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review

Acetonitrile as a Building Block and Reactant

B. H. Hoff

Biographical Sketches

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Bård Helge Hoff was born in Oslo, Norway in 1971. He received his Master's degree in 1995, followed by a Ph.D. in 1999 working with Professor Thorleif Anthonsen in the field of biocatalysis. In 2000 he joined Borregaard Synthesis, Norway, where he worked as a researcher and team leader until the end of 2005. In 2006 he joined the Department of Chemistry at the Norwegian University of Science and Technology, Trondheim, Norway as associate professor. He became full professor in 2016. Awards include Outstanding OIDD collaborator: Blinded synthesis award 2016 from Eli Lilly, the 'Gullegget' innovation prize from NTNU Technology Transfer Office in 2013, and an award for young organic chemists in Norway in 2011 by the Norwegian Chemical Society. His research is within the field of applied organic chemistry with the main activity in medicinal chemistry. He has lately also entered the field of organic electronic materials. Previous research includes biocatalysis, asymmetric synthesis, fluorinated building blocks, carbohydrate chemistry, cellulose and lignin chemistry, heterocyclic chemistry, and cross-coupling methodology.

Department of Chemistry, Norwegian University of Science and Technology (NTNU), Høgskoleringen 5, 7491 Trondheim, Norway

Bard.Helge.Hoff@chem.ntnu.no

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Abstract

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Acetonitrile is popular as a solvent for performing organic reactions, as a ligand in inorganic chemistry, as a mobile phase in chromatography, and as an electrolyte solvent in dye-sensitized solar cells. This is mainly due to its ability to dissolve both polar and nonpolar components. However, acetonitrile is also a valuable building block allowing atom-efficient transformations in synthetic organic chemistry. The aim of this review is to highlight synthetic transformations using acetonitrile, covering both classical approaches and modern strategies proceeding through radical intermediates or mediated by metal catalysis. Besides showcasing synthetic protocols useful for acetonitrile and analogues, warnings for when not to use acetonitrile as a solvent are also provided.

Key words

acetonitrile
cyanomethylation
cyanation
cyclotrimerization
Cu catalysis
Ritter reaction
pyridine synthesis

1 Introduction

Acetonitrile is a small polar molecule with a dipole moment of 3.92 D and a dielectric constant of 38. It is miscible with water and a number of organic solvents. Thus, acetonitrile is useful for dissolving both polar and nonpolar molecules, except for saturated alkanes. Moreover, acetonitrile is frequently employed as a solvent in preparative organic and inorganic reactions, in analytical sciences (HPLC, LC-MS, and UV), and also as part of the electrolyte of dye-sensitized solar cells.[1] In terms of sustainability, the main drawbacks with the use of acetonitrile as a solvent are waste treatment and the environmental impact of its production.[2]

Acetonitrile is also an important building block in synthesis. The two carbons and one nitrogen■■*OK*■■ of acetonitrile have different reactivity: the methyl proton is slightly acidic (pK_a 31 in DMSO[3]) and can be deprotonated to generate a nucleophile; the triple bonded carbon is somewhat electrophilic; and the nitrogen lone pair can act as a nucleophile on reactive electrophiles and as coordination site for metals. Radical-type addition involving acetonitrile is also common, and the recent literature even shows acetonitrile to be an efficient source of cyanide. On one hand the introduced nitrile functions are of importance as a number of drugs and drug candidates contain this functionality,[4] while on the other nitriles can be converted into various functionalities and more complex products.

The aim of this review is to give an overview of the various reactions involving acetonitrile, including atom-efficient processes for two-carbon extension of various materials, transformations to heterocycles, multicomponent reactions, and cyanation protocols without cyanide. As most of these transformation also can be performed with other nitriles, general knowledge on the synthesis of this compound class is provided. Guidelines are also given for when the use of acetonitrile as reaction solvent should be avoided.

2 Fundamental Reactions with Acetonitrile

2.1 Hydrolysis and Alcoholysis

Acetonitrile undergoes hydrolysis in basic and acetic medium, leading to acetamide or acetic acid. Table 1 summarizes the methods for converting acetonitrile into acetamide.

One approach is to use peroxides. Under these conditions acetonitrile reacts to form acetamide and molecular oxygen.[5,6] Various types of basic conditions can also be used.[7–9] Treating nitriles with trimethylsilyl chloride and trace amounts of water led to amide production (Table 1, entry 3).[10] Thus, during various silylation processes there is a potential risk of byproduct formation when there is a nitrile-containing functionality in the substrate or acetonitrile as solvent.

Table 1 Synthetic Methods for Converting Nitriles into Amides[5,7],[10–17]

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Entry	Reagent	Temp (°C)	Yield (%)	Ref.
1	urea–H_2O_2 adduct	rt	77	[5]
2	NH_3, CsOH, H_2O	100	60	[7]
3	TMSCl, H_2O	0–25	75	[10]
4	Ru(II), H_2O	100	99	[11]
5	$CoCl_2 \cdot 6H_2O$/Zn, O_2, EDA	120	74	[12]
6	MnO_2, H_2O/*i*-PrOH	70	99	[13]
7	Pd/C, H_2O, air	115	94	[14]
8	Os–NHC (cat.), H_2O, KOH	120	96	[15]
9	$Cu_4I_4(H_2O)_4$, H_2O	100	63	[16]
10	Ag nanoparticles, H_2O	90	73	[17]

Conversion of acetonitrile into acetamide has also been accomplished using catalysts based on ruthenium,[11],[18–20] nickel,[21,22] cobalt,[12] platinum,[23,24] palladium,[14,25] osmium,[15,26] gold,[27] silver,[17,28] and copper.[16,29] Manganese dioxide based systems have also been applied.[13,30] Thus, the use of acetonitrile as a reaction medium in metal-catalyzed processes is likely to result in an alteration in the composition■■*OK*■■ of the reaction medium as a function of reaction time. These transformations of acetonitrile are of no practical use, but this solvent should be avoided when conducting hydrolytic reactions.

The Pinner reaction is the partial solvolysis of a nitrile to yield an imidate (iminoether). Acetonitrile reacts with alcohols in the presence of dry acid to give an alkyl acetimidate hydrochloride (Scheme 1).[31]

Treatment of the alkyl acetimidate hydrochloride under various conditions gives different products (Scheme 1): (1) reaction with amines yields amidines (imidamides)■■*OK*■■; (2) acid hydrolysis under

mild conditions gives an alkyl acetate; (3) reaction with alcohols forms orthoacetates; (4) treatment with hydrogen sulfide and pyridine gives an *O*-alkyl thioacetate; finally (5) treating the hydrochloride with base gives an■■*OK*■■ alkyl acetimidate. The transformations are usually performed in ethanol, but can also be performed with other alcohols.[32]

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Scheme 1 Alcoholysis of acetonitrile and transformations from alkyl acetimidates

As a solvent, acetonitrile is unsuited in reactions involving alcohols and strong acids, such as, for example, esterification, ether formation, addition of hydrogen halides to alkenes, all reactions involving carbocation reactions (Ritter), and in the preparation of alkyl halides from alcohols.

2.2 Self-Condensation and Reaction with Other Nitriles

Acetonitrile contains an acetic proton and an electrophilic site. Deprotonation of acetonitrile in the absence of other electrophiles can lead to self-condensation yielding 3-iminobutyronitrile (Scheme 2).[33,34] Dimerization also occurs with rather weak bases such as tetramethylammonium fluoride.[35,36] Depending on the conditions further reactions can take different paths. Mixing acetonitrile and sodium hydride gave a 2:1■■*Hoff change*■■ ratio of 2,4,5-trimethyl-1*H*-imidazole and 2,4,6-trimethyl-1,3,5-triazine (Scheme 2).[37] Whereas the formation of 2,4,6-trimethyl-1,3,5-triazine appears to be a cyclotrimerization, the mechanism for the formation of 2,4,5-trimethyl-1*H*-imidazole is unknown. In contrast, when acetonitrile was treated with activated magnesium in a sealed tube at >120 °C the product was 2,6-dimethylpyrimidine-4-amine in 93% yield based on magnesium input (Scheme 2).[38] Acetonitrile also undergoes similar reactions with other nitriles such as pyridine-4-carbonitrile (Scheme 2).[39] Brønsted acids such as triflimide ($NHTf_2$) also promoted cyclotrimerization between acetonitrile and 4-chlorobenzonitrile (Scheme 2).[40]

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Scheme 2 Cyclization products observed with acetonitrile under different conditions (Zhang et al. 1995;[37] Burns et al. 1987;[38] Picci et al. 2001;[39] Herrera et al. 2014[40])

Condensation of acetonitrile with aromatic nitriles also constitutes a route to benzoylacetonitriles, e.g. the condensation of acetonitrile with 4-fluorobenzonitrile gives 3-(4-fluorophenyl)-3-oxopropanenitrile via 3-amino-3-(4-fluorophenyl)-3-oxoprop-2-enenitrile (Scheme 3).[41]

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Scheme 3 Synthesis of 3-(4-fluorophenyl)-3-oxopropanenitrile via 3-amino-3-(4-fluorophenyl)-3-oxoprop-2-enenitrile

2.3 Reaction with Amines

Lanthanide(III) ions are excellent coordinators of nitriles in the presence of amines. The $La(OTf)_3$ promoted reaction between acetonitrile and amines gives *N*,*N*′-dialkylacetimidamides in 50–70% yields (Scheme 4).[42] The monoalkylated intermediate was found to be unstable during distillation.

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Scheme 4 Lewis acid and amine induced reactions with acetonitrile

Using a lower excess of the secondary amine with a reaction time of several days gave 4-amino-substituted 2,6-dimethylpyrimidines and 2,4,6-trimethyl-1,3,5-triazine (Scheme 4). The triazine product dominated when the reaction was performed in a closed vessel hinting to the role of ammonia as an important component of the reaction.[42] Acetonitrile reacted with hexylamine in the presence of SmI_2 to give 2,4,6-trimethyltriazine in 60% yield.[43]

Acetonitrile contains an electropositive carbon atom which can be attacked by a nucleophile. The formed intermediate can then be hydrolyzed to the corresponding amide. Thereby, acetonitrile can be utilized as an acetylating agent for amines. Whereas this protocol could seem inconvenient, it appears

to be useful in some settings and it has been used for the preparation of *N*-acetylcysteine (Scheme 5).[44–46]

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Scheme 5 Acetylation of amines (L-cysteine acetylation;[44–46] Lu et al. 2004;[47] Cobley et al. 2000;[48] Davulcu et al. 2013[49])

Furthermore, a Pt(II) catalyst was used in the acetylation of primary and secondary amines to give the corresponding *N*-acetylamines in 60–73% yields (Scheme 5).[48] The reaction presumably occurs via amidines, which hydrolyze to the *N*-acetylamines. An acetylation process has been developed using $Zn(OTf)_2$ and hydroxylamine which is assumed to have the same mechanism (Scheme 5).[49] Copper catalysis was employed in the acetylation of 5-methyl-1*H*-pyrazol-3-amine that occurred to give *N*-acetyl-5-methyl-1*H*-pyrazol-3-amine, the product of acetylation at the 3-amino group, and not the product of acetylation at the pyrazole nitrogens (Scheme 5).[47]

2.4 Reduction of Acetonitrile

Acetonitrile is reduced to ethylamine by $LiAlH_4$, $LiAlD_4$,[50] or trimethylsilyl chloride/$NaBH_4$[51] (Scheme 6). Reaction with boranes also leads to ethylamine. For example, treatment of acetonitrile with pinacolborane in the presence of a Co(III) catalyst gave, after workup, ethylammonium chloride in 52% yield.[52] Bulky hydrides, such as diisobutylaluminum hydride (DIBAL-H),[53] or $SnCl_2$[54,55] give acetaldehyde as the product.

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Scheme 6 Common reduction products from acetonitrile

Hydrogenation of acetonitrile over various catalysts, such as Ni, Co, and Ru, gives ethylamine together with diethylamine[56–59] and triethylamine■■*OK*■■[56,59] as byproducts (Scheme 6). Thus, acetonitrile is not a good reaction medium for reductions.

2.5 Acetonitrile and Halogenating Agents

Although bromo- and chloroacetonitrile are frequently used in the cyanomethylation of heteroatoms, there are few reported studies on their preparation in the literature. A patent reported that the monochlorination of acetonitrile using chlorine gas and HCl under irradiation gave chloroacetonitrile in in 91% yield (Scheme 7);[60] trichloroacetonitrile was obtained by further chlorination of chloroacetonitrile. A similar method has been used to obtain trichloroacetonitrile.[61] Small amounts of chloroacetonitrile were also observed on photochemical treatment of chlorobenzenes in acetonitrile.[62] Irradiation of acetonitrile using bromine and HCl gave bromoacetonitrile in 47% yield (Scheme 7);[63] the reason for the use of HCl instead of HBr is unknown. The reaction between acetonitrile, molecular bromine, and uranium hexafluoride gave a salt that was analyzed and found to be $[Br(C_6H_9N_3)][UF_6]$, a 2,4,6-trimethyl-1,3,5-triazine bromide uranium hexafluoride, with both oxidizing and brominating properties.[64]

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Scheme 7 Halogenation of acetonitrile

A patent describes the trifluorination of acetonitrile using various nickel fluorides or HF in a special apparatus, but no yields were reported (Scheme 7).[65] Trifluoroacetonitrile is, however, more conveniently prepared by the dehydration of trifluoroacetamide.[66] The preparation of iodoacetonitrile has not been reported, but it was formed in situ in a radical-induced cyanomethylation,[67] and observed as a byproduct in a photocatalyzed Finkelstein reaction of arenes using acetonitrile as a solvent.[68]

2.6 Epoxidation with Acetonitrile

Hydrogen peroxide reacts with acetonitrile to from an imine oxide suitable for oxidizing alkenes. The epoxidation is best performed in the presence of a base, and acetamide is liberated as a byproduct in equimolar amounts. The oxidant is stable below 60 °C; above this temperature the complex decomposes to acetamide and oxygen. Some examples of successful transformations are shown in Scheme 8 ■■Hoff: insert ref 73-75 here■■. In 2014, it was shown that α,α,α-trifluoroacetophenone acts as an organocatalyst in these reactions.[69] Additionally this concept is used in asymmetric Weitz–Scheffer epoxidations.[70]

In an alternative oxidation protocol, bubbling dilute fluorine through aqueous acetonitrile forms a HOF–CH_3CN complex; this oxidant allows very rapid epoxidation of sensitive substrates (Scheme 8).[71] The HOF–CH_3CN complex is a very useful oxidant also in other settings.[72]

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Scheme 8 Epoxidation using acetonitrile (Sugai et al. 2007;[73] Frank et al. 1998;[74] Smith et al. 1994;[75] Rozen et al. 2004[71]) ■■*refs. 73, 74, 75 appear here but are not cited in the text, see comment above*■■

2.7 Use of Acetonitrile in the Dehydration of Amides

Dehydration of amides to nitriles is potentially a challenging task when the molecule in question contains labile groups. Mild conditions have been identified for performing this transformation; the dehydration system requires an aldehyde, formic acid, and acetonitrile.[76] The dehydration of amides containing an alkene, primary chloride, primary alcohol, or carboxylic acid gave the corresponding nitrile in 64–92% yield. The reaction failed for 3-phenylpropargylamide and THP- and TBDMS-protected alcohols. This methodology was used in the synthesis of vascular endothelial growth factor receptor 2 inhibitors.[77]

The proposed catalytic pathway is shown Scheme 9.[76] Formaldehyde is protonated by formic acid giving a protonated spices **I**, which reacts with acetonitrile to form the salt **II**. The substrate amide adds to this complex to form **III**, which rearranges to the nitrile and intermediate **IV**, which decomposes to acetaldehyde and acetamide. Acetamide can as well go through this catalytic circle to produce acetonitrile again.

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Scheme 9 Mechanism for converting amides into nitriles using the formic acid/aldehyde/acetonitrile system

An investigation of the palladium-catalyzed synthesis of pyridin-2-ones from α,β,γ,δ-unsaturated amides using Li_2PdCl_4, Et_3N, and acetonitrile found, however, that the product was an amide. Thus two dehydration protocols were developed for the synthesis of nitriles from amides (Scheme 10).[78] The transformation of aliphatic amides required the use of $PdCl_2$ (cat.)/AgOAc/LiCl/acetonitrile and while aromatic amides required $PdCl_2(PPh_3)_2$ (cat.)/$Cu(OAc)_2$/LiCl/acetonitrile, the latter method was also successful for aliphatic amides. As both acetonitrile and an acetate salt were required for the conversion, a mechanism is proposed as shown in Scheme 10.[78]

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Scheme 10 Dehydration of amides to nitriles catalyzed by Pd(II) in combination with acetonitrile and an acetate source

3 Cyanomethylation of Non-Aromatics

3.1 Reaction with Alkyl Halides and Epoxides

On treatment with an excess of strong base, acetonitrile is completely converted into the cyanomethyl anion, minimizing self-condensation. High yields have been observed in some alkylations of the cyanomethyl anion (Scheme 11),[79–81] while in other cases substantial amounts of the dialkylated product were found.[82,83] ■■Hoff insertion: Chercheja et al. reported on a double cyanomethylation using LDA resulting in a decent 63% yield (Ref 87) ■■ Under standard conditions (*n*-BuLi as base), challenging substrates appear to be allylic halides and benzyl halides that also contain halogen atoms susceptible to halogen–metal exchange.[84] In the case of allylic halides, the use of cyanomethylcopper ensures high reactivity at the halogen (Scheme 11).[85]

The reaction of acetonitrile with benzyl bromide in the presence of NaH was investigated and three different products were isolated (Scheme 11).[86] In addition to the expected alkylation product, byproducts originating from the reduced form of 3-iminobutyronitrile were found. Apparently, sodium hydride also acts as a reducing agent in this reaction.

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Scheme 11 Alkylation of acetonitrile (Yashimata et al. 2011;[80] Yu et al. 2013;[81] Chercheja et al. 2014;[87] Crich et al. 2006;[79] Corey et al. 1972;[85] Hesek et al. 2009[86]) ■■*ref. 87 appears here but is not cited in the text, see comment above*■■

■■Hoff: removed "Simple" ■■ Epoxides, also with rather complex structures, have been reacted with the cyanomethyl anion to give γ-hydroxy nitriles in good to yields (Scheme 12).[88–91] ■■Hoff: Insert ref 93 and 94■■ However, allylic epoxides can give product mixtures originating from both direct attack at the epoxide and nucleophile addition to the double bond.[92]

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Scheme 12 Examples of epoxide opening using the acetonitrile anion (Eagon et al. 2010;[91]■■*ref. now 91, OK*■■ Tolstikov et al. 1989;[92] MacLeod et al. 2010;[89] Schwarts et al. 2011;[90] Suzuki et al. 2001;[93] Lawton et al. 2009[94]) ■■*refs. 93, 94 appear here but are not cited in the text, see comment above*■■

3.2 Silylation

(Trimethylsilyl)acetonitrile has been prepared from bromo- or chloroacetonitrile and trimethylsilyl chloride.[95,96] There is one report of the direct preparation of (trimethylsilyl)acetonitrile from acetonitrile employing 1,1-dimethyl-2,2-bis(trimethylsilyl)hydrazine and methyl iodide and heating in a sealed tube at 100 °C (Scheme 13).[97] Acetonitrile also reacted with trimethylsilyl triflate to give two products in 57:43 ratio (overall yield 73%) (Scheme 13).[98] ■■Hoff: remove this sentence: "There are no other references to these trisilylated compounds"■■*correct? see refs 2–7 in ref 98, particularly ref 5*■■. ■■ Hoff insertion: Employing stonger bases such as *n*-BuLi or *t*-BuLi, depending on the conditions various silylated derivative were obtained, Ref: West, R.; Gornowicz, G. A. *J. Amer. Chem. Soc.* **1971,** *93*, 1714. ■■ A rather special silylation protocol has been reported in which acetonitrile reacts with a bis(silyl)iron complex under irradiation to give an *N*,*N*-bis(silyl)enamine (Scheme 13).[99]

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Scheme 13 Silylation of acetonitrile (Voronokov et al. 2005;[97] Emde et al. 1977;[98] Corriu et al. 1985[99])

3.3 Reaction with Aldehydes and Ketones

Acetonitrile reacts with aldehydes and ketones under basic conditions to yield cyanohydrins or cyanoacrylic derivatives (Scheme 14). On occasion this reaction requires some fine tuning in terms of the base and temperature.[100] In the condensation of acetonitrile with benzaldehyde, it was found that potassium *tert*-butoxide gave a higher yield than *n*-BuLi or sodium methoxide (Scheme 14).[101] The reaction of acetonitrile with benzaldehydes containing electron-donating substituents using tetrabutylammonium fluoride as the base gave the corresponding cyanohydrins in high conversion, while nitro- and trifluoromethyl-substituted benzaldehydes were prone to oxidation to give the corresponding benzoic acid■■*OK*■■ (Scheme 14).[102] Proazaphosphatranes promote the reaction of acetonitrile with both aliphatic and aromatic aldehydes.[103] Ketones are also easily cyanomethylated with acetonitrile using LDA[104] or *n*-BuLi (Scheme 14).[100]

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Scheme 14 Synthesis of cyanohydrins from aldehydes (Koenig et al. 1994;[101] Ko et al. 2006;[102] Eastgate et al. 2002;[105] Yu et al. 2015;[104] Xiao et al. 2015[100]) ■■*ref. 105 appears here but is not cited in the text, Hoff comment: remove reference 105, a new scheme will be provided* ■■

If the substrate aldehyde is incompatible with strong base, metal-catalyzed processes can be applied. Two copper-catalyzed methods were investigated.[106] The most practical variant used copper(I) *tert*-butoxide and 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand (Scheme 15). (Cyclooctadiene)methoxyrhodium(I) dimer, which was previously found efficient in aldol reactions, was also applicable in the cyanomethylation of aldehydes (Scheme 15).[107] Mechanistically, it might be assumed that both the aldehyde and nitrile are coordinated to rhodium, causing LUMO activation of the aldehyde and an increase in acidity of the nitrile. This approach was then developed to give the corresponding amides by including a hydrolytic step in a one-pot reaction;[108] the lowest yields were seen for furan- and thiophene-based aldehydes■■*refers to one-pot reaction?-yes*■■.

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Scheme 15 Various metal-catalyzed additions of acetonitrile to aldehydes (Suto et al. 2003;[106] Goto et al. 2008;[107] Wang et al. 2013;[112] Chakraborty et al. 2013[113])

The ruthenium-catalyzed cyanomethylation of aldehydes has also been developed, in which mechanistically acetonitrile is coordinated to ruthenium, which increases the acidity and promotes addition to the aldehyde.[109–111] In the palladium-catalyzed cyanomethylation of indole-2,3-diones with acetonitrile, the activated palladium complex presumably reacts with acetonitrile by a C–H bond insertion, followed by coordination of the carbonyl compound and transfer of the cyanomethylene group (Scheme 15).[112] The cyanomethylation of aldehydes with acetonitrile using a nickel catalyst (Scheme 15) is an attractive procedure because the nickel catalyst is both air- and moisture-stable and it was efficiently used at room temperature on a wide range of aldehydes.[113]

The reaction of carbonyl compounds with acetonitrile to give α,β-unsaturated nitriles (acrylonitriles) generally require the use of alkali hydroxide under refluxing conditions (Scheme 16).[114–116] The *E*-isomer is the major isomer formed with the *E*/*Z* ratio depending on conditions and substrate.[114,117] This reaction was also performed using *N*-methyl-*N*-(trimethylsilyl)acetamide or *N*,*O*-bis(trimethylsilyl)acetamide in combination with Amberlyst fluoride as a heterogeneous fluoride catalyst, thus avoiding the use of strong base■■*OK*■■.[118] Complementing the above approach for the synthesis of (*E*)-α,β-unsaturated nitriles, (*Z*)-α,β-unsaturated nitriles were synthesized from acetonitrile in a simple three-step single-pot procedure employing chlorodiisopropylborane (Scheme 16).[119]

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Scheme 16 Methods for making (*E*)- or (*Z*)-α,β-unsaturated nitriles (Dibase et al. 1979;[114] Tomioka et al. 2010[119])

3.4 Reactions with Imines

Ruthenium-based activation of imines can be used in the same way as described for aldehydes in Section 3.3. Both *N*-Boc[109,111] and *N*-(diphenylphosphoryl)imines[111] react to give β-amino nitriles in 79–91% yield (Scheme 17). The method appears to be unsuitable for aliphatic imines, which might be due to isomerization to the corresponding enamine.

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Scheme 17 Reaction of acetonitrile with imines (Kumagai et al. 2007;[111] Poisson et al. 2009[120])

Successful reactions with imines have also been executed by using LDA as a base.[121] Mild basic conditions for the cyanomethylation of *N*-arylbenzaldimines were developed using a combination of sodium 4-methoxphenoxide and ethyl (trimethylsilyl)acetate that gave β-arylamino nitriles in moderate to good yields (Scheme 17); however, the reaction was unsuitable for certain imines.[120]

The cyanomethylation of imines under radical conditions using potassium superoxide and DCC gave β-aryl-β-amino nitriles in 32–90% (GC) yield starting from aromatic imines, but a β-amino-β-cyclohexyl nitrile was obtained in 12% (GC) yield starting from *N*-phenylcyclohexylmethanimine.[122] Additionally, depending on the imine structure, various byproducts were observed (Scheme 18).[122] This highlights the challenge with employing acetonitrile as solvent in radical chemistry.

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Scheme 18 Cyanomethylation of imines under radical conditions

There is a single example of the activation of the imine by reaction with benzyne prior to the cyanomethylation to give a β-arylamino nitrile (Scheme 19).[123]

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Scheme 19 Activation of an imine by reaction with benzyne

3.5 Reaction with Esters

The acetonitrile anion can also react with esters as shown in Scheme 20. A strong base (NaH, LiHMDS, *n*-BuLi) is usually employed. Esters that do not contain a labile group give a high yield of the corresponding β-oxo nitrile.[124–128]■■*OK*■■ In the case of 3-aryl-3-oxopropanenitriles, higher functional group tolerance was experience when switching form sodium amide and alkoxide■■*OK*■■ bases to sodium hydride.[41] ■■ Hoff insert: This base was also successfully used in reactions with other benzoate esters Ref 128 and Ref 129, while lithium bis(trimethylsilyl)amide (LiHMDS) have been employed in condensation with indol derivatives Ref 30■■.

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■■ A new Scheme is provided, since one carbon was missing in one structure■■

Scheme 20 Reaction of acetonitrile anion with esters (Vong et al. 2003;[124] Nani et al. 2013;[126] Kadel et al.;[128] Kim et al.;[129] Ebiike et al. 2016[130]) ■■*refs. 129, 130 appear here but are not cited in the text, see comment above*■■

3.6 Conjugate Addition

There are relative few examples of conjugate addition of the cyanomethyl group to α,β-unsaturated carbonyl compounds (Scheme 21). A microwave method was investigated for the addition of acetonitrile to benzalacetone giving a mediocre 60% yield.[131] Cyanomethylcopper was found to be useful in the conjugate addition reaction with a rather complex amide,[132] while a manganese catalyst was employed in the reaction of acetonitrile with ethyl acrylate.[133] During the preparation of antihepatitis C virus agents, the simultaneous formation of a silyl enol ether and a cyanomethylation were performed in 75% yield; the intermediate that undergoes cyanomethylation is shown in Scheme 21.[134]

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Scheme 21 Conjugate addition using acetonitrile (Boruah et al. 1996;[131] Chen et al. 2010;[132] Nerush et al. 2016;[133] Watanabe et al. 2017[134])

3.7 Cyanomethylation of Alkenes and Alkynes

Acetonitrile can cyanomethylate alkenes under radical conditions (Scheme 22). For instance, 1,1-diarylalk-1-enes were found to undergo photoinduced radical type addition of acetonitrile in the presence of benzophenone as a sensitizer and *tert*-butylamine (Scheme 22).[135]

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Scheme 22 Radical-induced cyanomethylation (Yamashita et al. 1996;[135] Li et al. 2015;[136] Zhu et al. 2017;[137] Chatalova-Sazepin et al. 2015;[138] Bunescu et al. 2015;[139] Bunescu et al. 2015;[140] Wu et al. 2017[141])

Alternatively, the homolytic splitting of peroxides gives rise to alkoxy radicals that react with acetonitrile to give the cyanomethyl radical, which in turn can add to sp^2 and sp hybridized carbons. A catalyst (copper- or iron-based) is usually employed to assist in this process. Using CuI as the catalyst and dicumyl peroxide (DCP) as the radical initiator for the cyanomethylation of ω-acyloxy and ω-hydroxyalkenes resulted in anti-Markovnikov addition (Scheme 22).[136]

The carboamination of alkenes using benzoyl peroxide (BPO) as the radical initiator, a copper catalyst, and an acid together with excess acetonitrile resulting in the incorporation of two molecules of acetonitrile to give γ-acetamido nitriles in 36–84% yields (Scheme 22).[137] The first cyanomethylation step is assumed to be a radical process, while formation of the acetamide function probably proceed by a Ritter-type pathway.

1,1-Diarylalk-1-enes and α-alkyl-substituted styrenes underwent a three-component cyanomethylation and carboetherification to give γ-methoxy nitriles. The process proceeded under copper catalysis with di-*tert*-butyl peroxide (DTBP) in the absence of base using a 1:1 ratio of methanol and acetonitrile to give the products in 25–88% yields (Scheme 22).[138] One major side reaction is assumed to be polymerization.

Acetonitrile underwent addition to the C=C bond of an allylic alcohol to give tri- and tetrasubstituted epoxides (Scheme 22).[139] Mechanistically, this reaction could involve an attack on the alkene by a cyanomethylated Cu complex or a cyanomethylene radical; it is also assumed that Cu(II) assists in the epoxide formation.[139] Altering the reaction conditions slightly, using an α-arylallyl alcohol with R^1 = aryl and R^2 = alkyl or aryl then the product was a ketone formed by 1,2-aryl■■*OK, no, since the alkyl preferably migrate, it should be stated as a: 1,2-migration* ■■ migration (Scheme 22).[140] The highest yield and selectivity were obtained with R^1 = aryl and R^2 = alkyl.■■*OK*■■

A diverse set of alkenes was converted into γ,δ-unsaturated nitriles (Scheme 22). The choice of copper catalyst was essential to avoid production of the saturated analogue. Presumably, this is since the copper ligand assists in abstraction of a proton. Thus, employing $Cu(OPiv)_2$ as the catalyst, DTBP as the oxidant, and veratronitrile as an additive, which improved the solubility of the catalyst, gave γ,δ-unsaturated nitriles in 40–86% yields. The reaction showed a preference for the *E*-isomer, with the *E*/*Z* ratio dependent on the bulkiness of the alkene substituent.[141]

As is evident from these examples cyanomethylation can take different paths depending on the substrate structure and the exact reaction conditions.

Provided that other reactive sites are correctly placed, cyclization reactions can occur after the radical initiated cyanomethylation. *N*-(4-Hydroxyphenyl)cinnamamides underwent cyanomethylation followed by a radical-type cyclization in the presence of di-*tert*-butyl peroxide and iron(II) acetylacetonate to give cyanomethylated 1-azaspiro[4.5]decanes (Scheme 23).[142]

e0191_s23.eps

Scheme 23 Cyanomethylation followed by cyclization (Zhang et al. 2017;[142] Wang et al. 2018;[143] Yu et al. 2016[144])

N-Arylcinnamamides underwent a silver-induced cyanomethylation–cyclization process to give 3,4-dihydroquinolines via a benzyl radical intermediate (Scheme 23).[143]

In another study aryl alkynoates were converted into cyanomethylated coumarins in 60–80% yields in the presence of *tert*-butyl peroxybenzoate (Scheme 23).[144] The reaction is proposed to proceed through several radical intermediates. It should be mentioned that a good alternative in such processes is to use bromoacetonitrile as a starting material.[145]

The cross coupling of 2-aryl-1,2,3,4-tetrahydroisoquinolines with acetonitrile using $CuCl_2$ and TEMPO gives 2-aryl-1-(cyanomethyl)-1,2,3,4-tetrahydroisoquinolines in good to high yields (Scheme 24).[146] The reaction is proposed to involve a SET mechanism followed by TEMPO abstraction of hydrogen to give an iminium ion. Assisted by copper coordination, acetonitrile is deprotonated and added to the iminium ion. The use of 2-alkyl-1,2,3,4-tetrahydroisoquinolines or nitro-substituted 2-aryl-1,2,3,4-tetrahydroisoquinolines gave complex mixtures.

e0191_s24.eps

Scheme 24 Copper and TEMPO assisted cyanomethylation of 2-aryl-1,2,3,4-tetrahydroisoquinolines

3.8 Cyanomethylation of Heteroatoms

The cyanomethylation of oxygen and nitrogen atoms is usually performed by employing chloro- or bromoacetonitrile. Nitrogen-containing heterocycles and phenols were cyanomethylated by using a system that comprised of acetonitrile, sodium hydride, and perfluorobutane iodide (Scheme 25).[67]

e0191_s25.eps

Scheme 25 Cyanomethylation of heteroatoms

The proposed mechanism involves in situ formation of iodoacetonitrile by a radical process, which then undergoes an S_N2 type reaction with the N-heterocycle or phenol. The highest-yielding reactions are shown in Scheme 25. The obvious drawback of this method is generation of 1 mole equivalent of halogenated waste. ■■*so is this relevant, as it is the reaction of iodoacetonitrile not acetonitrile? It involves acetonitrile as starting material and therefore I feel it is relevant*■■

3.9 Cyanomethylation of Activated Aziridines

Aziridines were activated for cyanomethylation by N-arylation employing a benzyne precursor; the aziridinium intermediate formed underwent ring opening using acetonitrile as the nucleophile to give γ-arylamino nitriles, a highly functionalized building block for further synthesis (Scheme 26).[147] Other reactions of aziridines and acetonitrile are described in Section 5.4.

e0191_s26.eps

Scheme 26 Activation of aziridines for nucleophilic attack

4 The Acetonitrile Nitrogen as a Nucleophile

4.1 The Ritter Reaction

In the Ritter reaction a nitrile reacts with an alcohol or an alkene in the presence of an acid (sulfuric acid) to yield acetamides (Scheme 27). Any substrate capable of generating a stable carbenium ion is a suitable starting material. Primary alcohols do not react under these conditions, with the exception of benzylic alcohols. Progress in the field of the Ritter reaction was reviewed in 2012.[148] Mechanistically, the nitrile adds to the carbenium ion to give a nitrilium ion intermediate, which upon

aqueous workup undergoes hydrolysis to the corresponding amide. Some examples of products ■■Insert ref. 149, 150 and 151■■ are given in Scheme 27.

e0191_s27.eps

Scheme 27 Mechanism of the Ritter reaction and examples of products (Catagnolo et al. 2004;[149] Liu et al. 2006;[150] Blacklock et al. 1993[151]) ■■*refs. 149, 150, 151 appear here but are not cited in the text, see comment above*■■

Alkenes can also be activated for the Ritter reaction by electrophiles other than acids. A Ritter-type reaction of β-phenylthio alcohols on reaction with triflic acid in acetonitrile and water gave *N*-[2-(phenylthio)ethyl]acetamides (Scheme 28).[152,153] In this reaction, the hydroxy group was replaced by the nitrile through anchimeric assistance by the sulfur. The reaction proceeded with retention of configuration, and for some substrates without any racemization. A Ritter-type reaction has also been observed when treating alkenes with the fluorinating agent Selectfluor in the presence of acetonitrile (Scheme 28),[154] in electrochemical fluorinations[155] and in the nitration of glucals (Scheme 28).[156]

e0191_s28.eps

Scheme 28 Ritter-type reactions activated by other electrophiles (Toshimitsu et al. 1991;[153] Singh et al. 2004;[154] Kancharla et al. 2011[156])

4.2 Acetonitrile Reactions with Alkanes

An investigation of the fluorination of saturated alkanes with Selectfluor in acetonitrile gave acetamides in 45–54% yields; presumably, this reaction also proceed via cation intermediates.[157] This chemistry was developed further by the use of a C–H functionalization strategy using $CuBr_2$ in combination with the Selectfluor derivative F-TEDA-PF_6.[158] The reaction is proposed to proceed through a radical intermediate, decomposition to a carbocation, and a Ritter-type reaction with acetonitrile (Scheme 29). The yields were dependent on reaction conditions and the substrate used. The same principle was employed for the conversion of 2-methylbenzoic acids and some heterocyclic analogues into acylated isoindolin-1-one derivatives that allowed for selective intermolecular functionalization of benzylic C−H bonds■■, *the text was too close to the abstract of the original paper, I have simplified somewhat*■■ (Scheme 29).[159]

e0191_s29.eps

Scheme 29 A C–H functionalization strategy of alkanes using Selectfluor/Cu/Fe catalysis or F-TEDA-PF_6/Cu catalysis (Michaudel et al. 2012;[158] Liu et al. 2016[159])

4.3 Reaction with Epoxides in the Presence of Lewis Acids

In the presence of Lewis acids, epoxides react with acetonitrile to form oxazolines. Depending on the conditions and the substrate, regioisomers and stereoisomers can be formed. Scheme 30 shows the mechanism, which leads to inversion of configuration. The reaction can also proceed through an intermediate with carbocation character thus leading to racemization of the stereocenter (Scheme 30).[160] For some substrates, especially with phenyl substituents, byproducts originating from a Pinacol-type rearrangement are observed (Scheme 30),[161] while in other cases halohydrins are seen as byproducts.[160,162] 2,3-Epoxy esters and amides appear to give products with high regioisomeric■■*OK*■■ ratio (Scheme 30).[161],[163–165] Interestingly, for some epoxides, reactions under identical conditions result in, instead of the oxazoline, epoxide opening to yield amides (Scheme 30).[166] Whereas the ozazoline process is highly useful in its own right, it is also clear that the use of acetonitrile should be avoided when performing other types of acid-catalyzed epoxide openings.

e0191_s30.eps

Scheme 30 Oxazolines from acetonitrile and epoxide (Garcia Ruano et al. 2000;[161] Lin et al. 2013;[163] Umezawa et al. 1994;[160] Concellon et al. 2005[166])

4.4 Acetonitrile in Reactions with Aziridines: Imidazolines

N-Sulfonylaziridines reacted with acetonitrile in the presence of a Lewis acid to give imidazolines as the main product. This is a formal 3+2 cycloaddition that probably proceeds by a Ritter-type mechanism (Scheme 31).[167] Depending on the substrate and the Lewis acid employed, two regioisomers are possible (Scheme 31),[168] in addition to products such as 1,2-haloamines,[167,169] and acetamides.[167,169] Triflic acid[170] or metal triflates[167,170,171] are suitable catalysts. This chemistry has also been executed in a flow reactor.[172]

e0191_s31.eps

Scheme 31 Imidazoline synthesis using acetonitrile and the typical byproducts observed (Gandhi et al. 2007;[167] Ghorai et al. 2006[168])

4.5 Acetonitrile Addition to Alkynes

Ynamides react with acetonitrile and water in a *syn*-hydroamidation reaction catalyzed by $Yb(OTf)_3$ to give α-acetamido-α,β-unsaturated amines in 46–80% yields (Scheme 32).[173] A study of structurally related ynamides using triflic acid at –40 °C gave α-acetamido-α,β-unsaturated amines that were further cyclized to pyrimidines by reaction with another molecule of acetonitrile (Scheme 32).[174]

e0191_s32.eps

Scheme 32 Addition of acetonitrile to ynamides (Mallick et al. 2017;[173] Wang et al. 2017[174])■■*second equation, second arrow, CH_3CN missing, a new scheme will be provided*■■

An approach to 4-amidocinnolines employed some of the same principles.[175] *ortho*-Alkynylanilines were treated with *tert*-butyl nitrite and boron trifluoride in acetonitrile to give 4-amidocinnolines in 42–90% isolated yields (Scheme 33). The reaction is proposed to proceed by diazotization followed by intramolecular addition to the terminal nitrogen by the alkyne; the cation intermediate then undergoes a Ritter-type reaction.

e0191_s33.eps

Scheme 33 Cinnoline followed by amide formation

5 The Blaise Reaction

The Blaise reaction forms β-keto esters or β-enamino ketones from the reaction of zinc metal, an α-bromo or α-iodo ester, and a nitrile (Scheme 34).[176,177] This transformation has also been performed using a combination of indium and $InCl_3$ to give β-enamino-β′-keto esters as the product, albeit in low yield when acetonitrile was used as the nitrile (Scheme 34).[178]

e0191_s34.eps

Scheme 34 The Blaise reaction (Creemers et al. 2007;[176] Zylber et al. 1993;[177] Li et al. 2017[178])

The Blaise intermediate that is formed in this reaction can undergo further functionalization (Scheme 35). Treatment of the Blaise intermediate with *n*-BuLi and acetic anhydride gave a β-enamino-β′-keto ester,[179,182]■■*OK*■■ which was further converted into a 1-phenylpyrazole in 88% yield (Scheme 35).[182]■■*OK*■■ The Blaise intermediate was also treated with acrylates to yield 3,4-dihydropyridin-2(1*H*)-ones in 41–76% yields (Scheme 35).[180] A Blaise-type reaction gave a trisubstituted pyrrole as a byproduct, and the reaction was then optimized to give the trisubstituted pyrrole in 78% yield; the proposed reaction intermediates are shown in Scheme 35.[181]

e0191_s35.eps

Scheme 35 Reactions on the Blaise intermediate (Chun et al. 2008;[179] Ko et al. 2009;[182] Meng et al. 2015;[180] Rao et al. 2015[181])

6 Synthesis of Pyridines

6.1 2+2+2 Cyclotrimerization with Alkynes

Cyclotrimerization reactions involving nitriles are well known. Some examples involving acetonitrile are shown in Scheme 36. The synthesis of pyridine derivatives is dominated by cobalt catalysts,[183–187] but can also be performed using nickel-,[188,189] iron-,[190] rhodium-,[191] and iridium-based[192] systems (Scheme 36). A general challenge with the small-sized acetonitrile in these cyclizations is regioselectivity. For instance, the reaction of hex-1-yne with acetonitrile in the presence of a cobalt catalyst gave a 2:1 ratio of isomeric pyridines (Scheme 36).[183] Benzene derivatives are also produced.■■*ref: 183:* Diversi, P.; Ingrosso, G.; Lucherini, A.; Vanacore, D. *J. Mol. Catal.* 1987, *41*, 261and ref 191 Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P.*J. Mol. Catal.* **1987,** *40*, 337.■■ The chemoselectivity and product ratio is dependent on catalyst/ligand, ■■include ref 191:Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P.*J. Mol. Catal.* **1987,** *40*, 337. ■■; [185] the bulkiness of the alkyne■■ include ref 183: Diversi et al. 1987;[183] ■■ , and the alkyne/acetonitrile ratio ■■Changed ref to: ref 191 Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P.*J. Mol. Catal.* **1987,** *40*, 337) In reaction of unsymmetrical dienes electronic control of the regioisomer ratio can also be seen ■■Ref: include ref 183: Diversi et al. 1987;[183] ■■ Sugiyama et al. 2011;[184] ■■.■■. Higher yields and selectivity are seen when diynes are used and the alkyne moieties are separated by 3 atoms, and especially so if the central atom has bulky substituents (Thorp–Ingold effect). A few examples of such cyclotrimerisations are shown in Scheme 36 Ref Sugiyama et al. 2011;[184]; Staudaher et al. 2014;[189]; Richard et al. 2014[190]. Sterically encoumnered alkynes linked by 4 carbons have also be efficientyl reacted to complex pyridine derivatives as shown in Scheme 36, Ref: Fischer et al. 2012;[193]; McIver et al. 2008;[186].

e0191_s36.eps

Scheme 36 Metal-catalyzed cyclotrimerizations to give pyridine derivatives (Diversi et al. 1987;[183] Sugiyama et al. 2011;[184] Fischer et al. 2012;[193] McIver et al. 2008;[186] Staudaher et al. 2014;[189] Richard et al. 2014[190]) ■■*refs. 186, 189 are mentioned only in a general way in the text*■■ ■■*ref. 193 appears here but is not cited in the text, see inserted text*■■

Due to environmental concerns, non-metal-catalyzed methods are of major interest. Acetonitrile was reacted with arylacetylenes using triarylpyrylium salts as photosensitizers to give trisubstituted pyridines in 40–69% yields (Scheme 37).[194] Lewis acid catalyzed protocols have been successfully used with *N*-EWG ynamides (EWG = electron-withdrawing group) to give 2,4-diaminopyridines (Scheme 37).[195,196]

e0191_s37.eps

Scheme 37 Non-metal-catalyzed cyclotrimerizations with alkynes (Wang et al. 2017;[194] Wang et al. 2016[195])

6.2 Other Strategies for Pyridine-Containing Structures

A synthesis of 4-substituted pyridines started with homopropagylic alcohols and acetonitrile and used palladium-on-carbon as a catalyst and sodium amide as a reagent (Scheme 38).[197] In the mechanism it is proposed that the homopropagylic alcohol first binds to the palladium via both the hydroxyl and the alkyne moiety, which activates it for cyanomethylation at the nonterminal alkyne carbon.

e0191_s38.eps

Scheme 38 Synthesis of pyridine-containing structures using acetonitrile (Sakar et al. 2017[197] Salfeena et al. 2016;[198] Barluenga et al. 2008[199])

A one-pot three-component reaction of 2-benzylideneindan-1-ones, acetonitrile, and an arylacetylene using 3 equivalents of boron trifluoride gave N-acetylated indenopyridines and N-acetylated 1,2-dihydropyridines (Scheme 38).[198] Although yields were not excellent in all cases, the method provides highly complex structures in an easy manner.

A cyclization reaction of 7-methoxyhepta-2,4-dien-6-ynoate with acetonitrile promoted by both gold(I) and gold(III) gave pyridine derivatives in 62–75% yields (Scheme 38).[199] Mechanistically, Au(I) inserts at the alkyne allowing for cyanomethylation; this is followed by a hetero-Diels–Alder reaction and aromatization.

2-Phenylisoxazolo[2,3-*a*]pyridinium tetrafluoroborate salt was obtained by peroxide oxidation of 2-(phenylethynyl)pyridine. This salt is susceptible to nucleophilic addition, and by treatment with acetonitrile in the presence of potassium carbonate it gave 2-acetamido-6-(benzoylmethyl)pyridine in 90% yield (Scheme 39).[200]

e0191_s39.eps

Scheme 39 Amidation of a pyridinium salt by acetonitrile

7 Other Cyclization Reactions

7.1 Acetonitrile and α-Haloacetophenones

α-Haloacetophenones are highly reactive compounds that undergo reactions with acetonitrile. Electrochemistry has been employed as a means of forming pyrroles. A magnesium rod was used as the sacrificial anode and a stainless steel grid as the cathode for the reductive electrolysis of anhydrous acetonitrile, the solution of the 3-aminobut-2-enenitrile was added to the α-bromoacetophenone to give pyrrole-3-carbonitriles in 70–83% yields with no trace of the other isomer (Scheme 40).[201]

e0191_s40.eps

Scheme 40 Reaction involving α-bromoacetophenones and acetonitrile (Hamrouni et al. 2016;[201] Garcia Martinez et al. 1992;[202] Bruton et al. 2006[203])

Mixing α-bromoacetophenone with acetonitrile in the presence of triflic anhydride gave 4-bromopyrimidines (Scheme 40).[202] The proposed mechanism involves an initial attack on the ketone moiety giving a nitrilium ion, which reacts with another molecule of acetonitrile.

The reaction of acetonitrile and α,4-dibromoacetophenone gave 4-(4-bromophenyl)-2-methyloxazole in 37% yield (Scheme 40).[203] Acetamide was a much better reagent in this reaction.[204,205] However, it highlights the challenges of using acetonitrile as a reaction medium in transformations with halo ketones.

7.2 Acetonitrile in 1,3-Dipolar Additions

Nitriles reacts with sodium azide to give 2-substituted 1*H*-tetrazoles (Scheme 41). Some of the more recently developed methods in this area include: Cu(II)–NaY zeolite,[206] CoY zeolite,[207] CuO/aluminosilicate,[208] zinc salts,[209] and nanonickel ferrite ($NiFe_2O_4$),[210] while $Et_3N{\cdot}HCl$ has also be employed.[211] DMF is generally used as the solvent. In an extension of this methodology, an alkene was reacted with sodium azide, acetonitrile, and a bromine source to give a 1,5-disubstituted tetrazole;[212] the reaction is thought to proceed via attack of the nitrile nitrogen on the halonium ion followed by a 3+2 addition with the azide.[212,213] Performing this reaction using zinc triflate in combination with *N*-bromosuccinimide and trimethylsilyl azide gave tetrazoles in impressive yields in some cases (Scheme 41).[213] Other alkenes have been reacted this way using $AlCl_3/Br_2$.[214,215]

e0191_s41.eps

Scheme 41 Multicomponent reaction of acetonitrile/azide/alkene to give 5-methyl-1*H*-tetrazoles

Ketones (acetone and acetophenone) and acetonitrile react in the presence of $Fe(NO_3)_3$ or cerium ammonium nitrate to give 1,2,4-oxadiazoles (Scheme 42).[216] The reaction proceeds by nitration to form an α-nitro ketone, and this is then postulated to decompose by elimination of water to yield a nitrile oxide which undergoes 1,3-dipolar addition with acetonitrile.

e0191_s42.eps

Scheme 42 Synthesis of 1,2,4-oxadiazoles from ketones using acetonitrile

7.3 Oxazole Synthesis

Treatment of alkynes with acetonitrile, a Lewis acid, and an oxygen source gives oxazoles (Scheme 43).

e0191_s43.eps

Scheme 43 Examples of oxazole synthesis form alkenes and acetonitrile (Li et al. 2012;[217] Ming et al. 2014;[218] Yagyu et al. 2017;[219] Mallick et al. 2017[173])

During studies of alkyne-alkyne couplings, it was found that the use of acetonitrile as a solvent led to oxazole byproducts. Tuning of the process gave higher yields of oxazoles using 3 equivalents of acetonitrile and 5 equivalents of water, with boron trifluoride as an additive and nitromethane as the solvent (Scheme 43).[217] The substrate scope with respect to the alkyne was evaluated by reacting acetonitrile with ten different diarylacetylenes (72–85% yield) and but-2-yne (43% yield).

The reaction of 1,4-diarylbuta-1,3-diynes with acetonitrile using potassium or cesium hydroxide as a base with 5 equivalents of water and dioxane as the solvent gave 5-styryloxazoles (Scheme 43).[218] Employing symmetrical 1,4-diarylbuta-1,3-diynes gave 5-styryloxazoles in 52–84% yields; the lowest yields were for bromo-, chloro-, and fluoro-substituted derivatives. The reaction of unsymmetrical 1,4-diarylbuta-1,3-diynes resulted in almost equal amounts of the regioisomers.

Alkynes reacted with acetonitrile in the presence of 0.2 equivalents of aryl iodide, an oxidant, and Tf_2NH to give oxazoles with complete regioselectivity in 24–81% yields (Scheme 43).[219] Alternatively 2,4-disubstituted and 2,4,5-trisubstituted oxazole compounds were synthesized from alkynes, acetonitrile, iodosylbenzene, and TfOH or Tf_2NH.[220]■■*OK*■■

3-Arylpropynamines react with acetonitrile using $Yb(OTf)_3$ as the catalyst, 2 equivalents of water and with *N*-iodosuccinimide as a reagent to give trisubstituted oxazoles (Scheme 43).[173] When the aryl moiety in the ynamide was exchanged for a butyl group the reaction failed. There are two proposed mechanisms for the reaction.[173] In the absence of acetonitrile using dichloromethane as the solvent the reaction proceeded to give iodoimidates, while in the absence of NIS *syn*-hydroamidation of the ynamides was observed (see Section 4.5).

7.4 Triazolopyridazines

A 1,2,4-triazolo[1,5-*b*]pyridazine was synthesized from 3-amino-6-chloropyridazine in 63% yield using a cocktail of reagents that included copper(I) bromide, 1,10-phenanthroline, and zinc iodide. On larger scale (1.95 g product) the product was obtained in 75% yield (Scheme 44).[221]■■*OK*■■

e0191_s44.eps

Scheme 44 Synthesis of a 1,2,4-triazolo[1,5-*b*]pyridazine

8 Cyanomethylation of Arenes and Heteroarenes

8.1 Nucleophilic Aromatic Substitution

Electron-deficient aromatic structures containing chloro or fluoro leaving groups undergo substitution with the acetonitrile anion. This reaction is commonly used on N-heterocycles employing strong bases (*n*-BuLi, LDA or LiHMDS, NaHMDS or KHMDS).[222,223] ■■Scheme 45 includes examples for reaction of pyrimidine Ref: Chekmarev et al. 2006;[225], pyridines ref: Fier et al. 2013;[223] Nishigaya et al. 2014;[226] and thiazolopyridine Ref Roberts et al. 2016;[227]. ■■ For highly electron-deficient systems, the displacement of unconventional leaving groups is also observed (Scheme 45).[39] The reaction of 3,5-dichloropyridine-4-carbonitrile gave the expected 3,5-dichloropyridineacetonitrile in 73% yield together with a pyrimidine-substituted pyridine derivative as a byproduct that originated by a process discussed in Section 2.2.

e0191_s45.eps

Scheme 45 Nucleophilic aromatic substitution with acetonitrile (Chekmarev et al. 2006;[225] Fier et al. 2013;[223] Nishigaya et al. 2014;[226] Roberts et al. 2016;[227] Pocci et al. 2001[39]) ■■*ref. 223 mentioned only obliquely in the text, without the Scheme being specifically mentioned*■■ ■■*refs. 225, 226, 227 appear here but are not cited in the text, see changes above*■■

A cyanomethylation process starting from bromoarenes and using a ‘complex base’ consisting of sodium amide and the sodium salt of 2-(2-ethoxyethoxy)ethanol gave arylacetonitriles in 60–85% yields (Scheme 46).[224] It is proposed that this reaction operates via an aryne intermediate. Diarylated compounds were observed as byproducts.

e0191_s46.eps

Scheme 46 Cyanomethylation of aryl bromides (Carre et al. 1989;[224] Wu et al. 1990;[231] Yoshida et al. 2013[232])

Cyanomethylation of other aryl halides has also been reported using sodium amide[228,229] and other aryne precursors.[230] A similar transformation has been performed using potassium in ammonia under irradiation, which possibly occurs through radical intermediates by a photoinduced $S_{RN}1$ mechanism (Scheme 46).[231] A photochemical reaction of benzene and acetonitrile using a Pd/TiO_2 catalyst gave phenylacetonitrile (Scheme 46).[232] The rate-determining step was determined by isotope labelling to be the generation of the cyanomethyl radical. This reaction was extended to the use of aliphatic and aromatic hydrocarbons■■*OK*■■.[233]

Other substitution reactions are more complex. The so-called Catellani reaction[234] allows for both *ipso* and *ortho* functionalization of aryl iodides. For example, 2-iodotoluene reacts with acetonitrile and an alkyl bromide under $Pd(OAc)_2/P(p\text{-tolyl})_3$ catalysis in a reaction in which norbornene is a key reagent to give 2-alkyl-6-methylbenzeneacetonitriles in 32–50% yields (Scheme 47).[235] The reaction is proposed to proceed through a palladacycle and a 2-alkylated 6-methylphenylpalladium compound as key intermediates.■■*OK*■■

e0191_s47.eps

Scheme 47 Catellani reaction performed using acetonitrile (Lei et al. 2016;[235] Shang et al. 2017[236])

A cyanomethylation reaction has been developed based on anchimeric assistance from a sulfoxide group.[236] The reaction proceeds by addition of the acetonitrile nitrogen to the acid activated sulfur atom and then [3,3]-sigmatropic rearrangement followed by re-aromatization leads to cyanomethylated aryl thioethers. The most high yielding transformation was scaled up to 4 g. A challenge with some substrates was the formation of two regioisomeric products (Scheme 47). Thus, this protocol is most useful with symmetrical derivatives and substrates where one of the *ortho*-positions is substituted.

8.2 Cyanomethylation of Heteroarenes

Nitrogen-containing heterocycles without leaving groups are prone to attack at the *ortho* and *para* positions. Acridine was cyanomethylated in 78% yield using sodium amide as the base followed by a water quench (Scheme 48).[237] By a totally different strategy, quinoline, for example, was cyanomethylated in an electrochemical reaction, which is likely to operate by a radical-type mechanism (Scheme 48).[238] N-Heterocycles can also be activated as electrophiles by N-arylation via benzynes. In the presence of acetonitrile under basic conditions isoquinoline was both N-arylated and cyanomethylated in 85% yield (Scheme 48).[239] 2-Arylimidazo[1,2-*a*]pyridines have also been coupled with acetonitrile employing ferrocene as the catalyst and dicumyl peroxide as an oxidant (Scheme 48).[240] The proposed mechanism attack of the heterocycle by a cyanomethyl radical, followed by hydrogen abstraction resulting in rearomatization.[240] Another route for the cyanomethylation of this heterocycle employed bromoacetonitrile and photocatalysis.[241] A one-pot procedure for the reactions of indoles with acetonitrile involved homodimerization of the indoles followed by cyanomethylation catalyzed by TEMPO and $Pd(OAc)_2$ (Scheme 48).[242] Mechanistic details are unknown; however, it is proposed that dimerization occurs prior to cyanomethylation.

e0191_s48.eps

Scheme 48 Cyanomethylation of heteroarenes (Levine et al. 1974;[237] ■■*OK*■■ Windeck et al. 1996;[238] Jeganmohan et al. 2006;[239] Su et al. 2017;[240] Deng et al. 2017[242])

9 Acetylation of Arenes Using Acetonitrile

9.1 Hoesch Reaction

Electron-rich arenes, typically containing phenolic, ether, or amine substituents can be acetylated using acetonitrile in the Hoesch reaction.[243] Various Lewis acid catalysts can be used (Scheme 49).[244–249] The moderate yields in some examples are due to formation of several regioisomeric products.[250]

e0191_s49.eps

Scheme 49 Examples of the Hoesch reaction (Zhang et al. 2017;[245] Dohi et al. 2013;[246] Scott et al. 2011;[247] Zhou et al. 2010;[248] Raboisson et al. 2008[249])

9.2 Other Acetylation Reactions of Arenes

Grignard-type reactions are well known with nitriles and give alkyl aryl ketones as the products. This transformation is seldom performed with acetonitrile, probably because the products are more easily obtained by other methods. One example, however, is the acetylation of indeno[1,2,3-*cd*]pyrene (Scheme 50).[251]

e0191_s50.eps

Scheme 50 Acetylations of arenes using acetonitrile (Minabe et al. 1989;[251] Hsieh et al. 2012;[252] Zhou et al. 2004;[253] Wang et al. 2013;[259] Skillinghaug et al. 2014;[260] Zhou et al. 2015[258]) ■■*ref. 259 appears here but is not cited in the text, see below, ref 260 here should be 257* Skillinghaug B., Skoeld C., Rydfjord J., Svensson F., Behrends M., Saevmarker J., Sjoeberg P. J. R., Larhed M.; *J. Org. Chem.*; **2014**, *79*: 12018■■

The nickel-catalyzed acylation of aryl iodides gives acetophenones in 63–94% isolated yields (Scheme 50).[252] The ligand used was 1,3-bis(diphenylphosphino)propane (dppp) and metallic zinc was required to reduce Ni(II) to Ni(0). The proposed mechanism involves oxidative addition of the aryl iodide to Ni(0) followed by coordination and insertion of acetonitrile.

Protocols for the formation of alkyl aryl ketones have also been developed by the Pd-catalyzed C–H activation of an arene using $Pd(OAc)_2$/DMSO/TFA followed by carbopalladation of the nitrile

(Scheme 50);[253,254] in a reaction with tetraphenylene as the arene, $Pd(OAc)_2$/DMSO/TFA was used with CH_2Cl_2 as an additive.[255] Arylboronic acids also couple with acetonitrile to give methyl ketones ■■insert ref 159: Wang et al. 2013;[259] ■■. The yield was found to depend on the palladium source, the acid additive, and the solvent. This reaction also proceeds well with potassium trifluoro(phenyl)borate salts.[256]

Sodium arylsulfinates couple with acetonitrile using palladium(II) trifluoroacetate and 6-methyl-2,2′-bipyridyl as the ligand in the presence of TFA (Scheme 50).[260]■■ should be re 257 *Use:* Skillinghaug B., Skoeld C., Rydfjord J., Svensson F., Behrends M., Saevmarker J., Sjoeberg P. J. R., Larhed M.; *J. Org. Chem.*; **2014**, *79*: 12018,■■ The reaction is likely to proceed through intermediates similar to those of other cross-coupling reactions. Using this method, chlorinated arylsulfinates gave low yields probably due to competing coupling reactions. This transformation was also investigated in flow mode.[257]■■should be 260: *Use* Skillinghaug B., Rydfjord J., Saevmarker J., Larhed M.; *Org. Process Res. Dev.*; **2016**, *20*: 2005■■
Aromatic structures containing a pyridine, pyrimidine, or diazole substituent were acetylated with acetonitrile using a manganese catalyst to give aryl methyl ketones in 42–88% yields (Scheme 50).[258] The reaction is proposed to proceed via two manganacycles.

Aryne–zirconocene complexes can give rise to interesting functionalization reactions. The reaction of bromoarenes with *n*-BuLi gave an aryne that formed a complex with zirconocene, this then hydrolyzed to give the aryl methyl ketone product;[261,262] this approach is useful as it provides products different from those of the Friedel–Crafts acylation. Additionally, by changing the electrophile both iodinated products[261–263] and benzo[*d*]isothiazoles[261] were formed (Scheme 51).

e0191_s51.eps

Scheme 51 Functionalization of aromatics via an aryne–zirconocene complex

10 Synthesis of *N*-Arylacetamides

Generally (hetero)arenes■■*OK*■■ react with acetonitrile to form cyanomethylated compounds (Section 8) or aryl methyl ketones (Section 9). However, if aromatic cation character is generated, the acetonitrile nitrogen can act as a nucleophile, forming an *N*-arylacetamide. These products are more usually obtained by the Buchwald–Hartwig amidation, or by the conventional acetylation of anilines, so the practicality of some of these methods is questionable.

A copper-catalyzed protocol converted aryl halides and acetonitrile into *N*-arylacetamides (Scheme 52).[264] The process utilizes *N*,*N*′-dimethylethylenediamine (DMEDA) as the Cu ligand and a mixture of KOH and Cs_2CO_3 as a base. In the proposed mechanism, acetonitrile is hydrolyzed to an amide anion which coordinates to copper. This complex undergoes oxidative addition with the aryl halide. Finally, reductive elimination gives the *N*-arylacetamide. This protocol was later modified for the *para*-selective synthesis of *N*-arylacetamides.[265]

e0191_s52.eps

Scheme 52 Routes to *N*-arylacetamides using acetonitrile (Xiang et al. 2013;[264] Prakash et al. 2009;[266] Abitelli et al. 2012[271])

Treatment of arylboronic acids with xenon difluoride resulted in the production of *N*-arylacetamides as the main product (Scheme 52).[266] The highest yield was seen for the 4-methoxyphenyl derivative, while 4-nitrophenyl- and pentafluorophenylboronic acid were less reactive. The proposed mechanism explains this in terms of the ability of the group to stabilize radical cation formation. The chemistry requires dry-box handling and in a cautionary note the mixing of XeF_2 and arylboronic acid in dry form even under argon leads to spontaneous combustion. In the *ipso*-fluorination of aryltrimethylsilanes using xenon difluoride, the reaction was completely inhibited when the reaction was performed in acetonitrile, but instead acetanilides were formed■■*OK* ■■.[267] A less hazardous approach from arylboronic acids is the Cu-catalyzed method starting from phenylboronic acid and

acetonitrile with $CuBr_2$, potassium *tert*-butoxide, and *t*-BuOH as the catalyst/reagent/solvent system to give *N*-phenylacetamide in 79% yield.[268].

Aromatic cations can be generated under photochemical conditions. Investigations have shown that the reactivity of aromatic cations depends on whether the singlet or triplet state is formed. The singlet state preferably reacts with lone pair nucleophiles,[269,270] while the triplet state reacts with π-bond nucleophiles or by homolytic hydrogen abstraction. The silyl group has been found to stabilize the singlet state of methoxy-substituted aromatics,[270] and for such compounds nucleophile addition can be performed with acetonitrile. The reaction of 4-methoxy-2-(trimethylsilyl)benzene derivatives with acetonitrile/acetone/water was found to be dependent upon the leaving group (Scheme 52).[271]

The electrochemical acetamidation of benzene, benzoic acid, ethyl benzoate, and acetophenone was carried out using acetonitrile and a platinum electrode; no yields were reported.[272] The proposed mechanism involves the formation of a radical cation, which is attacked by the acetonitrile nitrogen. The formation of the *ortho*-isomer was favored in a ■■*ortho/para*■■9:1 ratio, which is explained by hydrogen bonding.

4+2 Cycloadditions of tetraynes in the presence of silver salts using acetonitrile as solvent gave highly functionalized benzene derivatives, e.g. reaction of *N*,*N*-bis[5-(trimethylsilyl)penta-2,4-diynyl)toluenesulfonamide to give a silylated isoindole in 72% yield (Scheme 53).[273] It is proposed that after the cycloaddition silver activates the aryne intermediate for attack by acetonitrile in a Ritter-type fashion.

e0191_s53.eps

Scheme 53 4+2 Cycloaddition followed by amide formation

11 Cyanation Using Acetonitrile as a Cyanide Source

In recent years there has been an interest in finding alternative reagents for cyanation reactions.[274,275] Although the CH_3–CN bond in acetonitrile is fairly strong (121 kcal/mol[276]) the use of Cu catalysis has paved the way for new transformations.[277] Additionally, gold cyanides are produced both under photochemical oxidative conditions and employing Fenton's reagent using acetonitrile as the cyanide source.[278,279]

Heteroaryl-substituted arenes undergo cyanation of the arene by anchimeric assistance from the nearby heteroatom of the heteroarene (Scheme 54).[280] Copper(II) mediated cleavage of acetonitrile assisted by hexamethyldisilane was used as the source of cyanide. The yield and product ratio of the mono- and dicyanated products varied without any apparent trend. The methodology was also useful for the cyanation of *N*-pyrimidyl and *N*-pyridylindoles (Scheme 54).

e0191_s54.eps

Scheme 54 Cyanation of aromatic using acetonitrile as cyanide source (Kou et al. 2013;[280] Zhao et al. 2015;[281] Zhu et al. 2015;[283] Xu et al. 2015[284])

Indoles■■*only indoles, well adaption to other substrates is cited below*:■■ can also be cyanated by a process that does not require the presence of Cu coordinating groups in the arene.[281] Initial iodination of the indole by NIS followed by cyanation under Cu catalysis, $Cu(OAc)_2$/1,10-phenanthroline with a reaction time of 2–4 days gave the cyanated products in 37–88% yields (Scheme 54). ■■Remove this sentence, it is covered by the last reference: Pyrrolopyridines were also cyanated■■. This reaction was extended to arenes,[282] and aryl- and heteroarylboronic acids were also cyanated in good yields (Scheme 54).[283]

Cyanation of arenediazonium ions using acetonitrile as the cyanide source utilized 10% $PdCl_2$ as catalyst and silver oxide as an additive; the yield of cyanated product depended on the substitution pattern, in part due to side reactions including biaryl and acetamide formation (Scheme 54).[284] Transformation of a bromine-substituted compound gave a moderate yield, which can be explained by

competing oxidative addition. Moreover, unsubstituted and methylated arenediazonium ions gave the *N*-acetylanilines as the major product (see Section 10). Sulfoximines underwent Cu-catalyzed *N*-cyanation under oxidative conditions.[285]

On one hand, these new transformations are interesting from a safety perspective. Of equal importance is that extra care should be observed when treating nitriles under oxidative conditions, especially in the presence of copper, gold, or platinum.

12 When To Avoid Acetonitrile as a Solvent

As acetonitrile is a significant solvent in organic synthesis, it is of uttermost importance to have some basic knowledge of its reactivity in different settings. Table 2 highlights conditions where there is a risk of byproduct formation caused by the use of acetonitrile as solvent.

Table 2 Potential Condition for Byproduct Formation Using Acetonitrile as a Solvent

Type of transformation	Conditions	Side reactions
alcoholysis/transesterification of esters	protic acids	imidates
alkene halohydrogenation	HBr/HCl	Ritter reaction
alkyne chemistry	Co catalysis Cu catalysis	pyridines oxazoles
amide chemistry	Pd(II) catalysis	nitrile formation
aromatic chemistry	Pd catalysis	acetylation of aromatics
aromatic substitution	base	cyanomethylation
boronic acids (aryl)	Pd catalysis	cyanomethylation
aziridine chemistry	Lewis acids	imidazolines etc.
α-bromo ketone chemistry	various	heterocycles
enolate chemistry	base	cyanomethylation of carbonyl
epoxide opening	Lewis acid base	oxazolines cyanomethylation
esterification	protic acids	imidates
fluorination	F_2/H_2O	strong oxidant formed
fluorination of alkenes	Selectfluor	1,2-fluoroamides
Friedel–Craft	Lewis acid	acetylation of aromatics
Grignard reactions	standard	acetylation of aromatics
halogenation	HX/X_2, light	haloacetonitriles
heteroaromatic chemistry	base, electrochemistry or oxidative conditions	cyanomethylation
hydrolysis (esters, acetals, amides, nitriles)	protic acids/water	acetamide/acetic acid
oxidation	H_2O_2 Cu/peroxides	efficient epoxidation reagent formed cyanide formation

photochemistry/radical chemistry	light/sensitizer or peroxides	cyanomethylation of aromatics/alkenes/alkynes pyridines from alkynes risk of cyanide formation
reduction	various	ethylamine, acetaldehyde, diethylamine, triethylamine
silylations	TMSCl/trace water	acetamide
sodium azide reactions	NaN_3	1*H*-tetrazoles

13 Conclusion

The cyano group is a commonly encountered functionality in drugs and materials, and a highly useful intermediate for further synthesis. This review focuses on the use of acetonitrile for the introduction of nitriles.

Employing classical protocols, alkyl halides, epoxides, and carbonyl compounds can be cyanomethylated under basic conditions. Metal-catalyzed processes have also been developed that are handy for base-sensitive aldehydes, ketones, and imines. Acidic conditions promote the acetonitrile nitrogen as a nucleophile by increasing the electrophilicity of the reacting species. Ritter-type reactions occur with alkenes and alcohols to give acetamides, epoxides are converted into oxazolines and while ring opening of aziridines yields imidazolines. Acetonitrile can also be employed to prepare other heterocyclic scaffolds including pyridines, pyrimidines, pyrroles, tetrazoles, and oxazoles.

Protocols for the cyanomethylation of alkenes and alkynes under oxidative or photochemical have been developed. Moreover, by careful planning, these transformations can be used to induce radical-type cyclizations leading to complex products.

Acetonitrile is also utilized for the functionalization of aromatic systems. In basic media, cyanomethylations occur on aryl halides by various mechanisms. A special variant includes the palladium-catalyzed Catellani reaction, which simultaneously installs both the cyanomethyl group and another alkyl group in the same process. The cyanomethylation of N-heterocycles has also been developed involving both basic and radical-type conditions.

Acetylation of arenes involving acetonitrile includes the Lewis acid catalyzed Hoesch acylation of electron-rich arenes, reaction with Grignard reagents, Pd-catalyzed processes from arenes, arylboronic acids, or sodium arylsulfinates.

Under oxidative conditions, typically involving peroxides and copper catalysis, cyanide or a cyanide equivalent is generated. This provides a convenient and safe source of cyanide, and protocols for the cyanation of arenes and heteroarenes have been developed. Obviously, care should be taken when reacting acetonitrile under conditions capable of splitting its C–C bond.

A shortcoming in some of the new methodologies developed is the relative high metal catalyst loading. These issues must be resolved for the processes to be industrial relevant. Hopefully, the future will also provide improved methods for asymmetric cyanomethylation of aldehydes, ketones, and imines.

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