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# **Catalysis Science & Technology**

# ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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# C−H bond cyanation of arenes using N, N-dimethylformamide and NH₄HCO<sub>3</sub> as CN source over hydroxyapatite supported copper catalyst

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Cu supported on hydroxyapatite [HAP:  $Ca_5(PO_4)_3(OH)$ ] catalyst has been found to be an efficient and reusable heterogeneous catalyst for safe cyanation of C-H bonds of hetero aryl compounds. Combination of NH<sub>4</sub>HCO<sub>3</sub> and DMF are identified as CN source under mild reaction conditions. A 10wt%Cu/HAP offered good to excellent yields compared to Ru/HAP and Pd/HAP catalysts. The surface basicity and Cu metal surface area of the catalysts played a significant role on the cyanation reaction through C-H bond activation. The catalyst was recovered and reused for five cycles that showed consistent activity and selectivity. The physicochemical characteristics of the catalysts are rationalized by H<sub>2</sub>-TPR, BET-SA, XPS, TEM and N<sub>2</sub>O titration techniques.

# Introduction

The methodology for the synthesis of aryl nitriles is an area of great interest. Nitrile compounds have wide range of applications in synthetic organic chemistry due to the fact that these nitriles are valuable in installation of functionalities such as aldehydes, amines, amidines, tetrazoles, acids and acid derivatives.<sup>1-3</sup> The aryl nitriles are also key motifs in natural products, pharmaceuticals, agrochemicals, dyes and electronic materials.<sup>4</sup> Aryl nitriles are often synthesized from aryl halides with stoichiometric amounts of CuCN which is being used in Rosenmund-von Braun reaction.5-9 Unfortunately, use of stoichiometric amounts of CN sources would lead to equimolar amounts of heavy metal waste. Therefore, transition metalcatalyzed methods have been explored, such as palladium, nickel and copper-based catalysts, using KCN,<sup>10,11</sup> NaCN,<sup>12,13</sup>  $Me_3SiCN$ ,<sup>14–16</sup> and  $Zn(CN)_2$ <sup>17–21</sup> as cyanating agents. However, these cyanation compounds have several drawbacks e.g. KCN and NaCN are highly toxic; Zn(CN)<sub>2</sub> leads to heavy metal waste and Me<sub>3</sub>SiCN is sensitive to moisture and easily liberate hydrogen cyanide. These limitations seriously restrict their



Significant, amount of work on cyanation reactions are reported by Chang and co-workers. They have used DMF and ammonia or ammonium salts as the combined 'CN' source to realize the cyanation of the carbon-hydrogen (heteroatom) bond.<sup>36</sup> Cyanation of aromatic halides by employing ammonium bicarbonate and DMF (or) DMSO as the combined 'CN' source is also achieved. These methods on cyanation reactions involved the combined 'CN' source contributing from DMF or DMSO provide the 'C' unit of 'CN' while the 'N' unit comes from ammonia or ammonium  ${\rm salts.}^{\rm 36,37}$  We have examined the cvanation of aromatic C-H bonds by using a combination of NH<sub>4</sub>HCO<sub>3</sub> and DMSO as 'CN' source over Pd(II) supported on Mg-La mixed oxide catalyst.<sup>38</sup> Most of these processes are involved either the use of expensive noble metals or the non-eco-friendly reagents. Therefore development of inexpensive base metal catalysts for the cyanation of aryl C-H bonds has become a topic of interest. Herein, we report the supported Cu catalysts for the cyanation of aromatic C-H bonds by using a combination of NH<sub>4</sub>HCO<sub>3</sub> and DMF as the 'CN' source to provide aromatic nitriles in good to excellent yields under mild reaction conditions. In the comparative analysis Cu/HAP demonstrated better nitrile yield than the Ru/HAP and Pd/HAP catalyst.

Hydroxyapatite  $[Ca_5(PO_4)_3(OH)]$  spawned great interest in view of its potentials usefulness as biomaterials, adsorbents, ionexchangers and as catalyst support.<sup>39</sup> Different transition metals supported on hydroxyapatite catalysts have been explored as an effective heterogeneous catalysts in the

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

DOI: 10.1039/C6CY01536K Journal Name

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oxidative cleavage of alkenes,<sup>40</sup> hydrogenation reactions,<sup>41</sup> oxidative coupling of alcohols and amines.<sup>42</sup> The hydroxyapatite has also been studied as a catalyst support for gold and ruthenium in water gas shift reactions as well as a stand-alone catalyst for the dehydrogenation and dehydration of alcohols.43-46 Recently, we have reported, highly basic Mg-LaO mixed oxide supported Pd as a solid base catalyst for the C-H bond activation of arenes in the cyanation reaction.<sup>38</sup> Kou et al reported a rate of 848  $\mu mol~(g_{Cu})^{^{-1}}~h^{^{-1}}$  with regio-isomers (57:33 ratio of) 483  $\mu mol~(g_{Cu})^{\text{-1}}~h^{\text{-1}}$  of 2-(pyridin-2yl)benzonitrile and 365  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup> of 2,6-dicyano phenylpyridine.<sup>31</sup> In the copper mediated direct aryl C-H cyanation reaction; Xu et al reported 647  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup> of 2-(pyridin-2-yl)benzonitrile.<sup>32</sup> Kim et al found 293  $\mu$ mol (g<sub>cu</sub>)<sup>-1</sup> h<sup>-1</sup> 4-methoxybenzonitrile in the conversion of 4methoxyphenylboronic acid.<sup>36c</sup> In the present study an enormous increase in the rate of 2-(pyridin-2-yl)benzonitrile ca. 1184  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup> is observed over a solid base catalyst composed of 10wt%Cu/HAP. In this investigation, we found hydroxyapatite as a support material for Cu for the safe cyanation of hetero aryl compounds. The Cu/HAP catalyst displayed moderate to strong basic sites on the catalyst surface. The physico chemical characteristics of the Cu/HAP catalysts are rationalized by various adsorption and spectroscopic techniques and the catalytic activities are correlated with cyanation of 2-phenylpyridine compounds under mild reaction conditions.

## Experimental

### **Preparation of catalysts**

The hydroxyapatite Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>(OH) was prepared according to an earlier report.<sup>43</sup> In a typical method, the solution of calcium nitrate tetrahydrate (0.326 mol) in 200 mL water was brought to a pH of 11-12 with concentrated (25%) ammonia solution and thereafter diluted to 500 mL. A solution of diammonium hydrogen phosphate (0.318 mol) in 300 mL water was brought to a pH of 11-12 with concentrated (25%) ammonia solution and thereafter diluted to 600 mL. Under vigorous stirring the phosphate solution was added drop wise to the solution of the calcium salt over a period of 2h to produce a milky white precipitate, which was then stirred and boiled for 30 min. The precipitate was washed thoroughly, filtered and dried at 100 °C overnight and then calcined in static air at 500 °C for 5h here after denoted as HAP. The HAP supported metal catalysts were prepared by a wet impregnation method. The required amount of metal precursor [(RuCl<sub>3</sub>xH<sub>2</sub>O, PdCl<sub>2</sub>, Ni(NO<sub>3</sub>)<sub>2</sub> 6H<sub>2</sub>O, and Cu(OAc)2. H2O AR Grade, supplied by Sigma-Aldrich] was taken to give corresponding weight percent of metal dissolved in double distilled water and mixed with HAP power. The solvent is then evaporated under constant stirring, followed by oven drying at 120 °C for 12h and subsequently calcined in static air at 450°C for 5h at a ramping rate of 5°C /min.

# XRD analysis of fresh and used catalysts

The X-ray diffraction patterns of HAP and Cu/HAP catalysts are reported in Figure 1. The diffraction lines at  $2\theta = 25.8^{\circ}$ ,  $29.1^{\circ}$ ,  $31.9^{\circ}$ ,  $32.2^{\circ}$ ,  $33.1^{\circ}$ ,  $34.1^{\circ}$ ,  $40.1^{\circ}$ ,  $46.9^{\circ}$ , and  $49.1^{\circ}$  are attributed to Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>(OH) phase (ICDD # 86-07640) and the diffraction signals due to CuO phase are observed at  $2\theta = 35.5^{\circ}$ ,  $38.67^{\circ}$ (ICDD # 45-0937). The XRD patterns clearly showed that the crystallite size of CuO is increased with increase in Cu loading. The CuO phase is clearly seen at above 5wt%Cu/HAP samples. No changes due to crystal structure and crystallite size of Cu in the fresh and used form of 10wt%Cu/HAP emphasizing the stability of the catalyst under the reaction conditions applied.



Figure 1: XRD patterns of a) Pure HAP, b) 2.5wt%Cu/HAP, c) 5wt%Cu/HAP, d) 7.5wt%Cu/HAP, e) 10wt%Cu/HAP f) 12.5wt%Cu/HAP and e') 10wt%Cu/HAP (used) samples.

#### H<sub>2</sub>-TPR analysis of Cu/HAP samples



Figure 2: H2-TPR profiles of (a) 2.5 (b) 5.0 (c) 7.5 (d) 10.0 and (e) 12.5wt% Cu supported on Ca5(PO4)3(OH) samples

The H<sub>2</sub>-TPR profiles of Cu supported on Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH samples presented in Figure 2 and their corresponding H<sub>2</sub> uptakes are reported in Table 1. It shows that CuO undergone two stage reduction in all the samples. The low temperature reduction signals (230-270 °C) is attributed to dispersed CuO and the high temperature peak (270-375 °C) is attributed to bulk or large size clusters of CuO species.<sup>47</sup> Upon increasing the Cu loading, the Tmax shifted to higher temperature which is an indication of bigger CuO crystals and broadness of the signal is probably due to CuO strongly interacted with hydroxyapatite. Increase in H<sub>2</sub> uptake with an increase in CuO loading suggests the bulk property of the TPR analysis [Table 1].

# CO<sub>2</sub>-TPD analysis of the Cu/HAP samples



Figure 3: CO<sub>2</sub>-TPD profiles of Cu supported on Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH (a) 0.0 (b) 2.5 (c) 5.0 (d) 7.5 (e) 10.0 (f) 12.5wt% catalysts.

The TPD of  $CO_2$  profiles of pure HAP and the Cu loaded HAP samples are reported in Figure 3. Figure 3, shows that pure HAP indicated two peaks corresponding to weak and moderate basic sites. Doping of copper on HAP the basicity of the catalysts is increased and  $T_{max}$  is shifted to high temperatures.<sup>41</sup> The shift in  $T_{max}$  towards high temperatures is gradually increased with increase in Cu content. The numbers of basic sites are found to increase with Cu loading up to 10wt%Cu/HAP.

Table 1: Physicochemical characteristics of the Cu supported on  $Ca_5(PO_4)_3OH$  samples.

Cu	BET	H <sub>2</sub> uptake	CO <sub>2</sub>	N₂O uptake	<sup>d</sup> S <sub>Cu</sub>
(wt%)	surface	(µmol/g <sub>cat</sub> ) <sup>a</sup>	uptake	(µmol/g <sub>cat</sub> ) <sup>c</sup>	/ m²
on	area		(µmol/g <sub>cat</sub> ) <sup>b</sup>		g <sup>-1</sup>
HAP	(m <sup>2</sup> g <sup>-1</sup> )				
0.0	54.0	nd	173	nd	nd
2.5	43.0	232.2	181	1.6	5.30
5.0	35.0	374.5	289	3.9	6.44
7.5	30.0	454.4	295	7.0	7.70
10.0	27.5	530.0	451	10.9	8.99
12.5	25.4	735.0	339	10.8	7.18

nd: not determined; <sup>a</sup>: measured from  $H_2$ -TPR; <sup>b</sup>: measured from TPD of  $CO_2$ ; <sup>cd</sup>: measured from  $N_2O$  titration method.

## X-ray photoelectron spectroscopic analysis

The binding energies obtained XPS analysis revealed that the  $Cu^{2+}$  species are stabilized on HAP surface. Figures 4A and 4B shows Cu 2p and O 1s XPS of fresh and used 10wt%Cu/HAP catalyst. The  $Cu^{2+}$  species are present on the catalyst surface which is confirmed by signals at binding energies 933.7 eV and 953.4 eV of Cu  $2p_{3/2}$  and Cu  $2p_{1/2}$ respectively.<sup>48</sup> These spectral lines ascribed to  $Cu^{2+}$  are retained on the catalyst surface even after 4 cycles of reuse.

DOI: 10.1039/C6CY01536K

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Figure 4: XPS of (A) Cu 2p (B) O 1s spectra of 10wt%Cu/HAP (a) fresh and (b) used catalyst.

#### Transmission electron microscopic analysis

TEM images of the fresh and used (after 1<sup>st</sup> cycle) of 10wt%Cu/HAP samples are reported in Figure 5. The copper particles are spherical in shape with uniform distribution in both fresh and used form. The average particle size of copper is found to be 26 nm and 29 nm on fresh and used catalysts, respectively. The particle sizes of copper in the fresh and used form are more or less similar, thus suggesting the stability of the copper species in the cyanation of aryl compounds.



Figure 5: TEM images of the 10wt%Cu/HAP: (A) fresh and (B) used catalyst (recovered after  $1^{st}$  cycle).

# **Reaction scheme**



#### **Optimization of reaction parameters**

The reaction parameters are optimized by using 2-phenylpyridine as the model substrate. Using 150mg of Cu/HAP catalyst, a combination of  $NH_4HCO_3$  (1.5 mmol) and

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DMSO (2 mL) as the cyanating agent, the desired product i.e. 2-(pyridin-2-yl)benzonitrile is obtained with 30% yield (Table 2, entry 1). Encouraged by this result, several experiments are conducted by altering the oxidant, nitrogen source and solvents. The results are summarized in Table 2.

Table 2: Screening of reaction parameters

Entry	Catalyst	Oxidant/mmol	N source/mmol	Solvent	Yield (%)
1	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMSO	30
2	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	78
3	10wt%Cu/HAP	Ag <sub>2</sub> O/2	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	0
4	10wt%Cu/HAP	TBHP(70% aqueous)/2	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	0
5	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	88
6	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	H2O	0
7	10wt%Cu/MgO	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	58
8	10wt%Cu/Mg- LaO	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	60
9	10wt%Cu/LaO	O <sub>2</sub>	$NH_4HCO_3/1.5$	DMF	55
10	10wt%Pd/HAP	O <sub>2</sub>	$NH_4HCO_3/1.5$	DMF	72
11	HAP	O <sub>2</sub>	$NH_4HCO_3/1.5$	DMF	0
12	10wt%Cu/HAP	O <sub>2</sub>	NH₃ (aq.)/1.5	DMF	0
13 <sup>b</sup>	10wt%Cu/HAP	O <sub>2</sub>	$NH_4HCO_3/1.5$	DMF	71
14 <sup>c</sup>	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	48
15 <sup>d</sup>	10wt%Cu/HAP	O <sub>2</sub>	NH₄HCO₃/1.5	DMF	52
16 <sup>e</sup>	10wt%Cu/HAP	O <sub>2</sub>	NH₄HCO₃/1.5	DMF	30
17	10wt%Cu/HAP	N <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	20
18	$10wt\%Cu/Al_2O_3$	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	10
19	10wt%Ni/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	28
20	10wt%Ru/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	40

<sup>a</sup> Reaction Conditions: 150 mg of 10wt%Cu/HAP catalyst, 2-Phenylpyridine (0.5 mmol), N source (1.5 mmol), Solvent (2 mL), Oxidant (O<sub>2</sub> balloon), 140 °C, 18h;<sup>b</sup> Reaction at 120 °C;<sup>c</sup> Reaction at 100 °C;<sup>d</sup>12h at 140 °C; <sup>e</sup> 6 h at 140 °C.

An improvement in the product yield is observed when DMSO is replaced with DMF (Table 2, enrty 2). Using various oxidants such as oxygen, Ag<sub>2</sub>O, and TBHP; oxygen has been identified as suitable oxidant for the reaction (Table 2, entries 3, 4). An improvement in the product yield is observed while the amount of NH<sub>4</sub>HCO<sub>3</sub> is increased from 1 to 1.5 mmol (Table 2, entry 5). When the solvent DMF is replaced with water the reaction is not occurred (Table 2, entry 6). From this it can be concluded that the presence of DMF is necessary to get the product in high yields. The use of other heterogeneous copper based catalysts such as Cu(II)/Mg-LaO, Cu(II)/MgO and  $Cu(II)/La_2O_3$  exhibited inferior activity when compared to the Cu(II)/HAP catalyst (Table 2, entries 7, 8 and 9). It is interesting to note that the other base and non-base metals such as Ni, Pd and Ru supported on HAP catalysts demonstrated lower activity when compared to Cu/HAP catalyst (Table 2, entries 10, 19, 20). The support alone did not show any activity (Table 2 entry 11). It has been observed that NH<sub>4</sub>HCO<sub>3</sub> is a suitable

nitrogen source for cyanation reaction when compared to ammonia solution (Table 2, entry 12). The reaction temperature had strongly influenced the catalytic activity as the yield of the product is decreased to 71% at 120 °C and to 48% at 100 °C (Table 2, entries 13 and 14). At a temperature of 140 °C; the yield is decreased to 52% when the reaction time maintained for 12h and similar situation observed wherein the yield further fallen to 30% after a reaction time of 6h (Table 2, entries 15 and 16). When the reaction is performed under N<sub>2</sub> atmosphere, only 20% yield observed, indicating that O<sub>2</sub> as the oxidant which is essential for the reaction (Table 2, entry 17). The Al<sub>2</sub>O<sub>3</sub> supported CuO catalyst showed very low activity with 10% yield (Table 2, entry 18).

Table 3, reveals the dependence of cyanation activity over various loadings of copper on HAP catalysts in the C-H bond cyanation of arenes at 140 °C. The nitriles formation is found to increase with increase in Cu loading up to a 10wt% and further increase leads to lower yields (Table 3). The decrease in the catalytic activity is due to agglomeration of copper particles at higher loadings. The pure HAP is found to be inactive for the nitrile formation under the similar experimental conditions (Table 3 entry 1). However, formation of nitriles is marginally low over 12.5wt%Cu/HAP catalyst. These results thus suggest a 10wt%Cu loading is an optimum composition, which demonstrated higher yields compared to other loadings on HAP.

Table 3: Influence of copper loading on HAP for the cyanation reaction

Entry	Catalyst	Oxidant	N	Solvent	Yield			
			source/mmol		(%)			
1	HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	0			
2	2.5wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	24			
3	5wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	37			
4	7.5wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	52			
5	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1	DMF	78			
6	12.5wt%Cu/HAP	O <sub>2</sub>	$NH_4HCO_3/1$	DMF	81			
7	10wt%Cu/HAP	O <sub>2</sub>	$NH_4HCO_3/2$	DMF	85			
8	10wt%Cu/HAP	O <sub>2</sub>	NH <sub>4</sub> HCO <sub>3</sub> /1.5	DMF	88			
Scale: 0.5mmol 2-phenylpyridine. O2-oxidant. DMF-2mL.								

# Substrate Scope

Based on the optimized conditions, several substrates are examined for the C-H bond cyanation using DMF (as solvent and "C" source as well) with  $NH_4HCO_3$  (1.5 mmol) and  $O_2$  as oxidant at a reaction temperature of 140 °C (Table 2).Using 4-methyl 2-phenylpyridine, the corresponding mono cyano derivative is obtained with 72% yield (2b). To some extent, the reaction is sensitive to methyl substitution on the meta position of the 2-phenyl ring (2c), delivering the product in a slightly lower yield than its para counterpart (2b and 2c). Whereas the para substituted methoxy group has offered 67% yield (2d). In contrast, the halo substituted 4-fluoro, 4-chloro and 4-bromo analogues showed yields in the range of 60 to 68% (2e, 2f and 2g). The other functional groups such as -Ph, -

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CN and  $-CF_3$  are also under gone cyanation reaction with the corresponding cyano derivatives of 2-phenylpyridine which showed reasonably good yields (2h, 2i and 2j). Remarkably, 1-naphthyl and 2-naphthyl derivatives of pyridine also furnished the cyanation product with moderate yields (2k and 2l). Interestingly, isoquinoline and quinoline could act as directing groups, delivering the corresponding aryl nitriles with about 61% and 63% yields, respectively (2m and 2n). Gratifyingly, benzo[h]quinoline also demonstrated good efficiency in the current cyanation reaction and produced the corresponding cyanation product with 57% yield (2o).



Plausible reaction mechanism



nitrile.

No reaction was occurred on HAP, although the pure HAP possesses basic sites *ca*. 173  $\mu$ mol g<sup>-1</sup>, indicating that basic sites present on the support have no role on the cyanation

process. Thus, indicating the inert behavior of HAP and the major role of CuO species dispersed on HAP for the cyanation reaction (Table 2, entry 11). From the N<sub>2</sub>O titration data, it can be inferred that higher the Cu metal surface area, the cyanation activity was high. We believe that the basic sites  $(O^2)$ ) present on copper species are responsible for the cyanation reaction. These sites are reversibly generated in the presence of  $O_2$ . It is also observed that there is a direct correlation between Cu metal surface area and the formation of 2phenylpyridine (Figure S1). The CO<sub>2</sub> TPD patterns of 10wt%Cu supported on Al<sub>2</sub>O<sub>3</sub>, MgO and MgLaO samples are presented in Figure S2 and their CO<sub>2</sub> uptakes are reported in Table S5. It shows that a higher CO2 uptake is observed over 10wt%Cu/MgLaO when compared to 10wt%Cu/HAP sample. The 10wt%Cu/Al<sub>2</sub>O<sub>3</sub> and 10wt%Cu/MgLaO both showed very strong CO<sub>2</sub> desorption peak above 650 °C which is attributed to very strong basic sites. However, the overall CO<sub>2</sub> uptake was very low on 10wt%Cu/Al<sub>2</sub>O<sub>3</sub> compared to other samples. In the comparative analysis the 10wt%Cu/HAP sample demonstrated more number of strong basic sites than the other samples. The normalized rate of 2-(pyridin-2-yl)benzonitrile over 10wt%Cu/Al<sub>2</sub>O<sub>3</sub> catalyst is found to be 134  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup>, which is much lower than on 10wt%Cu/HAP that showed ca. 1184  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup>. Whereas both the 10wt%Cu supported on MgO and MgLaO samples exhibited more or less similar rate 780 and 807  $\mu$ mol (g<sub>Cu</sub>)<sup>-1</sup> h<sup>-1</sup> respectively. Under the reaction conditions adopted, HAP seems to be a suitable support for Cu in the cyanation of arenes when compared to Cu/MgO and Cu/MgLaO. From the CO<sub>2</sub> desorption patterns and the cyanation activity data; we believe that moderate to strong basic sites present on the catalyst surface are effective for the C-H bond activation of arenes. Based on the experimental results and in conjugation with earlier reports, a plausible reaction mechanism is proposed and reported in scheme 2.49 In the first step; active sites on Cu particle activate the ortho C-H bond of 2-phenylpyridine to form (I). In the second step; ligand exchange of CN<sup>-</sup> generates the intermediate (II), which would occur in the presence of DMF and NH<sub>4</sub>HCO<sub>3</sub>. Finally, the intermediate (II) undergoes reductive elimination to produce the desired product and Cu(I) species, which subsequently re-oxidized to Cu(II) in the presence of  $O_2$  (a green oxidant).

#### **Catalyst activity studies**

A 10 mL round bottom flask was charged with 2-Phenylpyridine (77 mg, 0.5 mmol), Cu/HAP (150 mg), NH<sub>4</sub>HCO<sub>3</sub> (1.5 mmol), DMF (2 mL) and O<sub>2</sub> as oxidizing agent. The round bottom flask was kept stirring at 140 °C. After 18h of run the reaction was monitored by TLC, 5 mL of ethyl acetate was added to the reaction mixture. The catalyst was separated by simple centrifugation and the reaction mixture was treated with brine solution (10 mL). The organic layer was separated and the aqueous layer was back extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extract was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and it was concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel using ethyl acetate—hexane (10%)

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as an eluent (pale yellow oil, 88% yield). The catalyst was washed with distilled water for several times then dried in an oven at 100°C and used for the next cycle. Following the similar procedure the cyanation reaction was tested for 4 recycles.

# **Recyclability studies**

The recyclability of the catalyst is examined using 2-phenyl pyridine, NH<sub>4</sub>HCO<sub>3</sub> and DMF at 140 °C, which emphasized that the catalyst can be used for four consecutive cycles with consistent yields. In the recyclability process, catalyst is recovered by a simple centrifugation. The recovered catalyst is washed with distilled water, air-dried and used directly for the next cycle without any further purification. The ICP-OES analysis of fresh and used 10wt%Cu(II)/HAP showed 9.8% and 9.6% respectively. The XPS analysis of the fresh and used 10wt%Cu/HAP catalysts further confirmed that there is no change in chemical composition of the Cu, Ca, P and O (Table S3) at the near surface region. The activity data demonstrated that the catalyst can be reused for four consecutive cycles without loss of activity. The elemental analysis revealed that there is no leaching of Cu from the HAP surface suggesting the robust nature of Cu/HAP for the cyanation of aryl compounds.



# Conclusions

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The Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH has been identified as a suitable support for Cu in the C-H bond activation for the cyanation of hetero aryl compounds. The CuO supported on hydroxyapatite is active for the generation o 'CN' from a mixture of NH<sub>4</sub>HCO<sub>3</sub> and dimethylformamide. The basic sites on hydroxyapatite have no role on the catalytic activity on the contrary the basic sites contributed from copper surface are responsible for the cyanation reaction. A direct correlation between Cu metal surface area and cyanation activity is observed. An optimum copper loading is established (10wt%) under the experimental conditions adopted. In the comparative analysis the 10wt%Cu/Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH demonstrated better yields than the noble metal loaded (Ru and/or Pd) Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH catalysts. We developed a cheaper base metal catalyst i.e. Cu for the safe cyanation of hetero aryl compounds under mild reaction

conditions. The catalyst was recycled and used for four recycles that showed consistent activity and selectivity.

# Acknowledgements

The authors Venu and Vishali thank UGC for the award of fellowship. AV, JB thanks DST New Delhi for funding under Indo-Australia through AISRF program.

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C–H bond cyanation of arenes using N, N-dimethylformamide and NH<sub>4</sub>HCO<sub>3</sub> as CN source over hydroxyapatite supported copper catalyst

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Graphical abstract



Copper dispersed on  $Ca_5(PO_4)_3OH$  has been identified as an excellent heterogeneous catalyst for the in situ generation of 'CN' from  $NH_4HCO_3$  and N,N-dimethylformamide, in the C-H bond activation of 2-phenylpyridine. A direct correlation between Cu metal surface area and the cyanation activity is established.