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Recent advances and prospects in the palladium-catalyzed cyanation of aryl halides

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Aryl nitriles are compounds with wide significance. They have made their own space in various sectors including pharmaceuticals, industries, natural product chemistry, and so on. Furthermore, they are also key intermediates in various transformations in organic chemistry. Transition metal-catalyzed cyanation reactions have proved to be a better replacement for the existing traditional synthetic strategies for aryl nitriles. Palladium is one of the most studied transition metals other than copper and nickel owing to its wide functional group compatibility and catalytic efficacy. There have been drastic developments in the field of palladium-catalyzed cyanation since its discovery in the 1973. This review summarizes the recent developments in the palladium-catalyzed cyanation of aryl halides and covers literature from 2012–2020.

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1 Introduction

Cyanation in organic synthesis is the introduction of a cyanide group in to a reacting molecule resulting in the formation of diverse cyanides or otherwise called nitriles. Aryl nitriles are privileged compounds finding wide significance in various disciplines such as pharmaceuticals,^{1,2} industry,³ agrochemicals,⁴ *etc.* They have been building blocks in various natural

products, dyes and pigments. Some pharmaceutically relevant molecules containing nitrile moieties are portrayed in Fig. 1. The major highlight of nitriles lies in the fact that they can undergo smooth transformations into various other functional scaffolds like-aldehydes, amides, carboxyls, amidines, esters *etc.*⁵ This has been suitably exploited to synthesize and transform various molecules with structural complexity and diversity.

Pongratz in 1927, was the first to develop a strategy towards cyanation reactions.⁶ From then, cyanation achieved significant relevance and gained much acceptance. Some of the conventional synthetic methodologies towards aryl nitriles involved, the Sandmeyer reaction^{7,8} from anilines, the Rosenmund-von Braun reaction^{9,10} from halides and industrial ammoxidation reactions.¹¹ However, these reactions involved harsh conditions

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like high temperatures and utilized almost stoichiometric amounts of CuCN leading to the generation of heavy metal wastes in equimolar quantities. Hence, the situation demanded a much better alternative for the cyanide synthesis apart from these.

In this scenario, transition-metal catalyzed syntheses of aryl cyanides from aryl halides were explored and were found to be highly acceptable. Among them palladium,^{12–15} nickel^{16–18} and copper^{19–21} catalyzed cyanation have been well explored. Takagi *et al.* in 1973 introduced the first palladium-catalyzed cyanation from bromo and iodoarenes using potassium cyanide.^{22,23} They employed palladium(II) acetate/palladium(II) cyanide as the catalyst in DMF at 140–150 °C for 2–12 h. Later on, explorations on cyanations catalyzed by palladium were carried out extensively and above all, these investigations were the best in affording benzonitriles efficiently. Palladium has always intrigued scientists by virtue of its applications in the field of industry and laboratory.²⁴ With this aspect, they have gained a command over other transition metals. Palladium enables an easy pathway for many transformations which are otherwise difficult to occur by the means of conventional strategies.²⁵ It is a unique catalyst and is incorporated in homogeneous as well as heterogeneous catalysis. It catalyzes different organic reactions such as Heck,²⁶ Stille,²⁷ Tsuji–Trost,²⁸ Suzuki,²⁹ Wacker,³⁰ Sonogashira³¹ *etc.* Palladium is

usually associated with mild reaction conditions and could tolerate a range of functional groups.³² Also they exhibit good endurance towards air and moisture. The mechanisms of palladium are well comprehended and hence are very convenient. Palladium as palladium(II) is mostly chosen as the substrate owing to its stability. These are then reduced to palladium(0) motifs to carry out the catalytic action. CuCN, Zn(CN)₂, CUSCN, K₄[Fe(CN)₆], KCN, TMSCN and NaCN are the different metal and metalloid cyanation media, and cyanohydrin, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS), acetone cyanohydrin, aminoacetonitrile, benzyl cyanide, α -iminonitrile, ethyl cyanoacetate, formamide, hexamethylenetetramine and cyanuric chloride formed the class of organo cyanation motifs.³³

In 2003 and 2011, Beller *et al.* published two reviews solely on palladium catalyzed cyanation of aryl halides.^{34,35} Due to its wide applicability and importance, we intend to summarize the recent advances in palladium catalyzed cyanation of aryl halides using various cyanation strategies from 2012–2020. A model scheme for the palladium catalyzed cyanation of aryl halides is depicted in Scheme 1. For more clarity and simplicity, the review is classified based on the cyanating medium as reactions with metal-based cyanide sources and reactions with organic cyanide sources.



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research under the guidance of Dr G. Anilkumar in the School of Chemical Sciences, Mahatma Gandhi University, Kottayam.



Gopinathan Anilkumar was born in Kerala, India and took his PhD in 1996 from Regional Research Laboratory (renamed as National Institute for Interdisciplinary Science and Technology NIIST-CSIR), Trivandrum with Dr Vijay Nair. He did postdoctoral studies at University of Nijmegen, The Netherlands (with Professor Binne Zwanenburg), Osaka University, Japan (with

Professor Yasuyuki Kita), Temple University, USA (with Professor Franklin A. Davis), Leibniz-Institut für Organische Katalyse (IfOK), Rostock, Germany (with Professor Matthias Beller) and Leibniz-Institut für Katalyse an der Universität (LIKAT), Rostock, Germany (with Professor Matthias Beller). He was a senior scientist at AstraZeneca (India). Currently he is Professor in Organic Chemistry at the School of Chemical Sciences, Mahatma Gandhi University in Kerala, India. His research interests are in the areas of organic synthesis, medicinal chemistry, heterocycles and catalysis, particularly on ruthenium, iron, zinc, copper, manganese, cobalt and nickel catalyzed reactions. He has published more than 100 papers in peer-reviewed journals, 7 patents, three book chapters and edited a book entitled Copper Catalysis in Organic Synthesis (Wiley, 2020). He has received Dr S. Vasudev Award from Govt. of Kerala, India for best research (2016) and Evonik research proposal competition award (second prize 2016). His h-index is 29.



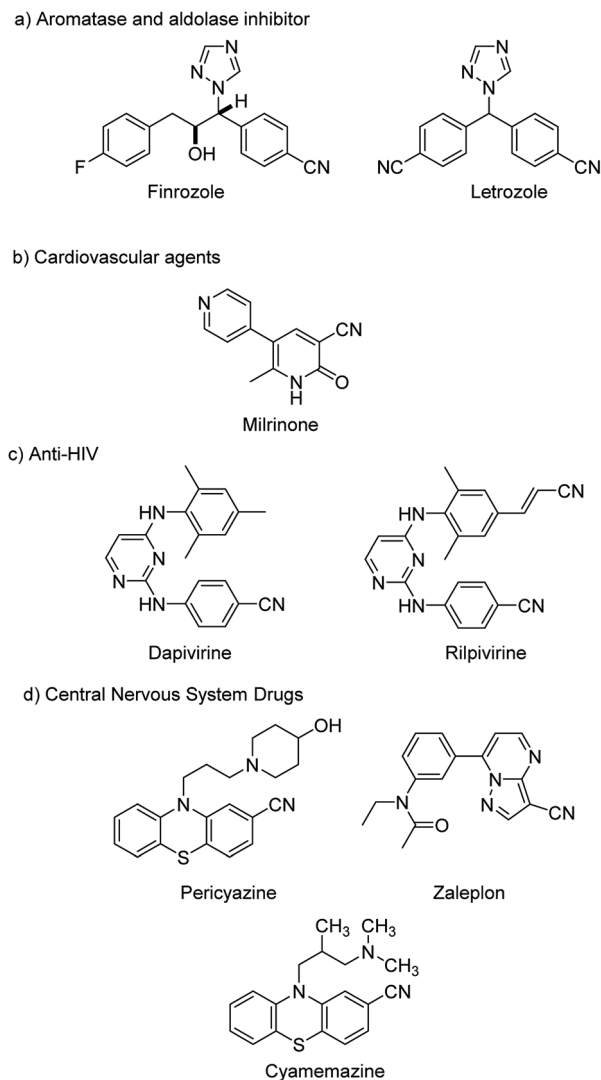
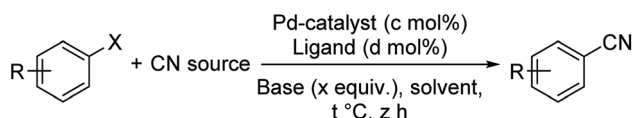


Fig. 1 Pharmaceutically significant motifs containing nitriles.

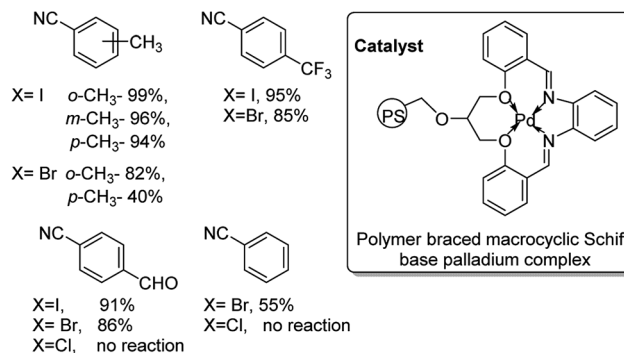
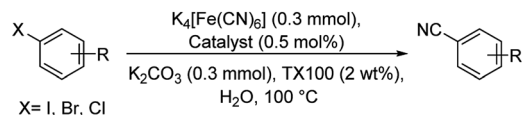
1.1. Reactions with metal-based cyanide sources

1.1.1. Potassium hexacyanoferrate. From 2013–2020 various investigations were carried out on the synthesis of aryl cyanides using potassium hexacyanoferrate as the metal cyanating medium. These approaches are discussed in brief here.

In 2013, palladium as a polymer aided macrocyclic palladium complex was utilized for the synthesis of various benzonitriles from a range of iodo and bromo arenes.³⁶ The reaction was performed in water in the presence of Triton X-100 as non-ionic surfactant and avoided the use of any organic solvents (Scheme 2). The synthesis was compatible with the electronic



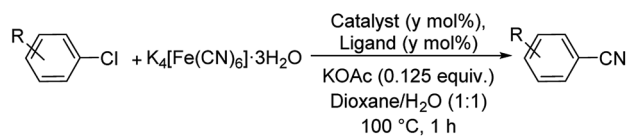
Scheme 1 General reaction displaying the formation of aryl cyanides from haloarenes.



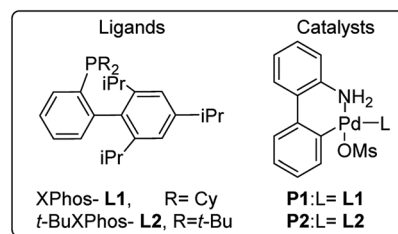
Scheme 2 Water-mediated synthesis of benzonitriles using polymer braced macrocyclic palladium complex.

effects and the steric effects exerted by the substituents on the aryl halides. Aryl chlorides were totally unreactive towards this reaction. Moreover, the catalyst was found to display exceptional recyclability, retaining its efficiency at the same time.

XPhos (**L1**) and *t*-BuXPhos (**L2**) were chosen as the best ligands forming two palladacycle precursor catalysts-**P1** and **P2** and cyanation of aryl and heteroaryl halides using $\text{K}_4[\text{Fe}(\text{CN})_6]$ in the presence of these palladacycle precatalysts was revealed by Buchwald and co-workers.³⁷ Aryl chlorides with substitutions by COOEt, OMe, Me, COMe, NH₂, SO₂NH₂, OH *etc.* underwent the reaction furnishing excellent yields (Scheme 3). In addition,

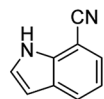
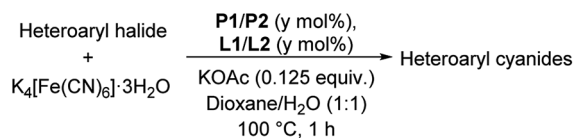


| R | Catalyst/Ligand/mol% | Yield (%) |
|-----------------------------------|------------------------|-----------|
| 4-COOEt | P1/L1 /0.2 mol% | 97 |
| 4-OMe | P1/L1 /0.4 mol% | 95 |
| 2,6-diMe | P1/L1 /0.6 mol% | 90 |
| 4-CONH ₂ | P2/L2 /0.8 mol% | 90 |
| 3-NH ₂ | P2/L2 /0.8 mol% | 91 |
| 4-OH | P2/L2 /3 mol% | 85 |
| 4-SO ₂ NH ₂ | P2/L2 /0.7 mol% | 92 |

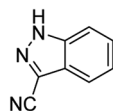


Scheme 3 Synthesis of aryl cyanides from aryl chlorides.

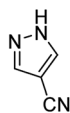




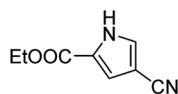
P1/L1/0.7 mol% : X=Cl : 95%



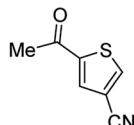
P2/L2/4 mol% : X=Cl : 94%



P2/L2/1 mol% : X=Br : 93%



P2/L2/1.4 mol% : X=Br : 92%



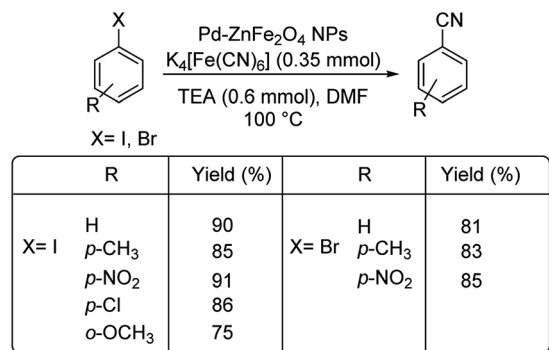
P2/L2/4 mol% : X=Cl : 91%

Scheme 4 Synthesis of heteroaryl cyanides from heteroaryl halides.

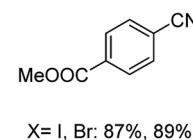
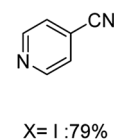
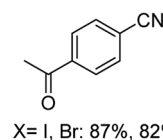
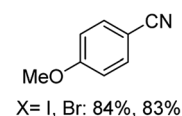
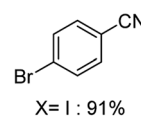
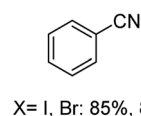
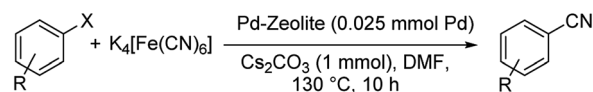
synthesis of various heteroaryl cyanides with indole, pyrrole, thiophene, pyrazole, indazoles *etc.* backbones were also carried out easily (Scheme 4).

Interestingly, palladium reinforced on zinc ferrite nanoparticles (Pd-ZnFe₂O₄) was investigated for its ability to catalyse cyanation of diverse aryl iodides and bromides.³⁸ The reaction was conducted using 10 mg catalyst, 0.35 mmol K₄[Fe(CN)₆] and 0.6 mmol TEA (triethylamine) in DMF at 100 °C (Scheme 5). It was observed that various aryl bromides and iodides with substitutions by H, NO₂, OCH₃, CH₃ and Cl, could endure the reaction well furnishing a maximum yield of 91%.

Pd-beta zeolite catalyzed synthesis of aryl cyanides using K₄[Fe(CN)₆] was developed by Sajadi and co-workers.³⁹ Zeolites are crystalline, microporous, hydrated aluminosilicates finding wide applications in catalysis,⁴⁰ surface chemistry⁴¹ and industry.⁴² Beta-zeolites are a class of zeolites acting as catalyst in various chemical transformations. The efficiency lies in the



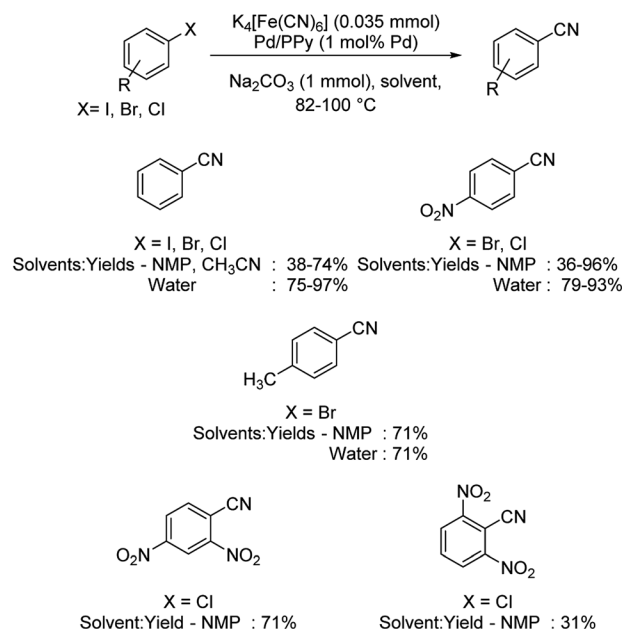
Scheme 5 Palladium–zinc ferrite nanoparticles catalyzed synthesis of aryl cyanides.



Scheme 6 Synthesis of diverse benzonitriles using Pd-beta zeolite as the catalyst at 130 °C.

high Si/Al ratio, thermal stability, large pore size and higher acidity of the zeolites. Suitable tuning of these beta-zeolites with palladium generated a highly efficient catalyst. A range of aryl bromides and iodides with different functional groups reacted well yielding the desired benzonitriles effectively (Scheme 6). 79% to 91% of overall yield of the product was reported.

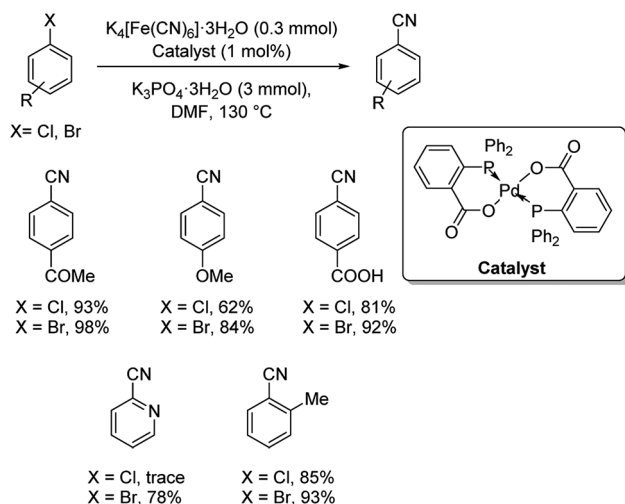
Magdesieva *et al.* in 2014 discussed the cyanation of haloarenes using a novel Pd/PPy (palladium–polypyrrole) nanocomposite.⁴³ Benzonitriles were effectively synthesized using K₄[Fe(CN)₆] in different organic solvents (Scheme 7). The reaction was also carried out using water as the solvent. In either of the cases, the presence of electron-withdrawing moieties improved the yields more than that by those with electron-donating ones. Contradiction to this, nitro and dinitro substitutions on aryl chlorides imparted lower yields. The major



Scheme 7 Aryl halide cyanation employing organic solvents and water as the solvent media.



Review

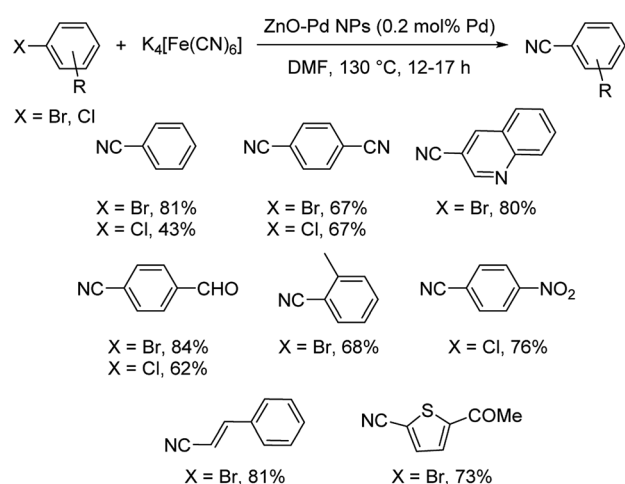


Scheme 8 Substrate scope studies towards the synthesis of various aryl cyanides.

highlight of the reaction is that even aryl chlorides, which are usually unreactive, also underwent the reaction, though the yield was only moderate.

P–O bidentate chelate palladium complex catalyzed synthesis of benzonitriles using $K_4[Fe(CN)_6] \cdot 3H_2O$ was put forward.⁴⁴ Cyanation of various aryl bromides and inert aryl chlorides were carried out efficiently by this strategy (Scheme 8). Presence of activating groups improved the yields of the reaction on comparison with electron-donating groups. Also, the reaction was extended to the cyanation of 2-bromopyridine and 2-chloropyridine, where 78% yield was obtained in the former case and traces in the latter one.

Palladium nanoparticles braced by zinc oxide as a potential catalyst for the cyanation of aryl bromides and chlorides was disclosed by Ranu *et al.*⁴⁵ This reaction employed no additives, ligands or base and still could achieve benzonitriles in moderate to good yields. The cyanation was performed using

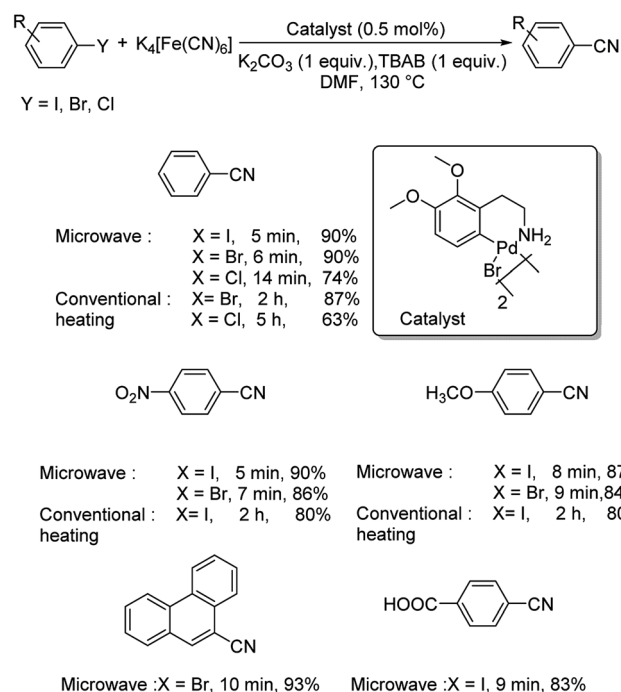


Scheme 9 Palladium supported on zinc oxide nanoparticles-catalyzed cyanation of aryl bromides and chlorides.

$K_4[Fe(CN)_6]$ in DMF solvent at 130 °C for 12–17 h (Scheme 9). Heteroaryl as well as styryl derived bromides could also undergo the reaction smoothly. High catalytic recyclability and low loading of catalyst are the highlights of the protocol.

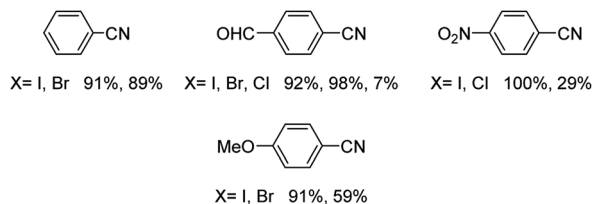
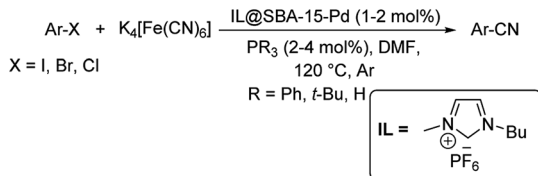
A microwave-assisted synthesis of aryl cyanides using a CN-dimeric *ortho*-palladated complex-[Pd{C₆H₂(CH₂CH₂NH₂)(OMe)_{2,2,3}(*m*-Br)₂}]₂ was also reported.⁴⁶ The cyanation of diverse aryl halides were performed using 0.5 mol% of catalyst, 22 mol% of $K_4[Fe(CN)_6]$, 1 equiv. of K_2CO_3 , 1 equiv. TBAB in DMF at 130 °C (Scheme 10). Under the microwave condition (600 W), a maximum of 93% of overall yield was obtained with varying reaction times for various aryl halides. Aryl chlorides furnished lower yields in comparison to aryl iodides and bromides and at a slower pace. Moreover, the reaction was also carried out under conventional heating conditions, where the yields obtained were slightly lower and the duration of reaction was higher with respect to microwave heating.

Ionic liquids (ILs) have always gained keen attention due to its green character. This insight led scientists to employ them in various chemical transformations. Ionic liquid assisted cyanation of diverse aryl halides was effected by Karimi *et al.*⁴⁷ Here, palladium was functionalized by SBA-15 (mesoporous silica) and was associated with ionic liquid to develop the catalyst for the cyanation reaction. The ionic liquid utilised for the reaction was 1-butyl-3-methylimidazolium hexafluorophosphate (Scheme 11). The IL stabilizes the Pd moiety and at the same time it also prevents their agglomeration and hence, improving the catalytic recyclability. Aryl bromides with a range of substitutions by electron-donating and electron-withdrawing groups underwent the reaction to furnish aryl cyanides in



Scheme 10 Investigations on cyanation of aryl halides catalyzed by CN-dimeric *ortho*-palladated complex via microwave and conventional heating.

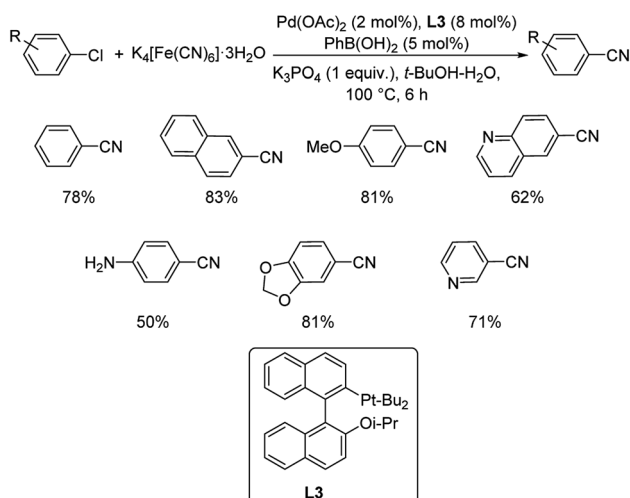




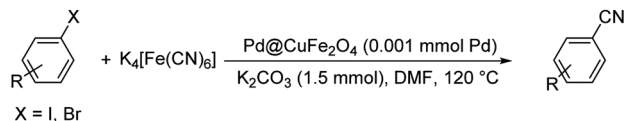
Scheme 11 IL@SBA-15-Pd catalyzed cyanation of aryl halides and its substrate scope studies.

good to excellent yields. Cyanation of aryl chlorides was also carried out, but the yield reported was very low. The studies on the activity of the catalyst revealed that, the superior catalytic efficiency was due to the ionic liquid which was present in the passages of mesoporous silica. The imidazolium ionic liquids could undergo phase transfer, which was exploited for faster penetration of $\text{Fe}(\text{CN})_6$ into the pores of the system. Thus, in the vicinity of Pd NPs, a highly concentrated site was accomplished which resulted in the higher activity of the catalyst.

Aryl chlorides have been mostly inert and unreactive towards cyanation reactions. So an approach for synthesis of aryl cyanides from unreactive chloroarenes *via* catalysis by palladium acetate in the presence of 2-di-*tert*-butylphosphino-2'-isopropoxy-1,1'-binaphthyl (L3) was disclosed by Xie and co-workers.⁴⁸ The cyanation medium employed was potassium hexacyanoferrate in 1 : 1 *t*-BuOH-H₂O (Scheme 12). Electron-donating groups on the aryl chloride were well tolerated by the reaction. Heterocyclic substrates also underwent the reaction giving good results. The activated palladium centre was



Scheme 12 Optimized reaction condition for the synthesis of various aryl cyanides catalyzed by $\text{Pd}(\text{OAc})_2$.



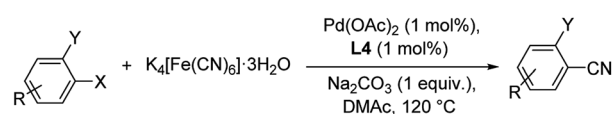
| X | R | Yield (%) | X | R | Yield (%) |
|---|-------------------|-----------|----|-------------------|-----------|
| I | H | 97 | Br | 4-NO ₂ | 78 |
| | 4-OMe | 94 | | 4-CHO | 71 |
| | 4-NO ₂ | 98 | | 4-Me | 73 |
| | 4-Cl | 98 | | 4-Cl | 75 |
| | 3-Me | 95 | | | |
| | 4-CHO | 95 | | | |

Scheme 13 Cyanation of haloarenes with $\text{K}_4[\text{Fe}(\text{CN})_6]$ in the presence of $\text{Pd@CuFe}_2\text{O}_4$.

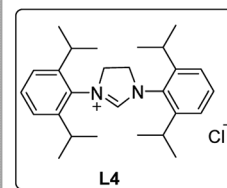
stabilised by the hemi-labile coordination of oxygen atom on the ligand with palladium. This assisted the oxidative addition of aryl chloride. At a later stage, the bulkiness of the ligand eased the reductive elimination to form the aryl cyanides.

Palladium nanoparticles anchored on (3-aminopropyl) triethoxysilane-modified copper ferrite as an efficient catalyst for the cyanation of bromo and iodo arenes was disclosed in 2015.⁴⁹ Diverse aryl iodides and bromides were analysed to provide very good results (Scheme 13). Moreover, due to the higher reactivity of Ar-I over Ar-Br, excellent yields were obtained in the former case than in the latter. The yields reported were more when the *para*-position of the aryl halides was substituted with electron-withdrawing groups than when it was substituted with electron-donating ones.

A combination of palladium and N-heterocyclic carbene (NHC) was employed as catalyst for the mono and dicyanation of various haloarenes by Shi *et al.*⁵⁰ The optimised condition was 1 mol% $\text{Pd}(\text{OAc})_2$, 1 mol% ligand L4 (NHC), 0.25 equiv. $\text{K}_4[\text{Fe}(\text{CN})_6] \cdot 3\text{H}_2\text{O}$, 1 equiv. Na_2CO_3 in DMAc (*N,N*-dimethylacetamide) at 120 °C (Scheme 14). Smooth conduct of the reaction was observed with electron-deficient and electron-rich aryl iodides. The reaction was tolerant to the steric effects offered by the substituents. The reaction was also amenable to aryl bromides as well as aryl chlorides, though the latter afforded

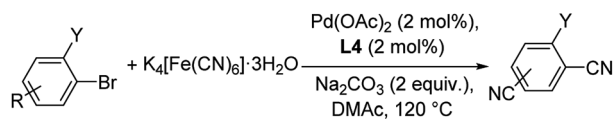


| X | R | Y | Yield (%) |
|----|-------------------|-----------------|-----------|
| I | H | H | 71 |
| I | 2-OMe | H | 90 |
| I | 3-CF ₃ | NH ₂ | 92 |
| Br | H | H | 66 |
| Br | 4-NO ₂ | H | 72 |
| Br | 2-F | H | 86 |
| Cl | 4-COMe | H | 63 |
| Cl | 4-NO ₂ | H | 46 |



Scheme 14 One pot mono-cyanation of various aryl halides using N-heterocyclic carbene and palladium.



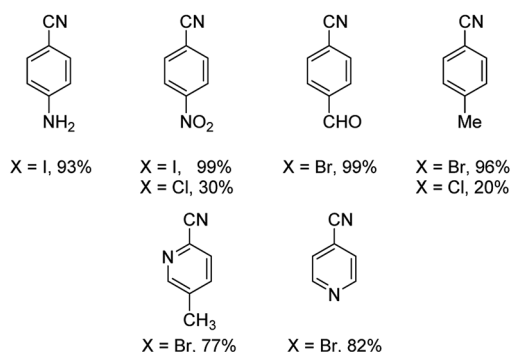
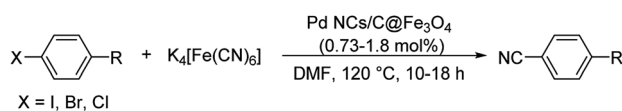


| R | Y | Time (h) | Yield (%) |
|------|---|----------|-----------|
| 2-Br | H | 10 | 86 |
| 2-I | H | 3 | 89 |
| 3-Br | H | 5 | 89 |
| 4-Br | F | 12 | 80 |
| 4-I | H | 1 | 90 |

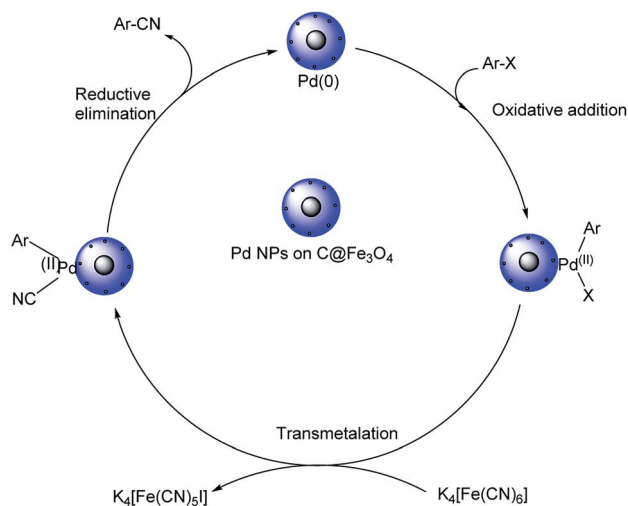
Scheme 15 Double cyanation of substituted aryl bromides catalyzed by palladium acetate and N-heterocyclic carbene.

only moderate yields. Double cyanation of different aryl halides was also analysed by the group and they noted that aryl bromides with iodide substitution required lesser time for the conversion to dicyano products than aryl dibromides and also provided slightly higher yields (Scheme 15).

Pitchumani *et al.* disclosed a strategy towards the synthesis of aryl cyanides using core-shell hybrid nano spheres (Pd NPs on C@Fe₃O₄) as the novel catalyst.⁵¹ The reaction could investigate a range of substrates and it was noted that the presence of electron-deficient substituents on iodo and bromoarenes gave slightly higher yields in comparison with electron-rich ones (Scheme 16). Chloroarenes underwent the reaction, but exhibited lower reactivity. The group could also carry out the cyanation of hetero aryl halides with good results. The catalyst displayed superlative properties such as good efficiency, exceptional stability and recyclability. A possible mechanistic trajectory was proposed where, initially, the haloarene undergoes oxidative addition to Pd(0). This generates a Pd(II) moiety. Subsequently, from the inner coordination sphere of K₄[Fe(CN)₆], a ligand exchange takes place to the Pd(II) species



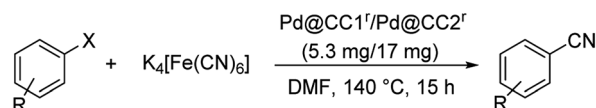
Scheme 16 Pd NPs on C@Fe₃O₄ catalyzed synthesis of diversely substituted haloarenes and heterohaloarenes.



Scheme 17 Possible mechanistic trajectory for the cyanation reaction. [This figure has been reproduced from ref. 51 with permission from AMERICAN CHEMICAL SOCIETY, copyright 2015].

forming a complex. A reductive elimination from the complex finally renders the aryl cyanides (Scheme 17).

Delightfully in 2016, covalent cages loaded with palladium nanoparticles were developed and found to catalyse the cyanation of various aryl halides effectively.⁵² The cages were designed from triphenylamine based trialdehydes and cyclohexane diamine. Two cages CC1^r and CC2^r are the ones that impregnate palladium. The optimised reaction condition was 5.3 mg/17 mg Pd@CC1^r/Pd@CC2^r, 0.17 mmol K₄[Fe(CN)₆]·3H₂O, in DMF, 140 °C, 15 h (Scheme 18). As is evident from the reaction condition, the reaction does not employ any additives. Various aryl halides underwent the reaction rendering excellent results.

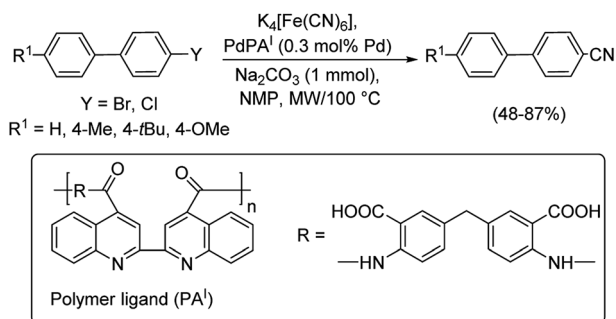


| X | R | Yields (%) Pd@CC1 ^r /Pd@CC2 ^r |
|----|-----------------|--------------------------------------------------------|
| Br | H | 99/99 |
| Cl | H | 97/94 |
| Br | NO ₂ | >99/>99 |
| Br | CN | 99/94 |

| | | |
|--------------------------------------------------------|-------|-------|
| X = Br, R = Br | | |
| Yields (%) Pd@CC1 ^r /Pd@CC2 ^r | 99/90 | 92/51 |

Scheme 18 Investigations on the synthesis of mono, di and tri-cyanoarenes using Pd@CC1^r/Pd@CC2^r.





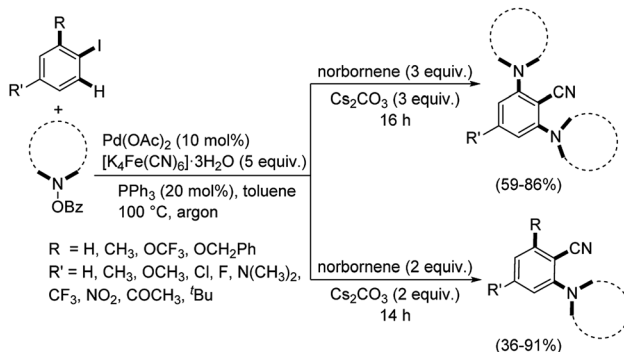
Scheme 19 Polymeric ligand PA^I mediated synthesis of different aryl bromides and chlorides.

It can also be noted that, dibromo and tribromobenzenes were transformed to dicyano and tricyanobenzenes respectively in very high yields. Here, the normally least reactive aryl chloride could also afford the desired cyanobenzene very efficiently.

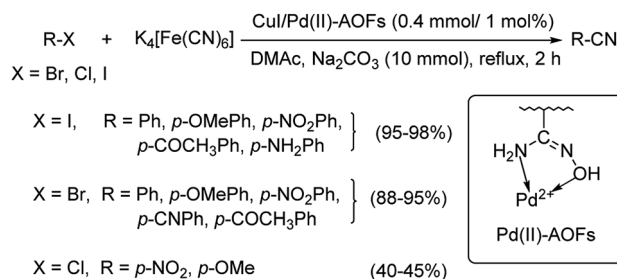
A polymer based catalyst having palladium(II) ions coordinated to biquinoyl fragments in the polyamic type polymer chain was introduced by Magdesieva *et al.* in 2016.⁵³ The source of cyanide was K₄[Fe(CN)₆] (Scheme 19). Here, the catalyst was capable of bringing about the cyanation of aryl halides in good yields. The catalyst was found to be stable under microwave as well as under conventional heating conditions.

Ranu and Majhi designed a strategy towards *ortho*-C-H-amination/*ipso*-C-I-cyanation of aryl iodides using palladium catalyst.⁵⁴ The cyanation media utilized was K₄[Fe(CN)₆]·3H₂O and the protocol was assisted by norbornene (Scheme 20). A range of 2-aminobenzonitriles were effectively synthesized with good results. Here, they could carry out an *ortho*-mono-C-H-amination and *ortho*-bis-C-H-amination along with the *ipso*-C-I-cyanation.

In 2017, Wu and co-workers have designed a facile protocol towards the synthesis of aryl cyanides from haloarenes using Cu(I)Pd(II)-AOFs (Pd-Cu bimetallic catalyst anchored on amidoxime fibres).⁵⁵ The synthesis of amidoxime fibres was carried out by the reaction between NH₂OH and polyacrylonitrile. The cyanation was brought about by K₄[Fe(CN)₆] and the reaction exhibited high endurance towards various substitutions on the



Scheme 20 Synthesis of *ortho*-mono/bis-C-H-amination and *ipso*-C-I-cyanation of aryl iodides.

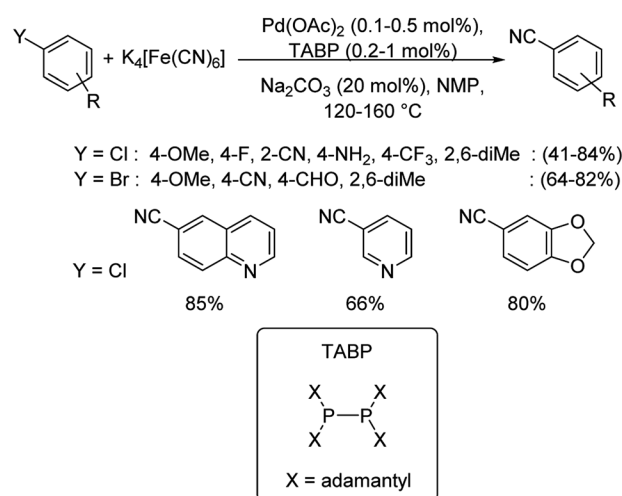


Scheme 21 Substrate scope for the cyanation of aryl halides by CuI/Pd(II)-AOFs.

haloarene. Excellent yields were reported with iodo and bromoarenes whereas, chloroarenes could impart only moderate yields (Scheme 21). Here, the coordination between Pd(II) ions and -OH/-NH₂ in AOFs result in Pd(II)-AOFs. CuI reduces Pd(II)-AOFs to Pd(0)-AOFs. CuI also enhances the dissociation of the nitrile ion from K₄[Fe(CN)₆]. The haloarene is then subjected to an oxidative-addition to the Pd(0)-AOFs forming Ar-Pd-X intermediate. Finally, a reductive elimination establishes the aryl nitriles and also the Pd(0)-AOFs is regenerated for the next catalytic cycle.

In most of the above reactions, the reactivity of aryl chlorides was found to be least in comparison to aryl bromides and iodides. Hence, Beller and co-workers in 2018 investigated the cyanation of aryl halides especially, aryl chlorides using TABP (tetraadamantylbiphosphine) as the efficient ligand along with palladium acetate as the catalyst.⁵⁶ This was the first report on the utilization of biphosphine ligands in coupling reactions catalyzed by palladium (Scheme 22). Substitutions by electron-rich, electron-deficient and sterically hindered moieties were well explored. Furthermore, the cyanation of heteroaryl halides were also analysed which afforded the products satisfactorily.

A straightforward approach using palladium nanoparticles as the catalyst for the synthesis of aryl nitriles was disclosed by Kandathil and co-workers.⁵⁷ Here, the aqueous ethanolic extract



Scheme 22 Synthesis of aryl and heteroaryl cyanides from chloroarenes and bromoarenes using TABP.



Review

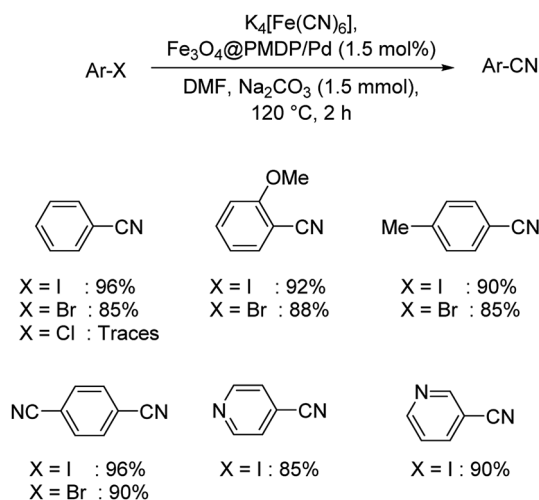


X = Br, I: R = H, CN, CHO, COMe, CPh, NO₂, OMe : 70-95%
 X = Cl: R = H, COMe : 65%, 30%

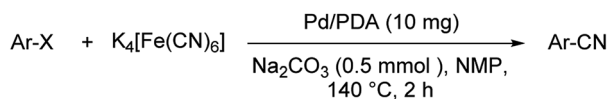
Scheme 23 Biogenetically synthesized palladium nanoparticles catalyzed formation of various benzonitriles.

of *Piper nigrum* (black pepper) biogenetically converted palladium acetate into palladium NPs. The synthesized palladium NPs and K₄[Fe(CN)₆] were employed for the transformation of haloarenes to aryl nitriles (Scheme 23). The conversion towards various cyanides were more effective in the case of bromo and iodoarenes, but least for chloroarenes.

A palladium based core-shell catalyst using poly-methyl dopa (PMDP)-coated Fe₃O₄ NPs and palladium NPs was designed by Veisi and co-workers.⁵⁸ Adsorption of the palladium ions on the Fe₃O₄@PMDP resulted in the generation of the catalyst (Scheme 24). The cyanation of diverse iodo and



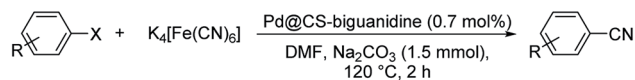
Scheme 24 Aryl halide cyanation catalyzed by Fe₃O₄@PMDP/Pd.



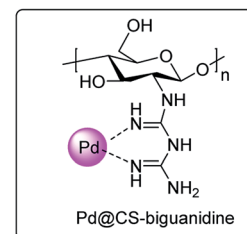
Yields for Scheme 25:

| | | |
|-----------------------------------------------------------------------------|-------------------|-----------------------------------------|
| X = Br : >99% | X = Br : >99% | X = Br : <5% X = Br; TBAB : 100% |
| X = I : 90% X = I; TBAB : 100% X = Br : <5% X = Br; TBAB : 13% | | |

Scheme 25 Substrate scope investigations of cyanation of aryl halides using Pd/PDA with and without TBAB.



| R | X | Yield (%) |
|-------|-----------|----------------|
| H | I, Br, Cl | 96, 90, Traces |
| 4-CN | I, Br | 96, 92 |
| 2-OMe | I, Br | 92, 90 |
| 4-Me | I, Br | 92, 88 |
| 4-Cl | I, Br | 96, 92 |

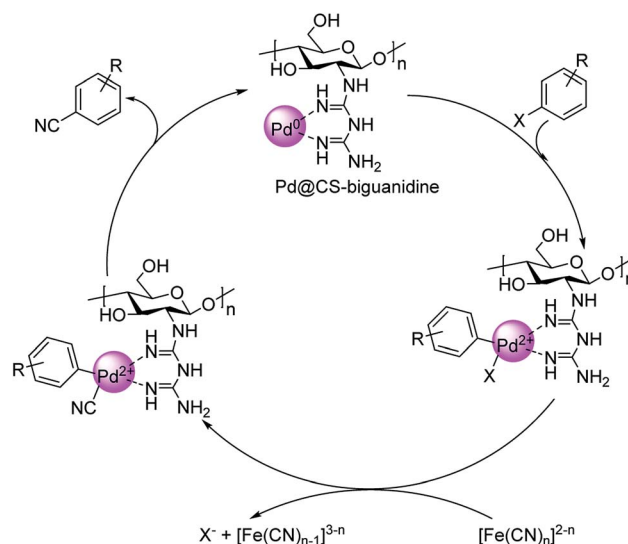


Scheme 26 K₄[Fe(CN)₆] mediated Pd@CS-biuguanidine catalyzed synthesis of various cyanobenzenes.

bromoarenes was carried out using K₄[Fe(CN)₆] and manifested excellent yields. However, it was noticed that chloroarenes were unreactive substrates in the reaction. Nitrogen heterocycles which are electron-deficient like 3-iodopyridine and 4-iodopyridine underwent the cyanation reaction exhibiting good results.

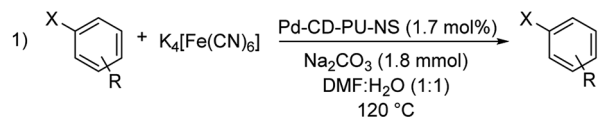
Palladium nanoparticles anchored by polydopamine (PDA) as catalyst for the synthesis of aryl nitriles was disclosed by Gazdag *et al.*⁵⁹ Initially, it was noted that under the optimised condition (10 mg Pd/PDA, 0.125 mmol K₄[Fe(CN)₆], 0.5 mmol Na₂CO₃ in NMP at 140 °C) the yields were favourable only for electron-deficient aryl halides, other substrates reacted less effectively (Scheme 25). But, the addition of tetrabutyl ammonium bromide (TBAB), improved the efficiency of the reaction and rendered moderate to good yields. This may be due to the potential of TBAB in stabilising the dissolved Pd(0) motifs in solution and thus displayed greater catalytic ability.

Haloarene cyanation using core-shell nanomaterial catalyst was established by Veisi in 2018.⁶⁰ Here, a matrix of biuguanidine-functionalized chitosan was impregnated with

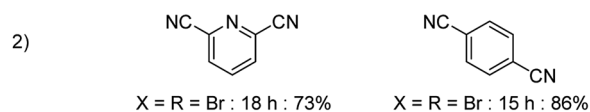


Scheme 27 Plausible mechanism for the formation of aryl cyanides. [This figure has been reproduced from ref. 60 with permission from ELSEVIER, copyright 2020].





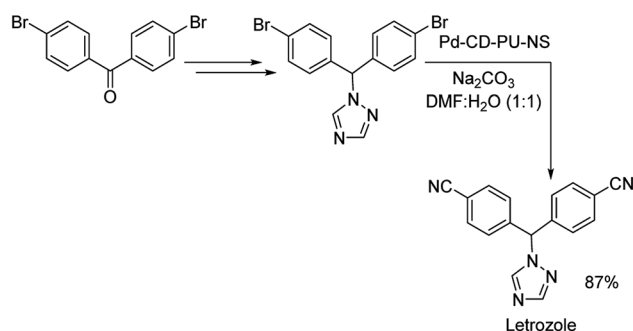
| R | X | Time (h) | Yield (%) |
|-------------------|-----------|------------|------------|
| H | I, Br | 15 | 70, 60 |
| 4-CHO | Br, Cl | 15, 18 | 91, 55 |
| 4-OMe | Br | 15 | 85 |
| 4-NO ₂ | I, Br, Cl | 10, 10, 12 | 92, 89, 75 |
| 4-NH ₂ | I, Br, Cl | 15 | 90, 88, 80 |
| 4-Br | I | 18 | 68 |
| 4-Cl | Br | 18 | 50 |



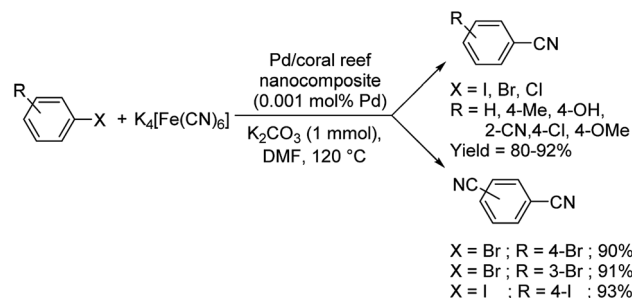
Scheme 28 (1) Mono-cyanation reactions catalyzed by Pd-CD-PU-NS. (2) Synthesized bis-cyanated products by the same protocol.

palladium NPs to form the core-shell-Pd@CS-biguanidine. The medium for cyanation was $K_4[Fe(CN)_6]$ in solvent DMF at a temperature of 120 °C (Scheme 26). Excellent yields of the aryl nitriles were observed with high catalytic recyclability. A mechanistic route towards the products is also depicted (Scheme 27) where an oxidative addition of the haloarene takes place on the catalyst, followed by the transfer of cyanide ion from $K_4[Fe(CN)_6]$. In the end, a reductive elimination completes the reaction, rendering the cyanobenzenes.

Nanosponge is one of the diverse forms of the available nanomaterials. Recently in 2019, a cyclodextrin-polyurethane based nanosponge was developed by Panahi and co-workers, where they immobilized palladium NPs to form Pd-CD-PU-NS.⁶¹ The catalyst was investigated for its efficiency in bringing about the cyanation of various aryl halides. Diverse functional groups were well tolerated and rendered good results (Scheme 28). Bis-halogenated substrates were also capable of affording the desired mono as well as bis-substituted compounds in good yields. Using the same catalyst, they could also synthesize a non-steroidal aromatase inhibitor letrozole in 87% overall yield (Scheme 29).



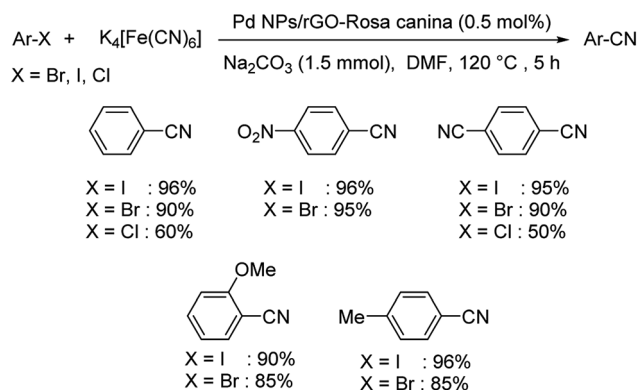
Scheme 29 Letrozole synthesis involving Pd-CD-PU-NS catalyzed cyanation as one of the steps.



Scheme 30 Formation of mono and dicyanoarenes via catalysis by Pd/coral reef nanocomposite.

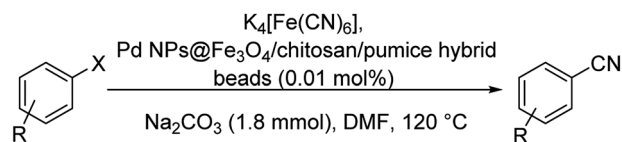
Nasrollahzadeh and co-workers established a lucid methodology for the formation of benzonitriles from haloarenes using Pd/coral reef nanocomposite and $K_4[Fe(CN)_6]$.⁶² In this approach, the extract from *Cucurbita pepo* leaves was employed as a reducing agent for palladium, converting it from Pd(II) to Pd(0) and also as a stabilising medium (Scheme 30). Diverse haloarenes reacted to render the benzonitriles in excellent yields. Also, a double-addition was observed when there were two bromo or iodo groups in the aryl halides *i.e.*, 1,4-dibromobenzene, 1,3-dibromobenzene and 1,4-diiodobenzene.

Rosa canina fruit extract modified graphene oxide decorated with palladium nanoparticles was showcased as a novel green catalyst for haloarene cyanation.⁶³ Here also $K_4[Fe(CN)_6]$ was the suitable cyanating medium. The optimised condition for the reaction was 0.5 mol% Pd nanoparticles (NPs)/reduced graphene oxide (rGO)-*Rosa canina*, 1.5 mmol Na_2CO_3 in DMF at 120 °C for 5 h (Scheme 31). It was observed that electronic factors were not much pronounced in this reaction. Iodo and bromoarenes displayed high reactivity providing excellent results while, chloroarenes reduced the yields of the products significantly. The catalyst was stable through seven catalytic cycles and thus displayed high efficiency. The proposed mechanism discusses an oxidative addition of the haloarene over the catalyst followed by the movement of the cyanide anion from the cyanating agent and lastly, a reductive elimination led to the formation of the desired product. This is similar to the



Scheme 31 One-pot approach towards the synthesis of various aryl cyanides using $K_4[Fe(CN)_6]$.





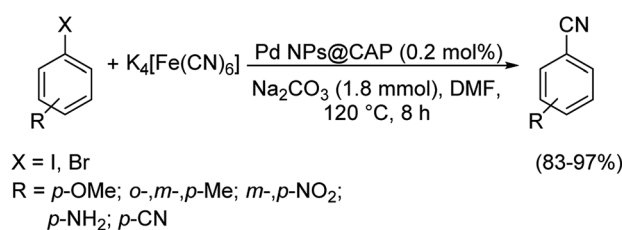
| X | R | Yield (%) |
|----|------------------------------------|------------|
| I | <i>p</i> -OMe | 94 |
| | <i>o</i> , <i>m</i> , <i>p</i> -Me | 91, 93, 95 |
| | <i>m</i> -NO ₂ | 97 |
| Br | <i>p</i> - <i>t</i> Bu | 82 |
| | <i>o</i> , <i>m</i> , <i>p</i> -Me | 85, 89, 91 |
| | <i>p</i> -NO ₂ | 98 |
| Cl | <i>p</i> -OMe | 83 |
| | <i>m</i> -NO ₂ | 80 |
| | <i>p</i> -Me | 80 |

Scheme 32 Synthesis of different aryl cyanide motifs from various aryl halides using Fe₃O₄/chitosan/pumice hybrid beads.

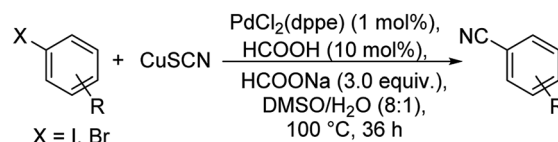
mechanism discussed in Scheme 27, but there Pd@CS-biguanidine was used as the catalyst instead of PdNPs/rGO.

Veisi *et al.* discovered a hybrid material as catalyst like in the previous report with the only change in the plant extract used.⁶⁴ Now they incorporated the extract of *Thymbra spicata* and developed Pd NPs/rGO-*T. spicata*. K₄[Fe(CN)₆] was again used as the cyanating agent. The catalyst was then evaluated for its cyanation capability and revealed that cyanation of a range of haloarenes was possible with similar substrate scope as above. Electronic as well as steric effects were tolerated imparting good yields. Here also it was noticed that bromo and iodoarenes required only lower reaction times than chloroarenes in affording the expected products.

Lately in 2020, palladium as Pd NPs@Fe₃O₄/chitosan/pumice hybrid beads for the effective cyanation of haloarenes for the formation of various benzonitriles was investigated by Baran.⁶⁵ The Fe₃O₄/chitosan/pumice hybrid beads acted as the stabilising agent and was suitably decorated with the synthesized palladium nanoparticles. The cyanation was carried out in the presence of K₄[Fe(CN)₆] as the cyanating agent (Scheme 32). The efficiency of the catalyst was obvious from the yields of the benzonitriles formed. A maximum yield of 98% was reported and the catalyst displayed good recyclability.



Scheme 33 Pd NPs@CAP catalyzed formation of various benzonitriles—a substrate scope analysis.

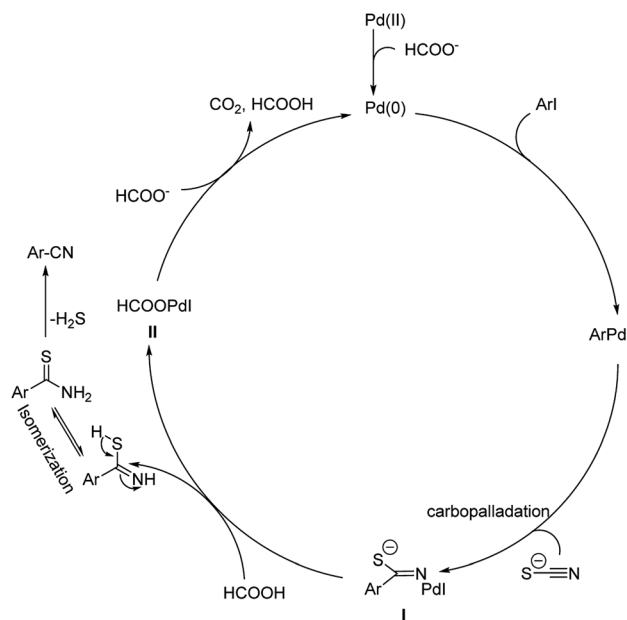


| Aryl halide | Yield (%) |
|------------------------------|-----------|
| 4-OMePhBr | 53 |
| 4-OMePhI | 83 |
| 4-OAcPhBr | 49 |
| 4-OAcPhI | 62 |
| 2,4-(OMe) ₂ PhI | 76 |
| 4-NH ₂ PhI | 68 |
| 4-NHAcPh | 70 |
| 4-OBnPhI | 76 |
| 2-COOMePhI | 58 |
| 2,4,6-(OMe) ₃ PhI | 80 |

Scheme 34 Reaction of various aryl halides with CuSCN to generate the corresponding aryl cyanides.

Baran and co-workers also prepared palladium nanoparticles on microbeads possessing chitosan, β -cyclodextrin and agarose forming the catalytic system-PdNPs@microcapsules (CAP).⁶⁶ This was as before investigated for cyanation of haloarenes using K₄[Fe(CN)₆] as the cyanating agent (Scheme 33). Bromo and iodoarenes were successfully converted into different benzonitriles with good yields. The formation of no by-products, high catalytic efficiency and easy purification are the most acceptable traits of the reaction.

1.1.2. Cuprous thiocyanate. In 2013, Cheng *et al.* could effectively carry out the cyanation of haloarenes using cuprous

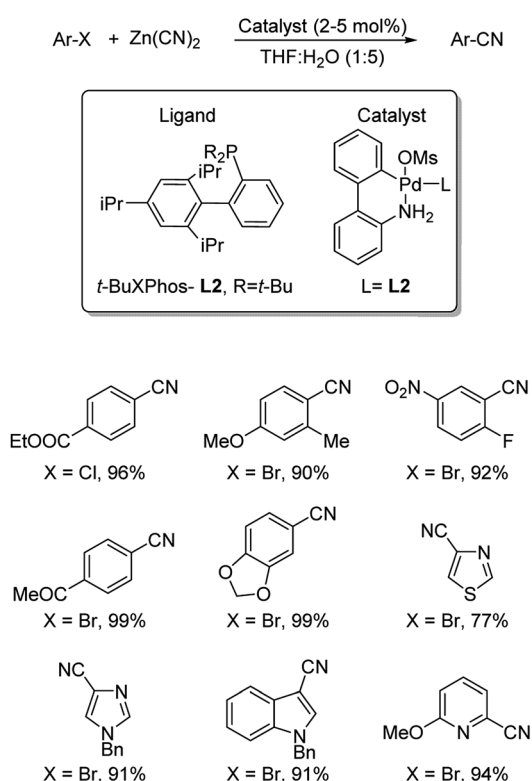


Scheme 35 Suggested mechanistic route towards the product synthesis. [This figure has been reproduced from ref. 67 with permission from AMERICAN CHEMICAL SOCIETY, copyright 2013].

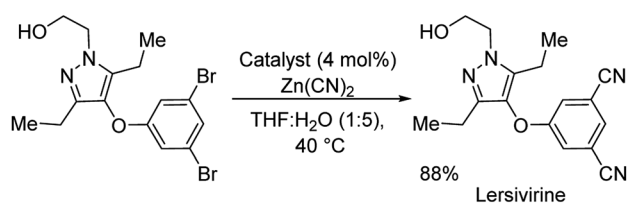


thiocyanate (CuSCN) *via* catalysis by palladium.⁶⁷ PdCl₂(dppe) was chosen as the catalyst in DMSO/H₂O solvent system. Formic acid and an additive sodium formate was also involved in the synthesis (Scheme 34). A range of functional moieties like OMe, NH₂, OBn, Ac, COOMe and NHAc were endured well in the reaction. But, it was noticed that electron-deficient groups yielded less compared to electron-rich ones. Steric effects did not have much role to play. Also, aryl cyanides were efficiently accessed from iodoarenes with mono, di and trimethoxy substitutions. A possible mechanism for the reaction was also suggested (Scheme 35). Initially, the sodium formate reduces Pd(II) to Pd(0). The aryl halide (ArI) then undergoes an oxidative addition to the Pd(0) forming ArPdI. It is followed by a carbopalladation step to generate an intermediate **I**. Formic acid then hydrolyses **I** to release **II**, at the same time it also fosters benzothioamide, which then undergoes an H₂S loss to yield the desired aryl cyanide. Formic acid and carbon dioxide are released in the next step when sodium formate and **II** reacts. Finally, Pd(0) is generated back *via* a reductive elimination strategy.

1.1.3. Zinc cyanide. Zinc cyanide as the cyanating medium for palladium catalyzed cyanation of aryl and heteroaryl halides was established by Cohen and Buchwald in 2015.⁶⁸ This was a facile and mild, yet potential method for the synthesis of aryl and heteroaryl cyanides. The reaction employed *t*-BuXPhos **L2** as the ligand in 1 : 5 THF : H₂O solvent (Scheme 36). Electron-deficient and electron-rich substituents on aryl bromides were well tolerated. Aryl chloride underwent the reaction providing



Scheme 36 *t*-BuXPhos mediated cyanation of aryl halides catalyzed by Zn(CN)₂.



Scheme 37 Formation of reverse transcriptase inhibitor-lersivirine inspired from the above protocol.

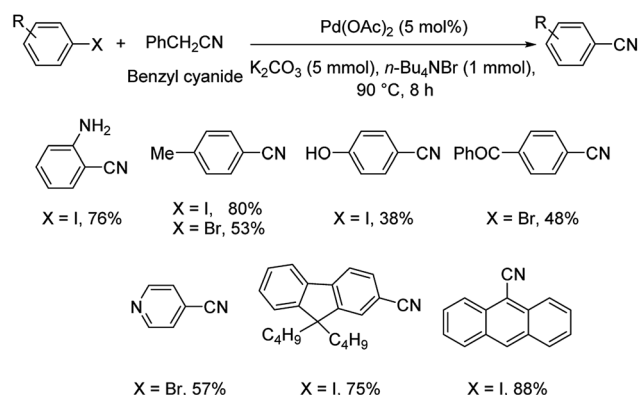
excellent yield. Various five and six-membered heterocyclic cyanides were also synthesized effectively. As a further application, the protocol was extended towards the synthesis of a reverse transcriptase inhibitor-lersivirine (Scheme 37). About 88% overall yield of lersivirine was reported.

1.2. Reactions with organic cyanide sources

Different protocols utilizing various organic cyanide sources such as benzyl cyanide, ethyl cyanoacetate, acetone cyanohydrin, formamide, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide, α -iminonitrile, hexamethylenetetramine and cyanuric chloride, during the period 2012–2020 are discussed below.

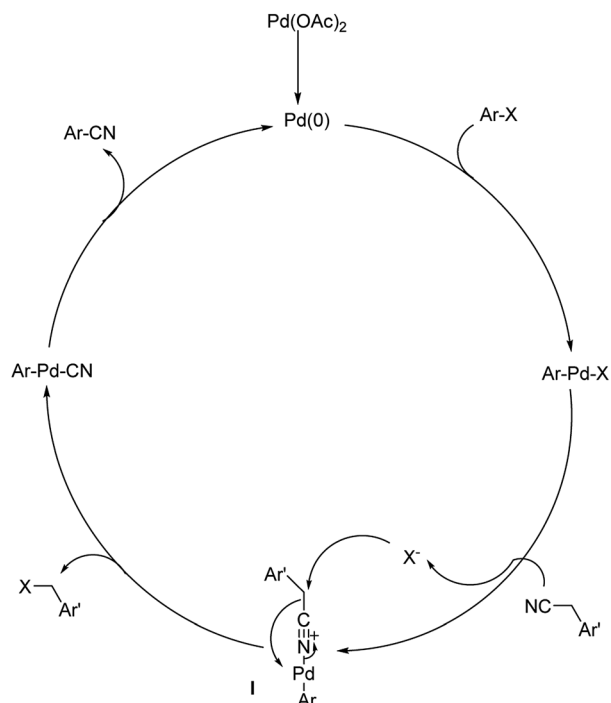
1.2.1. Benzyl cyanide. Benzyl cyanide was used for the synthesis of diverse aryl cyanides by Wang *et al.* in 2012.⁶⁹ This reaction was catalyzed by palladium acetate in DMF solvent. Haloarenes with electron-rich and deficient groups, hetero aryl halides and fused aryl halides were compatible in this protocol and yielded moderately (Scheme 38). The aryl halide undergoes oxidative addition to the Pd(0) species obtained from Pd(OAc)₂ (Scheme 39). Due to the presence of lone pair of electrons on the nitrogen of the benzyl cyanide, a ligand exchange takes place between the halide and the benzyl cyanide to form **I**. Benzyl halide is removed from **I** as a result of the nucleophilic attack of halide on carbon of the benzyl group. At the same time, a migration of palladium results in the formation of Ar-Pd-CN. A reductive elimination finally realizes the expected benzonitriles.

1.2.2. Ethyl cyanoacetate. Ethyl cyanoacetate was analysed to be an effective cyanation source for diverse aryl halides.⁷⁰ The



Scheme 38 Functional group tolerance of different aryl halides in the presence of benzyl cyanide.

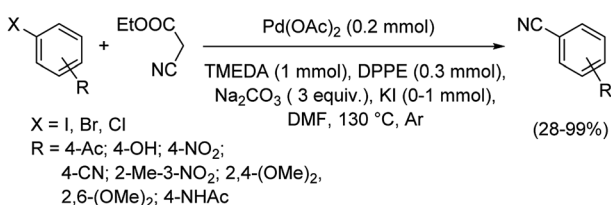




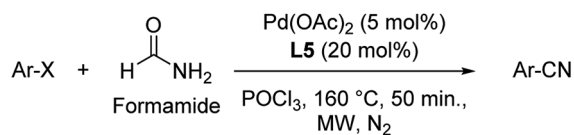
Scheme 39 The plausible trajectory through which the reaction proceeds. [This figure has been reproduced from ref. 69 with permission from ROYAL SOCIETY OF CHEMISTRY, copyright 2020].

best reaction condition for the cyanation was 0.2 mmol Pd(OAc)₂, 1 mmol TMEDA (*N,N,N',N'*-tetramethylethylenediamine), 0.3 mmol DPPE (1,2-bis(diphenylphosphino)ethane), 3 equiv. Na₂CO₃, 1 mmol KI in DMF at 130 °C under argon atmosphere (Scheme 40). A range of aryl nitriles were generated in the reaction with moderate to good yields. Besides this, substitutions at various positions (*ortho*, *meta* and *para*) were also well endured by the substrates.

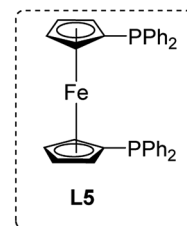
1.2.3. Formamide. The use of microwave-mediated protocol for the palladium catalyzed cyanation of haloarenes was established by Sawant and Bhanage.⁷¹ This facile and effective technique utilised Pd(OAc)₂/dppf L5 (1,1-bis(diphenylphosphino)ferrocene) as the catalytic system and formamide as cyanation medium and thus is a cyanide-free approach. Different functional groups on the iodoarene such as Me-, CF₃-, OMe-provided good yields of benzonitriles (Scheme 41). Similarly, *ortho* substitutions on the iodoarenes were also accepted well. Aryl bromides could provide only traces of the desired



Scheme 40 Ethyl cyanoacetate mediated palladium catalyzed synthesis of benzonitriles.



| Ar-X | Yields (%) |
|-------------------------------|------------|
| PhI | 75 |
| <i>p</i> -OMePhI | 78 |
| <i>p</i> -MePhI | 72 |
| <i>o</i> -OMePhI | 71 |
| <i>o</i> -MePhI | 74 |
| <i>p</i> -CF ₃ PhI | 69 |
| PhBr | 9 |



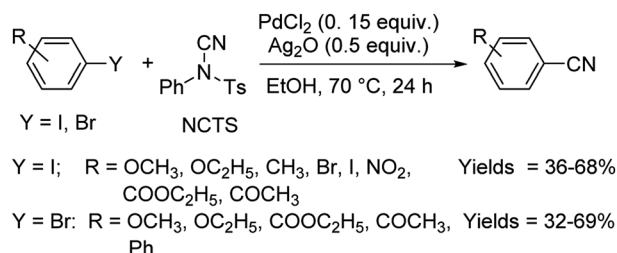
Scheme 41 Substrate scope studies of the cyanation of aryl iodides and bromides using formamide.

products. Microwave heating significantly improved the reaction yield and pace in comparison with traditional heating.

1.2.4. *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide. *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) is an efficient cyanide source having diverse benefits like being stable and innocuous.⁷² Li and co-workers employed NCTS as the cyanation source for the cyanation of various aryl halides.⁷³ The reaction was catalyzed by palladium chloride and utilised ethanol as the solvent (Scheme 42). Aryl bromides, chlorides and iodides with a range of functionalities like OCH₃, CH₃, NO₂, Br, OC₂H₅, Ph *etc.* were analysed and undergo transformation into various aryl cyanides. It was observed that, the reaction proceeded smoothly for aryl bromides and iodides providing a maximum yield of 69%. In the case of aryl chlorides, the result was only in trace amounts.

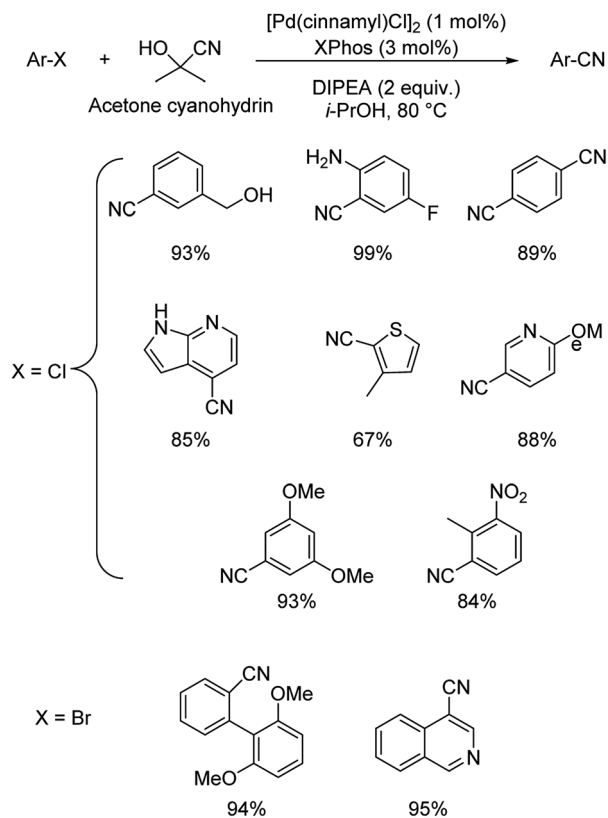
1.2.5. Acetone cyanohydrin. Acetone cyanohydrin as a cyanation means for aryl halides was effected by Guimond and co-workers.⁷⁴ They designed a homogeneous condition for the same using [Pd(cinnamyl)Cl]₂ as the catalyst and XPhos as the suitable ligand for the reaction (Scheme 43). It was observed that the electronic and steric effects offered by the substituents on the aryl halides (aryl bromides and chlorides) played no major role in deciding the yields of the products. Various aryl cyanides were synthesized in moderate to good yields.

1.2.6. Hexamethylenetetramine. Cyanation of iodoarenes using hexamethylenetetramine as the cyanating medium was developed.⁷⁵ The reaction was carried out under the conditions



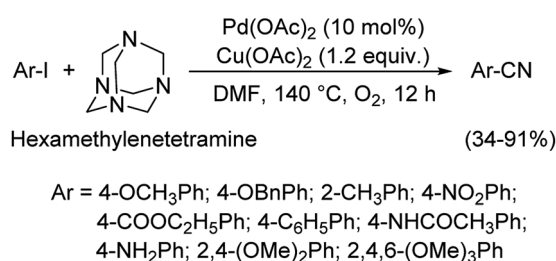
Scheme 42 Functional group tolerance of various aryl halides towards cyanation and their yield range.



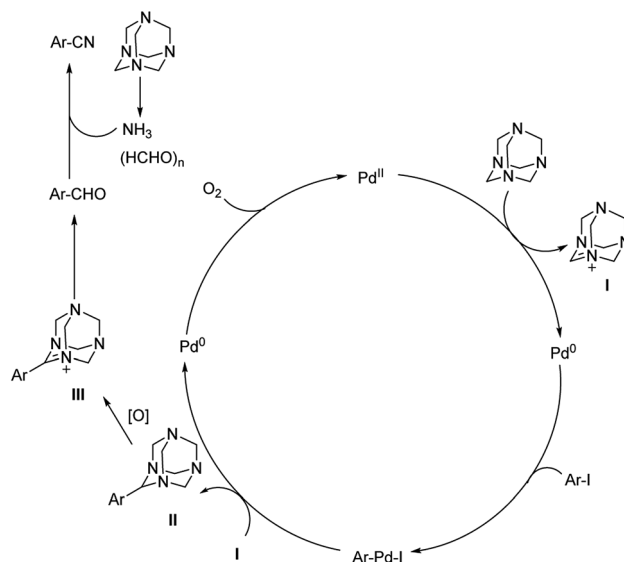


Scheme 43 Acetone cyanohydrin-mediated formation of diverse aryl cyanides.

of 10 mol% Pd(OAc)₂, 1.2 equiv. of Cu(OAc)₂ in DMF at 140 °C under oxygen atmosphere for 12 h. The presence of functional groups such as nitro, methoxy, phenyl, chloro, benzyloxy, amino *etc.* on the aryl iodides were tolerated well (Scheme 44). The mechanistic route suggests an initial formation of iminium intermediate **I** by the oxidation of HMTA (Scheme 45). Pd(0) is formed along with this and it is followed by the oxidative addition of aryl iodide (ArI) to Pd(0) to form ArPdI, which then undergoes insertion to the iminium intermediate **I** to form **II**. In this step the release of Pd(0) occurs. The released Pd(0) is then oxidized back to Pd(II) by oxygen or Cu(II). **II** then converts to **III** *via* oxidation by Cu(II). In the last stage, **III**, in the presence of water is modified into benzaldehyde, which finally get converted into cyanides.



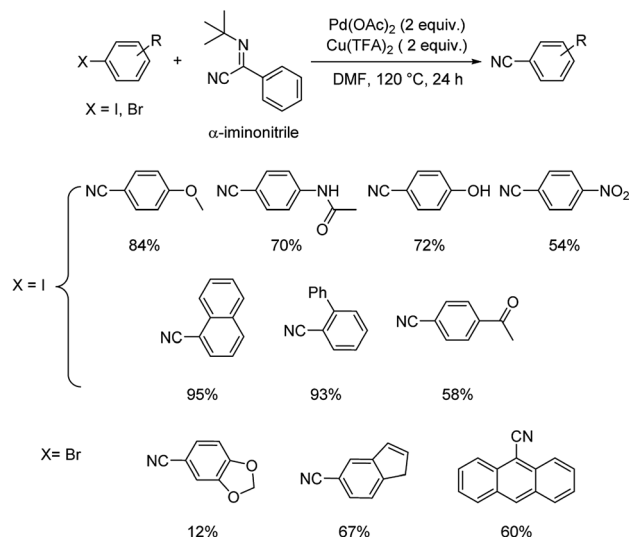
Scheme 44 Cyanation reaction of different iodoarenes assisted by hexamethylenetetramine.



Scheme 45 Synthetic pathway for the cyanation reaction carried out by HMTA. [This figure has been reproduced from ref. 75 with permission from AMERICAN CHEMICAL SOCIETY, copyright 2017].

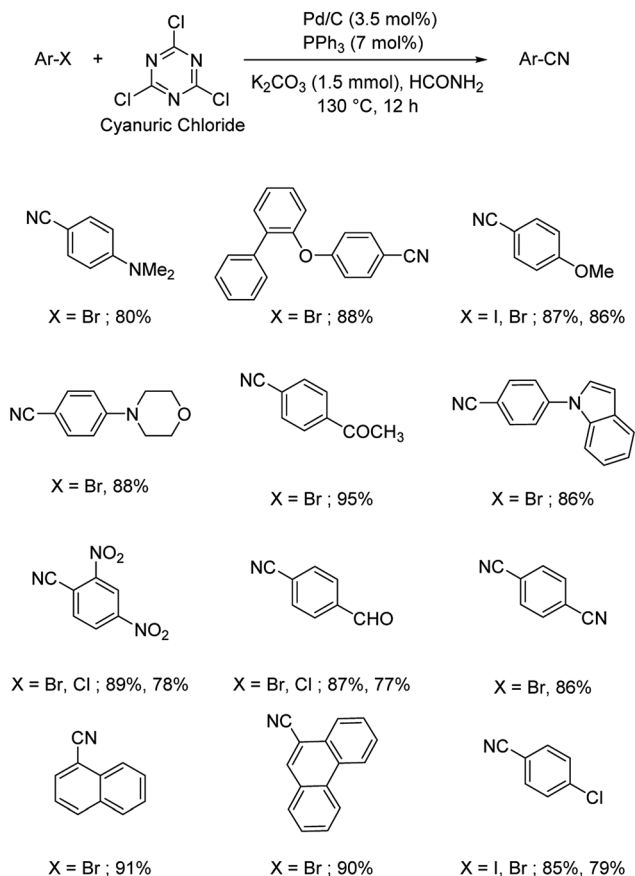
1.2.7. α -Iminonitrile. Zhu *et al.* could synthesize aryl cyanides by a novel protocol using palladium without the aid of any ligand.⁷⁶ They employed α -iminonitrile as the cyanide medium. Substitution by electron-donating moieties on the aryl halide were found to afford better yields than by electron-withdrawing ones (Scheme 46). Moreover, when the *ortho*-position of the substrate was substituted with large conjugated ring, the reaction proceeded well rendering excellent results.

1.2.8. Cyanuric acid. Recently, a novel strategy towards cyanation of aryl halides using easily available 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) and formamide was reported.⁷⁷ The reagent employed proved to be a non-toxic,



Scheme 46 Synthesis of various benzonitriles from aryl iodides and bromides catalyzed by Pd(OAc)₂.





Scheme 47 Wide range of substrate scope towards the synthesis of various cyanobenzenes in the presence of cyanuric chloride.

economic and readily accessible one. A model reaction was carried out using *p*-methoxybromobenzene as the substrate. The cyanation of the substrates was performed under the optimized conditions of 3.5 mol% Pd/C, 7 mol% PPh₃, 1.5 mmol K₂CO₃ in formamide at 130 °C for 12 h (Scheme 47). Amine, aldehyde, cyano, keto, halogens, ether and nitro groups as substituents were well tolerated. Polyaromatic haloarenes, bihalides, haloarenes with heterocyclic substitution, and bromo-functionalized aryl-aryl ether moieties could undergo the reaction furnishing good results.

2 Conclusions

Cyanations reactions have a pivotal role in synthetic organic chemistry, as it synthesizes aryl cyanides finding superior relevance in pharmaceuticals, natural products, industries *etc.* Recently, there have been many developments in the cyanation chemistry particularly, the ones catalyzed by transition metals. Palladium, copper and nickel are the major transition metals acting as catalysts for cyanation reactions. Palladium catalyzed cyanation has always gained much importance due to its high catalytic efficiency. Various palladium sources such as palladium acetate, palladium chloride, ligand-palladium complexes, palladium nanoparticles, nanoshells, nanospheres, nanobeads, core-shells and so on have been widely employed.

K₄Fe(CN)₆, Zn(CN)₂, CuSCN, NCTS, α -iminonitrile, ethyl cyanoacetate *etc.* are the different cyanating media utilized. Among these, the studies have revealed that K₄Fe(CN)₆ is the one majorly used. This may be due to its innocuous nature, low cost and easy handling properties. Various investigations on the aryl halide cyanation using these catalysts and cyanation media are discussed briefly in the present review focussing mainly on the functional group compatibility, synthetic yields of the aryl cyanides and the mechanisms involved. Being a flexible functional group, the nitriles can be efficiently transformed into various other functionalities. Diverse approaches on their synthesis as well as transformations are under study. Aryl nitriles hence form a field with high applicability. Cyanation catalyzed by palladium, as summarized in this review, is a well emerging field having its very roots from the mid 1970's and it inspires scientists to prove their potential to finally realize some major outputs that impart high relevance to the scientific world. This may be projected as a practical and functional approach for the synthesis of aryl nitriles for diversely oriented disciplines.

Conflicts of interest

There are no conflicts to declare.

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