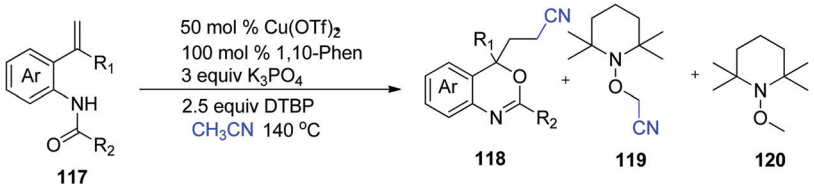
Scheme 44 The Fe-catalyzed cyanomethylation of aldehydes with acetonitrile.

functionalization of aryl ketones and ketonitriles by *t*-butyl peroxybenzoate mediated direct alkylation was reported in 2015 by Chu (Scheme 45).[102] The reaction involves a radical addition/1,2-aryl migration under metal free reaction conditions. In the same year, Cu-mediated oxycyanomethylation of olefinic amides was developed by same group for the formation of benzoxines involving a radical cyclization process.[103] The reaction under mild condition led to good to excellent yields of the cyanomethylated product. The radical mechanism was confirmed by using 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) in the given system (Scheme 46).

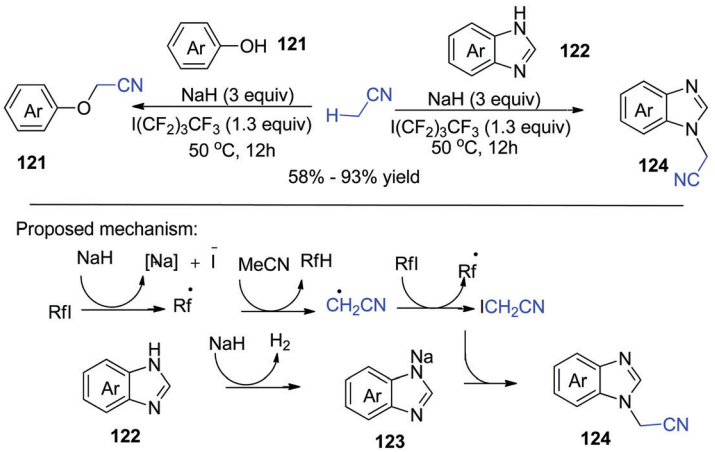
In 2015, Zhang and co-workers reported the cyanomethylation of azole and phenol derivatives by perfluorobutyl iodide in the presence of NaH as the reducing agent *via* the radical cleavage of the C–H bond (Scheme 47).[104] The reaction proceeds under mild conditions, giving rise to cyanomethylated products in moderate to high yields (58–93%). This reaction proceeds through the activation of a C–I bond in the presence of per-fluoroalkyl iodide and NaH to generate the perflouroalkyl radical ($R_f^{\bullet}$) (Scheme 47). The R_f radical underwent abstraction of a proton radical from MeCN to form the cyanomethyl radical ($^{\bullet}CH_2CN$) and R_fH radical (Scheme 47). Subsequently, the cyanomethyl radical ($^{\bullet}CH_2CN$) attacked perflouroalkyl iodide to generate the key intermediate iodoacetonitrile along with the per-fluoroalkyl radical (Scheme 47). Finally, the sodium salt of benzimidazole reacted with I–CH_2CN to afford the cyanomethylated product (Scheme 47). In 2016, Zhangqin reported Csp^3–H bond activation of acetonitrile through *in situ* generated radical by *p*-anisidine as the promoter *via* the diazonium salt of alkene using *t*-butylnitrite (Scheme 48).[105] This methodology afforded moderate to good yields of cyanomethylated products in the absence of a transition metal or photocatalyst. In the mechanistic point of view, a *p*-methoxyaryl diazo radical intermediate was generated by the homolysis *via* thermal process. The resulting cyanomethyl radical added to the C=C bond and afforded the intermediates **126a** and **126b** generated *via* cyclization (Scheme 48). Acetonitrile was also used for α-cyanomethyl-β-dicarbonyl synthesis in the presence of an Fe-catalyst by a cross-dehydrogenative coupling reaction in 2016.[106]



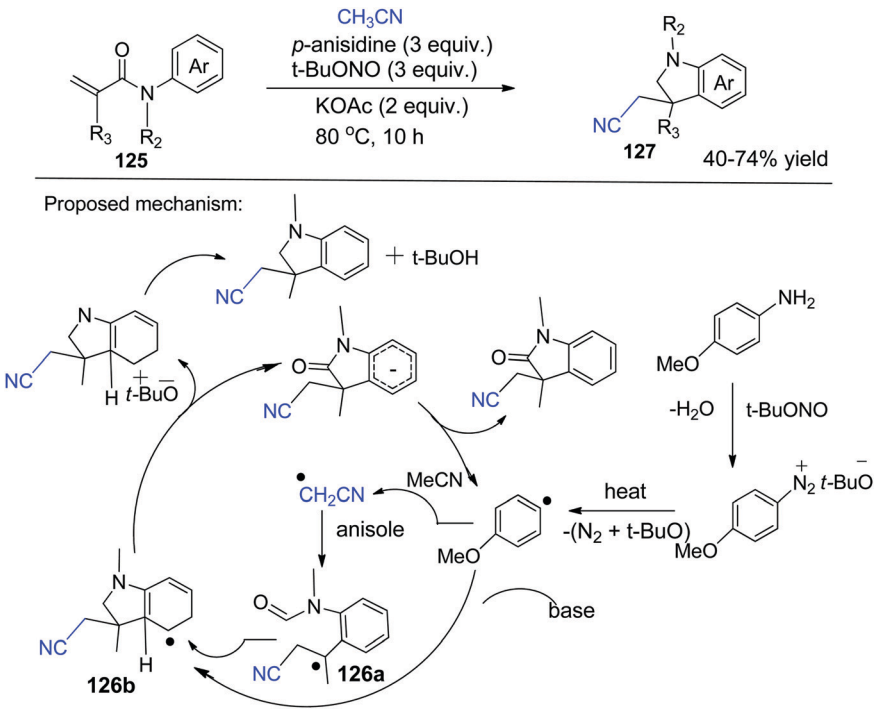
Scheme 45 The Cu-catalyzed cyanomethylation of oxidoles with acetonitrile.



Scheme 46 Radical-trapping experiments involving tetramethylpiperidine *N*-oxide.



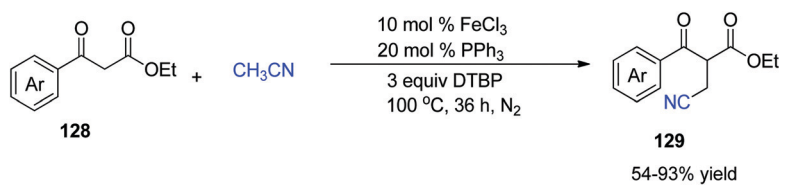
Scheme 47 Cyanomethylation with perflouroalkyl iodide and acetonitrile.



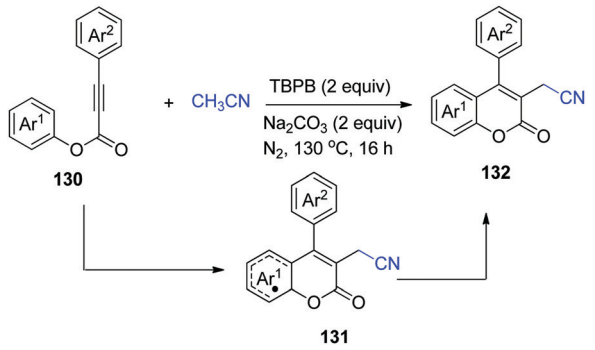
Scheme 48 Cyanomethylation of oxidoles with acetonitrile *via* a diazo radical promotor.

The reaction products were formed in moderate to excellent yields (54–93%) for a variety of 1,3-dicarbonyl substrates with 10 mol% $FeCl_3$ and 20 mol% PPh_3 (Scheme 49). The control experiment shows that the reaction underwent through four radical pathways.

In 2016, Yu and co-workers reported cyanomethylation with acetonitrile to synthesize Coumarins by *via* cyclization of aryl alkynoates in the presence of *t*-butyl peroxybenzoate with excellent yields (50–87%) (Scheme 50).[107] In this reaction, *t*-butyl peroxybenzoate decomposed into the benzoyloxy radical and



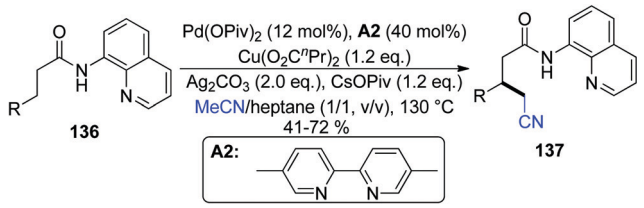
Scheme 49 α-Cyanomethyl-β-dicarbonyl formation with acetonitrile.



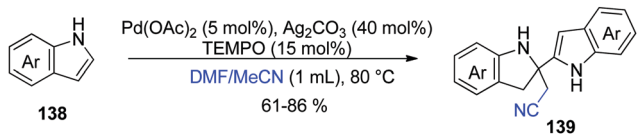
Scheme 50 Cu-catalyzed coumarin formation with acetonitrile.

t-butoxy radical at a high temperature. The cyanomethyl radical formed by the abstraction of a proton radical from CH_3CN and added to alkynoate to yield the alkenyl radical (Scheme 50).

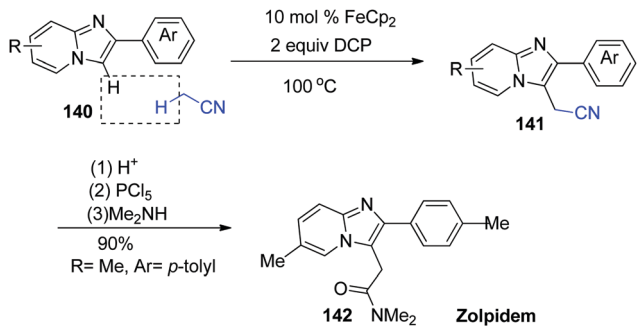
Moreover, intramolecular spirocyclization generated a spiro-radical and further ester migration *via* a carboxyl radical as an intermediate. Finally, the desired product was produced by oxidation/deprotonation of intermediate **131** in this methodology (Scheme 50). In 2016, we developed a cyanomethylation of tetrahydroisoquinolines with acetonitrile used as the nucleophile *via* the activation of the sp^3C–H bond.[108] An efficient oxidative system ($CuCl_2$/TEMPO/Cs_2CO_3) was used for the cross-dehydrogenative coupling with moderate to good yields (37–85%) under mild reaction conditions (Scheme 51). We proposed Cu(II)/TEMPO for the transformation of tetrahydroisoquinolines into a cation radical by a single electron transfer (SET) which was confirmed by a control experiment *via* the generation of TEMPOH (Scheme 51). For acetonitrile Csp^3–H bond activation, copper coordinated with acetonitrile and generated a Cu–$NCCH_2$ intermediate with the Cs_2CO_3 by the abstraction of a proton radical from acetonitrile in this Cu(II)/TEMPO oxidative reaction system (Scheme 51). In 2016, Liu reported a direct cyanomethylation through the Csp^3–H least activated bond of aliphatic amides in the presence of a palladium catalyst and mono-dentate directing group (DG) (Scheme 52).[109]



Scheme 52 The Cu-catalyzed cyanomethylation of aliphatic amides with acetonitrile.

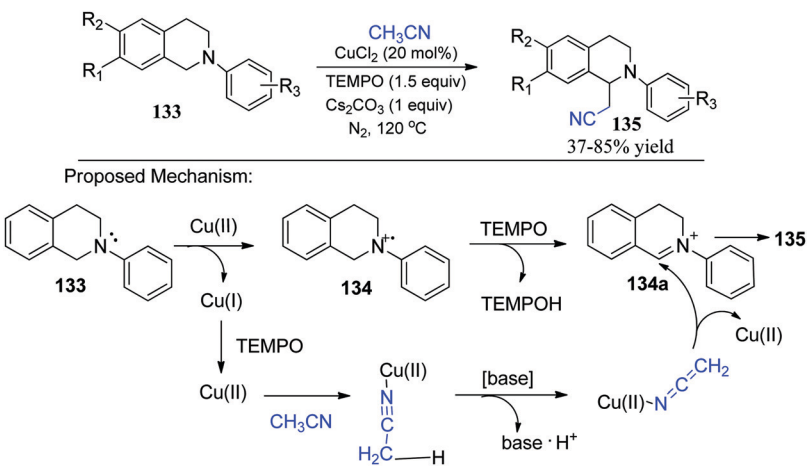


Scheme 53 The Pd/Ag catalyzed cyanomethylation of 2-arylimidazo[1,2-α]-pyridine with acetonitrile.

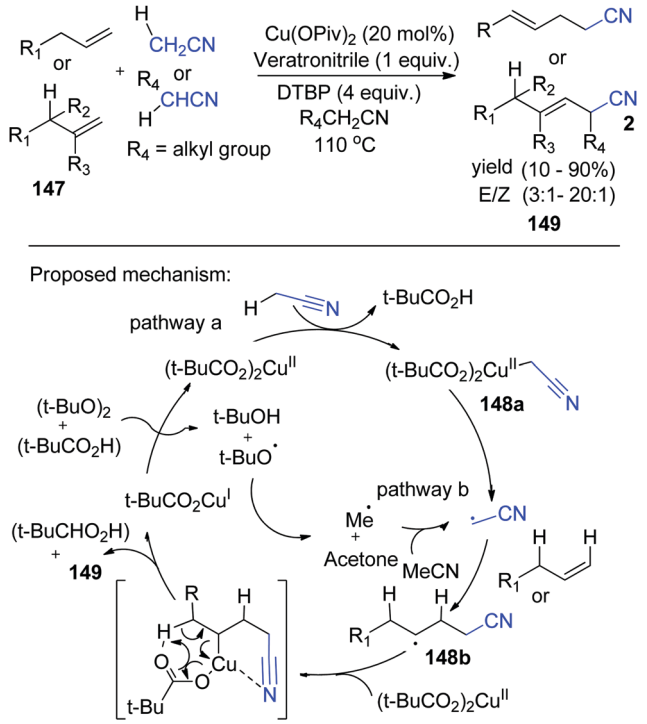


Scheme 54 The Fe-catalyzed cyanomethylation of arylimidazo-pyridine derivatives with acetonitrile.

Another combinative oxidative system for cyanomethylation and homo dimerization of indole derivatives catalyzed by TEMPO/$Pd(OAc)_2$ was demonstrated by Deng in 2017.[110] The protocol illustrated a broad scope of substrates with high yields of 2-(2-(1*H*-indol-3-yl)-3-oxoindolin-2-yl)acetonitrile products with excellent yields (61–86%) (Scheme 53).

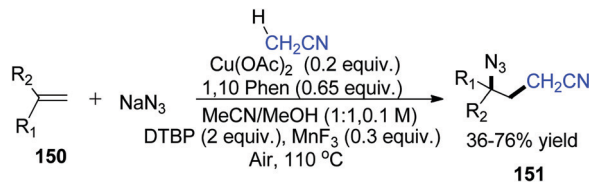


Scheme 51 The Cu-catalyzed cyanomethylation of tetrahydroisoquinolines with acetonitrile.

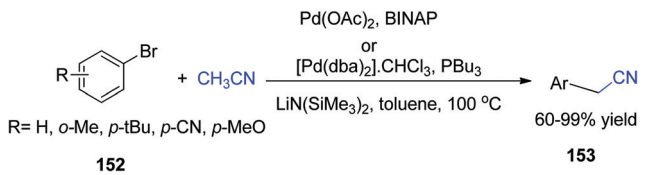


Scheme 55 Olefine transformation into γ,δ-unsaturated nitriles using a Cu catalyst.

In 2017, Su and co-workers reported another cross dehydrogenative sp^3–sp^2 coupling between 2-arylimidazo-pyridines and acetonitrile *via* a direct oxidative C–H bond activation followed by heteroarylacetonitrile synthesis in the presence of an Fe-catalyst.[111] The utility of the protocol associated biological and industrial synthetic features with a rapid conversion into the cyanomethylated product in moderate to good yields (38–70%) (Scheme 54). A platinum-loaded photocatalyst has been used for the activation of both the aliphatic and aromatic hydrocarbons with acetonitrile to afford the corresponding radical species before their cross coupling (Scheme S4, ESI†).[112] In contrast, the cyanomethylation of benzene was carried out in the presence of the Pd/TiO_2 or Pt/TiO_2 hybrid photocatalyst, where the palladium catalyst was supported by Al_2O_3. The dependence of the reaction rate on temperature proved that the palladium nanoparticles on the titanium dioxide photocatalyst act as a catalyst. Although, for the cyanomethylation of aliphatic hydrocarbons, the catalytic effect of the metal particles was not observed, it might be possible that the radical coupling took place in the absence of a metal catalyst (Scheme S4, ESI†). In 2017, Dong and co-workers reported olefine transformation of γ,δ-unsaturated nitriles through a radical cleavage of acetonitrile and other alkylnitriles in the presence of DTBP $(t\text{-BuO})_2$ as the oxidant (Scheme 55).[113] Moreover, pivalate assisted the loss of protons from acetonitrile or alkylnitrile, generating cyanoalkyl Cu species (**148a**) and Cu^I species. However, Intermediate species **148a** was generated by the addition of the alkylnitrile radical into olefines. Moreover, a Sigma nitrile product was formed by carboxylate elimination from species **148a**. For regioselectivity, the gamma proton was shielded by the π-bonding of the cyano group with Cu^{III} and in this way a direct proton abstraction occurred from the Sigma position of olefine. Moreover, Cu^I species converted into Cu^{II} by the redox radical behavior of DTBP (Scheme 55). In 2017, Bunescu reported the Cu-catalyzed cyanomethylation of alkenes *via* the Csp^3–Csp^3 and Csp^3–N bond activation of γ-azido alkyl nitrile as an addition type of reaction with an excellent favored product (36–76%) (Scheme 56).[114]



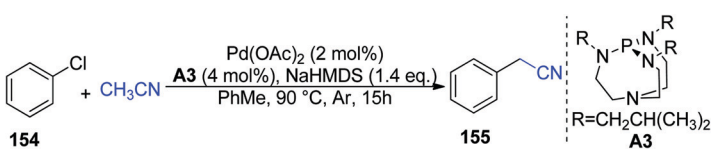
Scheme 56 The Fe-catalyzed cyanomethylation of arylimidazo-pyridine derivatives with acetonitrile.



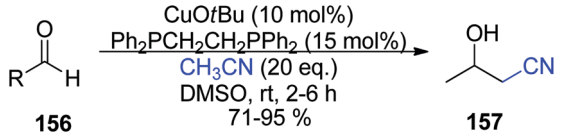
Scheme 57 The Pd-cyanoalkylation of aryl bromides with acetonitrile.

The easy conversions of γ-azido alkyl nitrile to γ-amino nitriles, 1,4 diamines, γ-lactams and γ-azido esters illustrated the synthetic significance of this methodology. According to the reported mechanism, firstly acetonitrile coordinates with Cu^{II} species to generate the cuprate-acetonitrile intermediate by deprotonation of acetonitrile. Secondly, that intermediate affords a cyanomethyl radical *via* homolytic C–H bond cleavage of acetonitrile. Addition step leads to a benzyl radical intermediate which reacts with $Cu^{II}LN_3$ and delivers the cyanomethylated product with the regeneration of the Cu^I salt. Finally, oxidation of Cu^I to Cu^{II} may occur either by MnF_3 or DTBP in this protocol (Scheme 56).

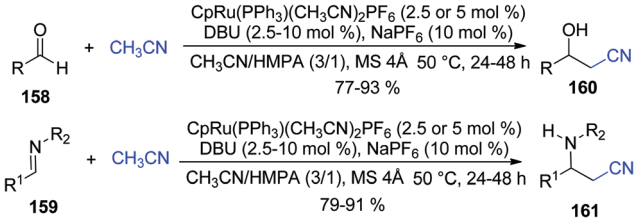
The reactivity of acetonitrile inferred by the catalytic generation of cyanoalkyl radicals and metallated nitriles. The Pd-catalyzed functionalization of electronically diverse aryl bromide with acetonitrile (alkylnitrile) was developed in 2003.[115] This protocol



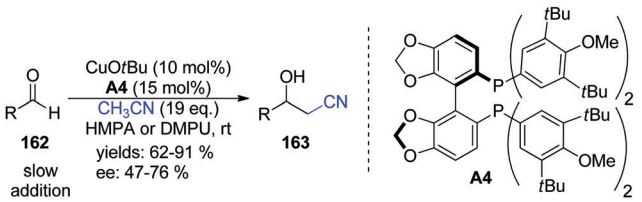
Scheme 58 The Pd-cyanoalkylation of arylchlorides with acetonitrile.



Scheme 59 The cyanoalkylation of aldehydes using a Cu catalyst with acetonitrile.



Scheme 60 The Ru-catalyzed addition of MeCN to imines and aldehydes.



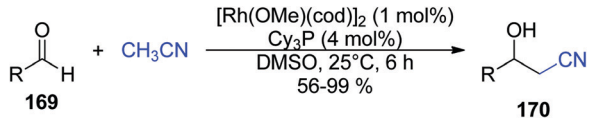
Scheme 61 The Cu-catalyzed enantioselective cyanomethylation of aldehydes with acetonitrile.

tolerated a good yield of nitrile product in the presence of a lower Pd-catalyst loading (Scheme 57). Another approach to improve the synthetic version of the cyanoalkylation of acetonitrile consisted of the use of Pd catalyst along with proazaphosphatrane as the ligand in 2003.[116] The product formed after arylchloride participation in the catalytic adduct and afforded an excellent yield (Scheme 58).[116]

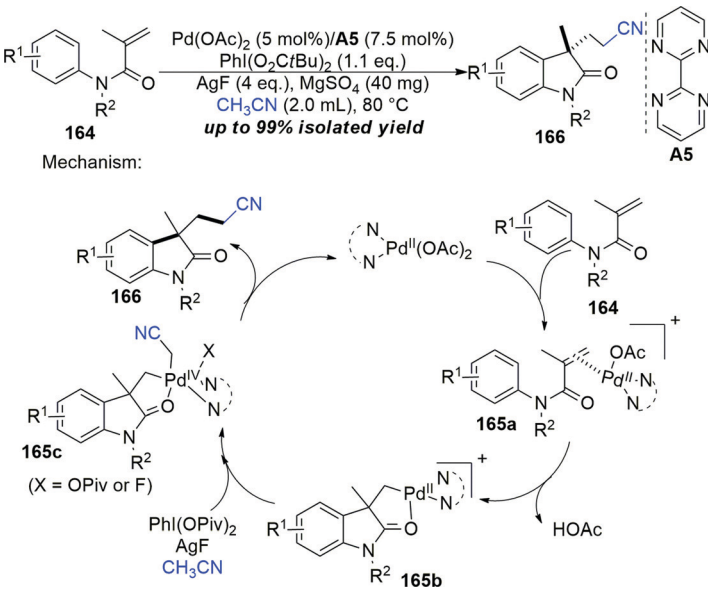
1.5. Aldol-type stereoselective/non-stereoselective cyanomethylation and miscellaneous reactions

In 2003, Suto described the interaction between Cu and CN which polarized the carbon hydrogen bond of α-proton in the complex which was deprotonated by the alkoxide anion (Scheme 59).[117]

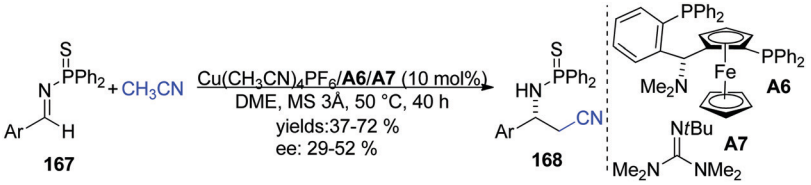
After this study, Shibasaki and co-workers reported cationic ruthenium complexes as Lewis acids (LA) to promote the direct addition of MeCN to imines and aldehydes in the presence of common amine bases.[118] Cooperative action of the Ru complex,



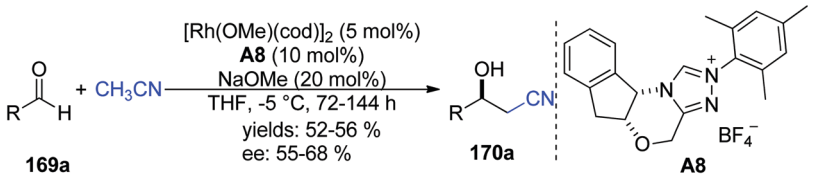
Scheme 64 The Rh-catalyzed aldol-type reaction of aldehydes with acetonitrile.



Scheme 62 The Pd-catalyzed oxidative cyanomethylation of alkenes with acetonitrile.



Scheme 63 The Cu-catalyzed enantioselective addition reaction of *N*-thiophosphinoylimines with acetonitrile.



Scheme 65 The Rh-catalyzed aldol-type reaction of heterocarbenes with acetonitrile.

$NaPF_6$ and DBU enabled the aldol-type reaction for aliphatic and aromatic aldehydes as well as activated imines to synthesize the corresponding β-amino and β-hydroxy nitriles (Scheme 60). In this process, Ru predominantly coordinates with acetonitrile and the Lewis acid (LA) to increase the acidity (pK_a) of the α-proton of MeCN which was deprotonated by the amidine base.

In 2005, The first stereoselective direct aldol-reaction of acetonitrile was applied using $CuOBu^t$ in the presence of chiral phosphine ((R)-DTBM-SEGPHOS) ligands.[119] The reaction proceeds to the corresponding alkyl nitrile containing moieties with excellent yields and enantioselectivities (Scheme 61).

In 2011, a convincing Pd-catalyzed oxidative cyanomethylation of alkene was demonstrated by Wu (Scheme 62).[120] This strategy was applied to synthesize cyanomethyl bearing indoles with moderate yield. A drawback was that the reaction was unable to produce cyanomethylated products without substituents including electron deficient functional groups at the α-position of the nitrogen containing center. In contrast, the methodology did not work with other alkyl nitrile sources like isobutyronitrile and so on. In 2013, an excellent mode of acetonitrile activation extended to the enantioselective Cu-catalyzed Mannich addition of acetonitrile to *N*-thiophosphinoylimines (Scheme 63).[121]

In this case, the catalytic system consisted of the cationic copper source $[Cu(CH_3CN)_4]PF_6$, Barton's base and the chiral phosphine (R,Rp)-Ph-T aniaphos ligand afforded moderate to good yields and ee (Scheme 63). Moreover, a Rh-catalyzed aldol type reaction also involved the activation of acetonitrile through some intermediates, although the mechanism of the reaction is still unclear. Usually, aliphatic and α,β unsaturated aldehyde substrates are studied and huge numbers of excellent results are obtained (Scheme 64).[122,123]

In the same way, a complex that consists of rhodium alkoxide and achiral N-heterocyclic carbene, generated from the triazolium salt, has been identified to promote aldehyde cyanomethylation with moderate yields and enantioselectivities (Scheme 65).[124,125]

Outlook and summary

Here we report that considerable efforts have been devoted to exploring the catalytic generation of cyano carbanions and metalated cyanides species. However, the synthesis of organometallic complexes using acetonitrile is an attractive field in the modern scientific era. Progress toward effective modes of acetonitrile activation and a number of various direct catalytic cyanomethylation and cyanation strategies are summarized in this review. Moreover, almost all the literature reported for acetonitrile, with a substrate scope such as aryls substituted with a variety of functional groups, has been evaluated. Cyanations by acetonitrile *via* C–CN activation in the presence of transition metal catalysts for aldoarenes, arenes carbonyls, aryl halides, diazo-arenes, boronic acids, sulfoximines, and arene substrates, along with the C–H functionalization of indoles, are described. Cyanomethylation through free radical reactions with acetonitrile for 2,2,6,6 tetramethylpipyridine, phenazines, cycloalkenes, arenes, arene-ketonitriles, diarylethenes, aldehydes, C_2-quaternary indolin-3-ones, aliphatic amides, diazonium salts, azoles, allylic alcohols, arylacrylamides, alkenes, 1,3-dicarbonyls, benzaldehyde, and coumarin substrates with practical synthetic features of natural scaffolds are mentioned.

In our view, the use of acetonitrile as a versatile source for transformations involving organometallic complexation, cyanation, and cyanomethylation *via* C–CN bond cleavage is a hallmark for future developments. This new progress relating to green nitriles and metal-catalyzed cross-coupling reactions may help to fill a gap in the knowledge of green cyano sources.

Conflicts of interest

There are no conflicts to declare.

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