

## **Chapter II**

### **Fe<sub>3</sub>O<sub>4</sub>-nanoparticles catalyzed an efficient synthesis of nitriles from aldehydes**

#### **Section A**

##### **(A general introduction of nitrile and its synthetic background)**

###### **II. A. Nitrile:**

An organic compound with -CN functional group is considered as nitrile whereas for inorganic compounds they are known as cyanide. Besides, any organic compound contains many -CN group are known as cyanocarbon in industrial literature. Applicability of these function group is well documented and we already discussed it in our general introduction section (chapter I) of this thesis. Here we only discussed about the structure, occurrence and some sort of synthetic background of the functional group.

###### **II. A. 1. Discovery of organo nitriles:**

In 1972, C. W. Scheele was the first, who prepared hydrogen cyanide and nitrile of formic acid. Later on, J. L. Gay-Lussac in 1811 prepared the very toxic and pure acid. Friedrich Wöhler and Justus von Leibig, first prepared the nitrile of benzoic acids but was unable to examine the physical or chemical properties, for the low yield of the product. In 1834, Théophile-Jules Pelouze has synthesized propionitrile and suggesting it as the ether of propionic alcohol and hydrocyanic acid. In 1844 Hermann Fehling discovered a method (by heating ammonium benzoate), to get sufficient benzonitrile for chemical research. Hermann Fehling devised the name nitrile, for the newly found substance and became the name for this group of compounds.

###### **II. A. 2. Structure of -CN group:**

*sp*-Hybridization of the triple bonded C of -CN, give it a linear skeleton with a bond distance around 1.16 Å. Also, electronegativity differences between nitrogen and carbon make it a polar group with high dipole moment.

### II. A. 3. Natural occurrences of nitrile:

Naturally, organo-nitriles are found in some plants, certain seeds and fruit stones (e.g., those of apples, peaches and apricots etc.) and also produced by some fungi, bacteria and algae. In plants, -CN groups are present as cyanogenic glycosides (an amygdalin skeleton; Fig. II. A.1.); in which they are attached with a sugar moiety and helping to protect plants from herbivores. In tropical countries a potato-like food, Cassava roots has grown (also named manioc; used to make tapioca), also contain cyanogenic glycosides.

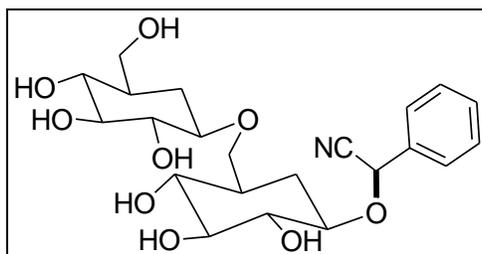


Fig. II. A. 1. Cyanogenic glycosides

### II. A. 4. Classical method for nitrile synthesis:

#### II. A. 4. 1. Hydrocyanation:

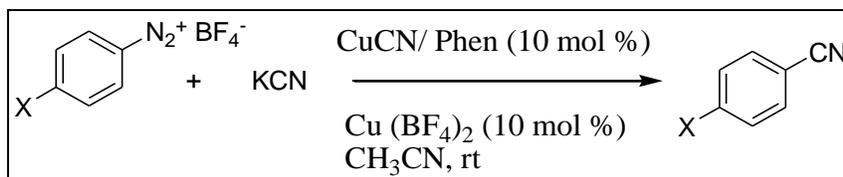
Hydrocyanation<sup>1</sup> is the industrial process of formation of nitrile using an alkene and hydrogen cyanide. The process involves a thermodynamically favorable  $H^+$  and  $CN^-$  addition to an activated  $C=C$ , such as  $C=C$  bond of  $\alpha, \beta$ -unsaturated carbonyl compound. For this process sufficiently activated substrates are required thus inactivated alkenes were unfavorable for this reaction. But this is conquered by transition-metal catalysis. By, using transition-metal catalyst addition of  $CN^-$  across  $\pi$ -bonds occurs in a Markovnikov/anti-Markovnikov fashion to provide fully saturated nitriles. The most commonly used transition-metal complexes for the purpose is nickel (0) and palladium (0) complexes. For industrial purposes the reaction is widely used in preparation for adiponitrile ( $NC-(CH_2)_4-CN$ ); a predecessor for hexa-methylene diamine; from 1, 3-butadiene using Ni-complexes (scheme. II. A. 1.).



Scheme. II. A. 1. Modern process for adiponitrile synthesis

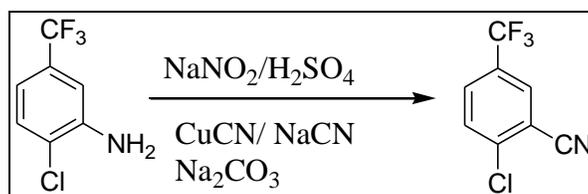
### II. A. 4. 2. Sandmeyer reaction:

This method involves the direct cyanation of azobenzene using cuprous cyanide to get aryl nitrile. But the use of more toxic metal cyanide and less selectivity results the process less useful industrially. Recently P. Beletskaya et al. have reported the catalytic version of Sandmeyer reaction using Cu(I)/ Cu (II) catalyst (scheme. II. A. 2.)<sup>2</sup>.



**Scheme. II. A. 2.** Catalytic version of sandmeyer reaction

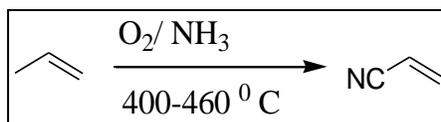
Now, industrially the reaction is used to synthesis a key intermediate for the anti-psychotic drug Fluanxol (scheme. II. A. 3)<sup>3</sup>.



**Scheme. II. A. 3.** Synthesis of the key intermediate for Fluanxol

### II. A. 4. 3. Ammoxidation reaction:

In ammoxidation<sup>4</sup> technique reaction of hydrocarbon is takes place with ammonia by the presence of oxygen and a suitable catalyst. Usually alkenes are used as the hydrocarbon source and partially oxidized by oxygen in presence of ammonia (e.g. preparation of acrylonitrile scheme. II. A. 4).

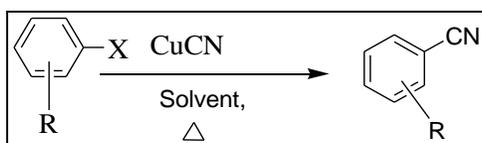


**Scheme. II. A. 4.** Preparation of acrylonitrile

Besides, derivatives of benzonitrile, iso-butyronitrile and phthalonitriles are also prepared by this method. The first acknowledge commercial plant on the basis of the reaction was built by Sohio (now BP international). They used  $\text{Bi}_2\text{O}_3/\text{MoO}_3$  as their catalyst.

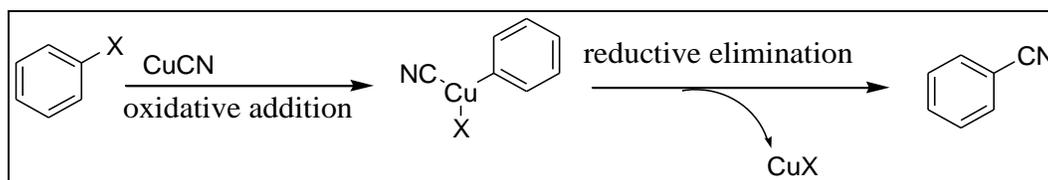
#### II. A. 4. 4. Rosenmund–von Braun reaction:

By this process aryl halides undergoes cyanation reaction with excess of Cu(I) cyanide in a polar organic solvent such as pyridine, DMF etc. under refluxing condition (scheme. II. A. 5).



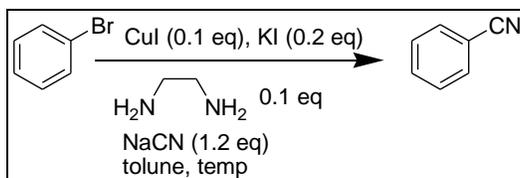
**Scheme. II. A. 5.** General reaction for Rosenmund-von Braun method

During the process it is assumed that the reaction takes through an oxidative addition of aryl halide to the copper cyanide and makes it Cu (III) species followed by reductive elimination to get the product (scheme. II. A. 6).



**Scheme. II. A. 6.** Mechanistic path-way for Rosenmund- von Braun reaction

The method was good for aryl iodide but it fails to satisfy for aryl bromides. Besides, it also has some other limitations regarding harsh reaction condition and also for separation of products from the copper halide side product. Most recently, S. A. Buchwald et al. have reported a modified technique for aryl-bromides (scheme. II. A. 7) <sup>5</sup>. They suggest a domino halide exchange-cyanation during the reaction.

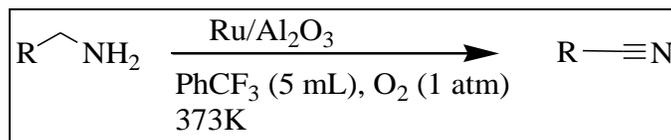


**Scheme. II. A. 7.** S. A. Buchwald method for aryl bromides transformation into nitrile

## II. A. 5. Modern methods for synthesis of nitriles:

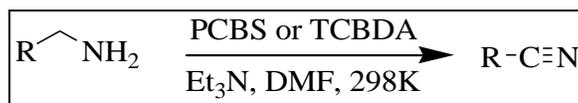
### II. A. 5. 1. Synthesis of nitriles from primary amines:

Primary amines can be converted into nitrile by partial oxidation using suitable oxidizing agent and catalyst. There are so many protocols present for this transformation. Such as Noritaka Mizuno et al. have synthesized nitrile from their corresponding amines (both activated and non-activated) by direct oxidative process using Ru/Al<sub>2</sub>O<sub>3</sub> (1.4 wt. % of Ru) as heterogeneous catalyst, 1 atm dioxygen or air in PhCF<sub>3</sub> (trifluoro toluene) as a solvent (scheme. II. A. 8) <sup>6</sup>.



**Scheme. II. A. 8.** Oxidative transformation of primary amines

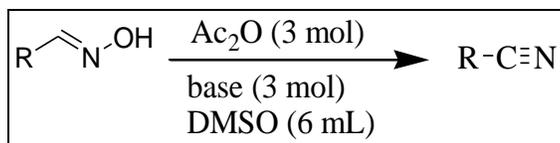
Again, another research group Ramin Ghorbani-Vaghei et al. recently transformed primary amine to their corresponding nitriles using *N, N, N', N'*-tetrachlorobenzene-1, 3 disulfonamide (TCBDA) or poly (*N, N'*-dichloro-*N*-ethylbenzene-1, 3- disulfonamide) (PCBS), triethyl amine (TEA; acts as a base) and DMF (as a solvent) at 298 K temperature (scheme. II. A. 9) <sup>7</sup>.



**Scheme. II. A. 9.** PCBS or TCBDA catalysed transformation of primary amine to nitriles.

### II. A. 5. 2. Synthesis of nitriles from oximes:

Another alternative precursor for nitrile preparation is oxime. This process involves the dehydration of oximes to get their corresponding nitrile. Generally common dehydrating agent (such as conc. H<sub>2</sub>SO<sub>4</sub> or P<sub>2</sub>O<sub>5</sub>) can be used for the process but less selectivity of the reaction makes it inapplicable for industrial purpose. There are a number of alternatives available such as, Guangyu Xu et al. used acetic anhydride as a dehydrating agent at weak alkaline condition (Scheme. II. A. 10). <sup>8</sup>

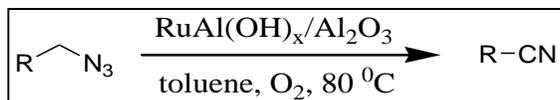


**Scheme. II. A. 10.** Conversion of oxime into nitrile

Again, Youquan Deng et al. convert aldoximes to their corresponding nitriles with the help of chlorosulfonic acid as a dehydrating agent in toluene <sup>9</sup>. Lei Yu et al. reported the precatalytic dehydration of aldoxime to nitrile using mild, tolerable and stable catalyst PhSe(O)OH <sup>10</sup>.

### II. A. 5. 3. Synthesis of nitrile from azide:

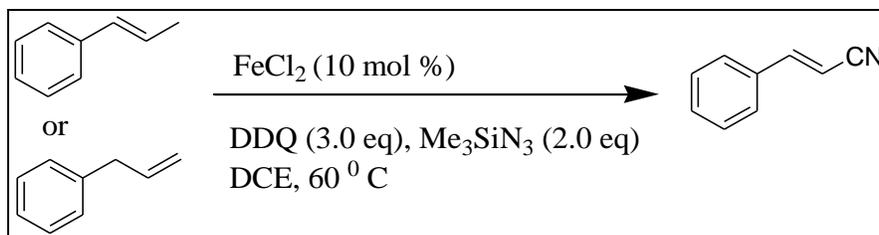
Another important method is the oxidative transformation of azides into nitriles. In 2005, Rozen et al. reported the direct conversion of organic azide into nitrile through BrF<sub>3</sub> promoted reaction without any incorporation of bromine or fluorine <sup>11a</sup>. Again, recently Noritaka Mizuno et al. have reported the transformation of primary azide into nitriles through an aerobic oxidation, using heterogenous ruthenium hydroxide catalyst [Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub>] for their synthesis (scheme. II. A. 11) <sup>11b</sup>.



**Scheme. II. A. 11.** Ru (OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalysed transformation of azide to nitrile.

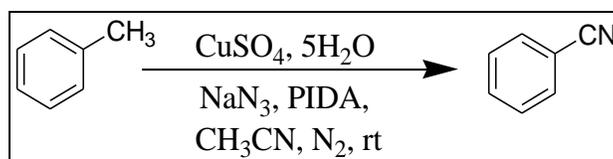
### II. A. 5. 4. Synthesis of nitriles from benzyl or allyl halides, alkenes, methyl arenes and alkynes:

Direct transformation of benzyl/allyl halide, alkenes or methyl arenes by an elongation of one carbon to the parent precursor is also well known. Ning Jiao et al. have recently reported these transformations separately for halides, alkenes and methyl arenes. For alkene or allylarenes they used inexpensive iron catalyst using dry DCE (2 mL) as solvent to get the nitrile (scheme. II. A. 12). <sup>12</sup>



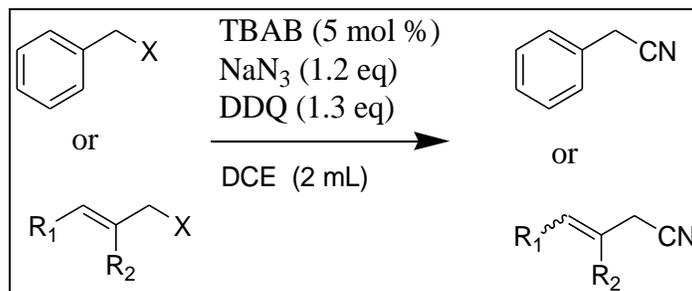
**Scheme. II. A. 12.** Conversion of alkene to nitrile

Again, for methyl arenes they have reported C(sp<sup>3</sup>)-H functionalization at room temperature using PIDA (1.6 mmol), NaN<sub>3</sub> (2.0 mmol) and CuSO<sub>4</sub>·5H<sub>2</sub>O (0.25mmol) as a catalyst in acetonitrile under N<sub>2</sub> atmosphere (scheme. II. A. 13)<sup>13</sup>.



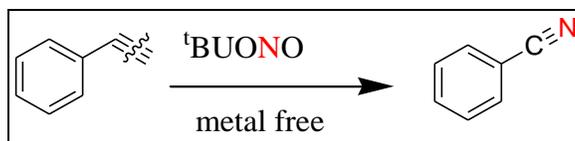
**Scheme. II. A. 13.** C(sp<sup>3</sup>)-H functionalization for nitrile preparation.

Again, in continuation of their finding, they explore the direct conversion of benzyl/allyl halides to their respective nitriles by substitution and subsequent oxidative rearrangement (scheme. II. A. 14.)<sup>14</sup>.



**Scheme. II. A. 14.** Conversion of benzyl/allyl halides to benzyl/allyl nitriles

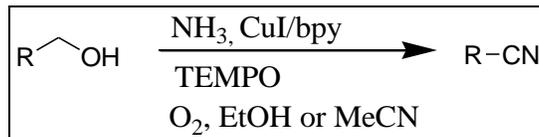
Recently D. Maiti et al. has reported the transformation of alkynes to their corresponding nitriles through a C≡C bond cleavage using *tert*-butyl nitrile as a reagent under metal free reaction condition (scheme. II. A.15)<sup>15</sup>.



**Scheme. II. A.15.** Conversion of nitrile from alkynes

### II. A. 5. 5. Synthesis of nitriles from alcohols acids and amides:

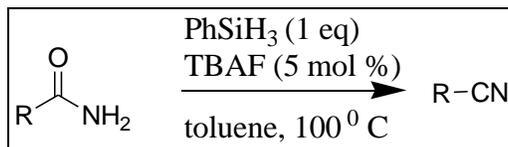
Recently Y. Haung et al. describe the aerobic double dehydrogenation reaction for the conversion of alcohol to nitrile CuI-bpy catalytic system and TEMPO under O<sub>2</sub> atmosphere. The process enabled a one pot transformation for various aromatic/aliphatic alcohols to nitriles (scheme. II. A. 16)<sup>16</sup>.



**Scheme. II. A. 16.** CuI- bpy and TEMPO catalysed transformation of alcohols.

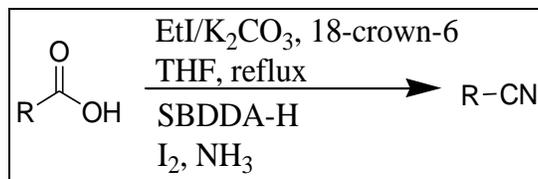
Again, J. M. Vatèle converts alcohols to nitrile through an in situ highly chemoselective oxidation-amination-aldehyde oxidation reaction sequences using TEMPO, iodosobenzene diacetate and NH<sub>4</sub>OAc<sup>17</sup>. This process serves well for a wide range of aliphatic/benzylic/hetero aromatic alcohols to give their respective nitrile in excellent yield.

Matthias Beller et al. reported the conversion of aliphatic and aromatic nitriles by catalytic dehydration of aromatic/aliphatic amides using silanes and catalytic amounts of tetra-butyl ammonium fluoride (TBAF) (scheme. II. A. 17)<sup>18</sup>. The protocol show higher selectivity under mild conditions.



**Scheme. II. A. 17.** Transformation of nitrile to amides

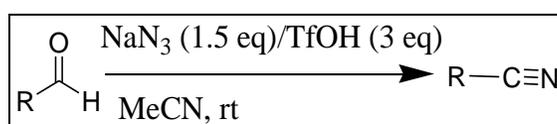
H. Togo et al. recently reported the treatment of organo acids with ethyl iodide/18-crown-6/ $K_2CO_3$  followed by treatment with SDBDA-H and finally with molecular iodine in aqueous ammonia converts it into corresponding nitriles (scheme. II. A. 18) <sup>19</sup>.



**Scheme. II. A. 18.** Conversion of acids to nitriles

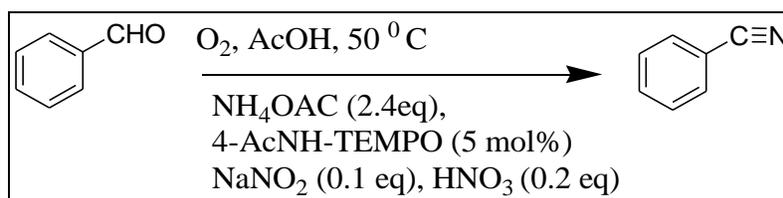
### II. A. 5. 6. Synthesis of nitriles from aldehydes:

Aldehydes can easily have converted into nitriles through Schmidt type reaction as reported by J. R. Prabhu et al. (scheme. II. A. 19) <sup>20</sup> via in situ formation of hydrazoic acid by treatment of sodium azide with triflic acid (Tf OH).



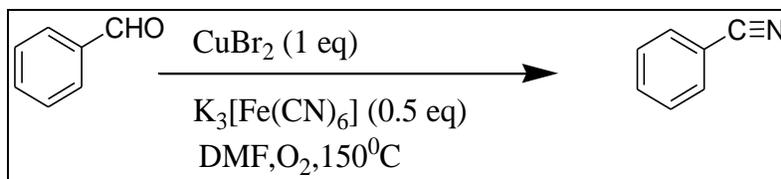
**Scheme. II. A. 19.** Schmidt type synthesis conversion of aldehyde to nitrile

There are also other methods present (e.g. J. Kim et al reported condensation of an aldehyde with  $NH_4OAc$  using catalytic amount of  $NaNO_2$ ,  $HNO_3$  and 4-AcNH-TEMPO under dioxygen atmosphere produces nitrilesselectively; scheme. II. A. 20) <sup>21</sup>.



**Scheme. II. A. 20.** Condensation of aldehyde with  $NH_4OAc$  to get nitriles

J. You et al. describe the direct conversion of aldehyde with a copper promoted -CN bond cleave of cyanide ion from coordination complex in dioxygen atmosphere (scheme. II. A. 21) <sup>22</sup>.



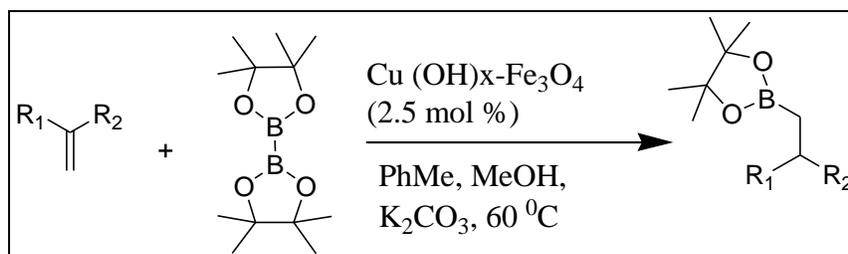
**Scheme. II. A. 21.** Copper promoted nitrile formation from aldehyde.

## II. A. 6. Reaction catalysed by Fe<sub>3</sub>O<sub>4</sub> nano-particle:

Magnetic nanoparticles (MNPs) of Fe<sub>3</sub>O<sub>4</sub> are attractive growing interest in recent years in many different fields owing to their intrinsic properties such as low toxicity, high surface area and easily availability of starting material for their preparation. Besides, superparamagnetic behaviours of the nano particles are allow controlling their motion by an external magnetic field. In catalytic prospectus, this is translated into an easy recovery and separation from the reaction medium by magnetic decantation. Additionally, almost all ferrites behave as metal oxides with a large number of hydroxyl groups on their surfaces. This characteristic allow to build a well-defined shell of other materials around the ferrite core, also helps to grafting functional groups and make it suitable for the supporting of all kinds of ligands, catalysts and actuators, by covalent bonds. For this unique physical property of magnetite, they appear as an interesting, reusable and easily recoverable catalyst for many reactions. Recent literature survey reveals the catalytic usage of MNPs particles in many reactions, such as for addition, oxidation and also for coupling reactions.

### II. A. 6. 1. Application of Fe<sub>3</sub>O<sub>4</sub> nano-particle for addition reaction:

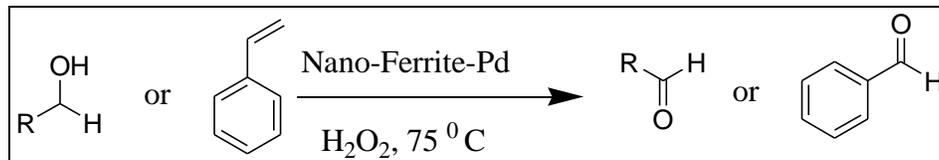
M. Yus et al. recently reported the catalytic effect of magnetite impregnated with copper towards the addition reaction of C=C and alkoxydiboron (scheme. II. A. 22)<sup>23</sup>. Again, M. Yus and co-workers use the same catalyst for propargyl-amines via a multicomponent reaction<sup>24</sup>.



**Scheme. II. A. 22.** Cu impregnated-Fe<sub>3</sub>O<sub>4</sub> catalysed addition reaction.

### II. A. 6. 2. Application of Fe<sub>3</sub>O<sub>4</sub> nano-particle for oxidation reaction:

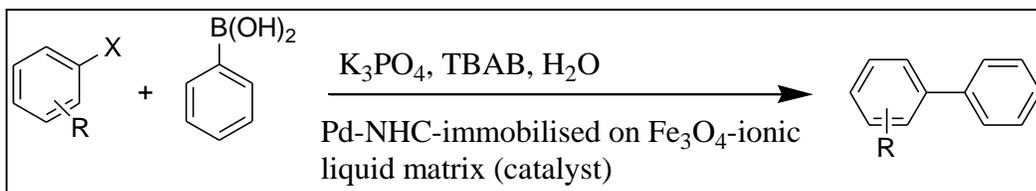
Magnetic nanoparticle supported-Pd catalysed oxidation of alcohol/olefin to their corresponding aldehydes has also been reported by R. S. Varma et al., (scheme. II. A. 23) <sup>25</sup>.



**Scheme. II. A. 23.** Nano magnetite supported-Pd catalysed oxidation reaction.

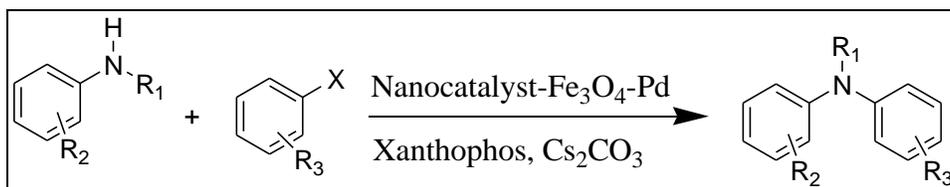
### II. A. 6. 3. Application of Fe<sub>3</sub>O<sub>4</sub> nano-particle for coupling reaction:

M. Beller and co-workers reported coupling of sulfonamides and alcohol using nano Ru/Fe<sub>3</sub>O<sub>4</sub> catalyst <sup>26</sup>. M. J. Jin et al. reported the effectiveness of magnetite nanoparticle ionic liquid matrix immobilized Pd-NHC catalyst for Suzuki reaction in water (scheme. II. A. 24) <sup>27</sup>.



**Scheme. II. A. 24.** Suzuki reaction in water medium

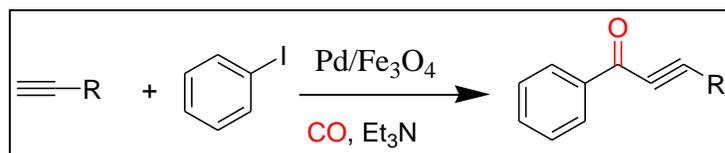
Again, Gawande et. al., used Pd-magnetite nano-catalyst for Buchwald-Hartwig type amination reaction of amines/ amides (scheme. II. A. 25) <sup>28</sup>.



**Scheme. II. A. 25.** Magnetite immobilized Pd catalysed Buchwald-Hartwig amination reaction.

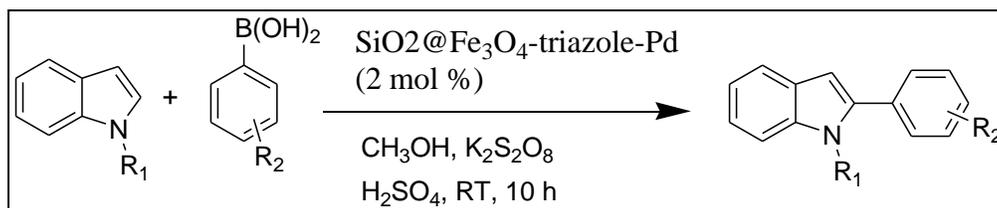
Moreover, there are so many literatures are present regarding the uses of magnetic nano-particle for Sonogashira (e.g., Liu and colleagues developed magnetically retrievable super magnetic Pd/Fe<sub>3</sub>O<sub>4</sub> nano-catalyst and successively used in carbonylative Sonogashira coupling reaction as a catalyst; scheme. II. A. 26) <sup>29</sup>, Stille (e.g., Pd-SiO<sub>2</sub>/Fe<sub>3</sub>O<sub>4</sub> catalysed cross-coupling of

arylchlorides (for both electron-deficient and electron-rich) with organo-stannanes)<sup>30</sup>, Hiyama (e.g., Zhang et al., used  $\text{Fe}_3\text{O}_4@ \text{SiO}_2\text{-Pd}(\text{OAc})_2$  nano-catalyst for Hiyama coupling)<sup>31</sup>, Ullmann (e.g., Gawande et al., synthesized  $\text{Fe}_3\text{O}_4\text{-CuO}$  nano-catalyst in aqueous medium using inexpensive material and checked its catalytic activity for Ullmann type condensation reaction)<sup>32</sup>, C-O (e.g., Sharma et. al., reported the catalytic usages of  $\text{Cu-2QC}@ \text{Am-SiO}_2@ \text{Fe}_3\text{O}_4$  nano-catalyst for the reaction of 2-carbonyl substituted  $\beta$ -keto-ester/phenol and formamides)<sup>33</sup> and C-S (e.g., Varma and Baig reported C-S coupling of substituted aryl halides and thiophenols catalysed by  $\text{Fe}_3\text{O}_4\text{-DOPA-Cu}$  nano-catalyst)<sup>34</sup> coupling reactions.



**Scheme. II. A. 26.** Carbonylative Sonogashira coupling reaction catalysed by  $\text{Pd}/\text{Fe}_3\text{O}_4$  nano-catalyst.

In addition, with above mentioned reactions magnetite nano particle also proved its utility for other coupling reactions; such as,  $\text{SiO}_2@ \text{Fe}_3\text{O}_4\text{-triazole-Pd}$  catalysed cross coupling reaction between substituted phenylboronic acid and N-substituted indole (scheme. II. A. 27)<sup>35</sup>.



**Scheme. II. A. 27.**  $\text{SiO}_2@ \text{Fe}_3\text{O}_4\text{-triazole-Pd}$  catalysed cross coupling reaction.

## II. A. 7. Other application of $\text{Fe}_3\text{O}_4$ nano-particle:

Besides, synthetic uses magnetite nanoparticles also have medicinal uses, such as M. G. Bawendi et al. recently developed a compact Zwitter ion coated magnetite nano-particle and discuss its biological activity<sup>36</sup>. Again, D.G. Anderson et al., recently reported the effectiveness of lipidoid-coated magnetite nanoparticle for DNA and s-RNA delivery<sup>37</sup>. Furthermore, T. Hyeon and co workers describe the extremely high  $r_2$  relaxivity of ferrimagnetic iron oxide nano-cubes for Highly Sensitive in Vivo MRI of Tumors<sup>38</sup>. S. O' Brien have developed and successfully

applied immune-targeted super magnetic iron oxide nano-particle for in-vivo MRI and potential drug delivery for kidney diseases<sup>39</sup>. Besides, carbon matrix implanted magnetic nanocrystal can acts as a super anode material for lithium-batteries<sup>40</sup>. The versatile catalytic activity, application in medicinal chemistry, magnetic recyclability and low toxicity make magnetite nano-particles as an ecological, industrial and economic benefit.

## **II. A. 8. Conclusion:**

Nitriles are not only serving as biologically important functional group but also used as very useful intermediate for many functional group transformations and also for the preparation nitrogen containing heterocyclic compounds. From literature survey, it seems that most of the reported methodologies are suffered by one or more disadvantages such as use of strong oxidant, expensive catalyst and long reaction time and also by lack of straightforward process. Therefore, author felt the necessity to develop a milder protocol by using less toxic, inexpensive and environmentally benign  $\text{Fe}_3\text{O}_4$ -nano catalyst for the one-pot synthesis of nitriles.