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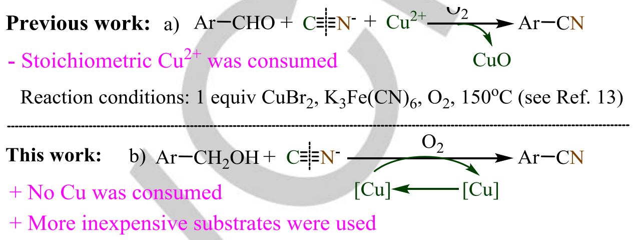
Cu_2O-Catalyzed Conversion of Benzyl Alcohols Into Aromatic Nitriles via the Complete Cleavage of the C≡N Triple Bond in the Cyanide Anion

Wenbo Liu+,[a] Peichen Tang+,[b] Yi Zheng+,[a] Yun-Lai Ren,*[a] Xinzhe Tian,*[a] Wankai An,[a] Xianfu Zheng,*[a] Yinggang Guo,[a] and Zhenpeng Shen[a]

Abstract: Nitrogen transfer from cyanide anion to the aldehydes is emerging as a promising method for synthesis of aromatic nitriles. However this method still suffers from a disadvantage that a use of stoichiometric Cu(II) or Cu(I) salts is required to enable the reaction. In the present article, we overcame this drawback, and developed a catalytic method for the nitrogen transfer from cyanide anion to the alcohols via the complete cleavage of the C≡N triple bond using phen/Cu_2O as the catalyst. The present condition allowed a series of benzyl alcohols to be smoothly converted into aromatic nitriles in moderate to high yields. In addition, the present method could be extended to the conversion of cinnamic alcohol to 3-phenylacrylonitrile.

Introduction

Aromatic cyanation is an important kind of organic reactions because the resulting products not only constitute the key components of many agrochemicals, pharmaceuticals and dyes,[1] but also can serve as versatile intermediates for various synthetic targets such as aryl aldehydes, nitrogen-containing heterocycles, amidines, tetrazoles amines, etc.[2] Among various strategies for the aromatic cyanation,[3] transition-metal catalyzed cyanation of aryl halides has been extensively investigated.[4] Another kind of convenient methods is the oxidative condensation between aryl aldehydes and ammonia or its surrogate.[5] By comparison, it seems to be more fascinating to use benzyl alcohols[6] as the substrate because the alcohols are more inexpensive and easily available. For example, Wang, Yang, Xiao and co-workers have used the Ru catalyst to enable the amination-dehydrogenation of alcohols with ammonia as the nitrogen source.[7] Recently, Singh and co-workers have described photocatalytic conversion of the alcohols to aryl nitriles via the nitrogen transfer of sodium azide.[8] In addition, ammonium formate,[9] $TMSN_3$ (trimethylsilyl azide)[10] and NH_2OH [11] have been used as the nitrogen source to carry out the amination-dehydrogenation of alcohols.



Scheme 1. Methods for the synthesis of aromatic nitriles via the C≡N triple bond cleavage of CN^-.

Compared with the methods above, the formation of nitriles via the nitrogen transfer of CN^- is more challenging because the C≡N triple bond is quite difficult to be broken.[12] Recently, this challenge has been overcome by You, Lei and their co-workers who have used a stoichiometric copper salt to enable conversion of aldehydes to nitriles via the complete cleavage of the C≡N triple bond in CN^- (Scheme 1a).[13] Subsequently, Jin, Li and their co-workers have described an analogous example where aryl methyl ketones have been used as the substrates.[14] However, the procedures above for the nitrogen transfer of CN^- require using a stoichiometric amount of Cu(II) or Cu(I) salts because the used Cu(II) or Cu(I) salt is converted to CuO that is inert as the promoter for the present reaction. By all appearances, it should be desirable and challenging to develop an effective catalyst to avoid the consumption of stoichiometric Cu salts.[15] Aiming at this challenging, we have screened a large number of Cu compounds and found that Phen/Cu_2O is very effective as the catalyst to enable the conversion of benzyl alcohols into aromatic nitriles with $K_4[Fe(CN)_6]$ as the nitrogen source via the complete cleavage of the C≡N triple bond, providing a promising method for synthesis of aromatic nitriles from benzyl alcohols with less toxic and readily available $K_4[Fe(CN)_6]$ as the nitrogen source, and the results are herein reported (Scheme 1b).

Results and Discussion

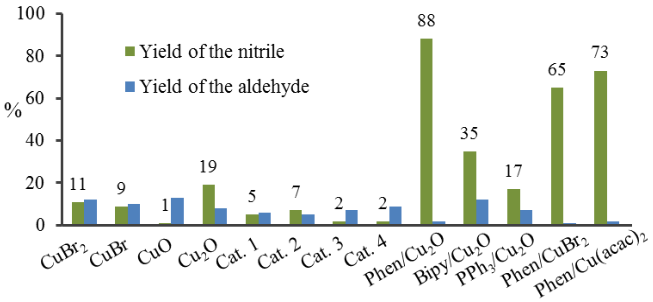


Figure 1. Reaction of 2-methylbenzyl alcohol catalyzed by various catalysts (reaction conditions: 0.5 mmol substrate, 0.3 mmol $K_4Fe(CN)_6$, 0.075 mmol Cu compound or Cat. 1-4, 2 mL DMSO, 2 MPa O_2, 40 h, 140 °C; the loading of phen, bipy or PPh_3 was 0.5 mmol in the case of the last five experiments in this figure, while these ligands were not used in the other cases).

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Initial investigations were carried out with 2-methylbenzyl alcohol as the model substrate to identify a suitable catalyst system. As shown in Figure 1, when 15 mol% $CuBr_2$ was used as the catalyst, 2-methylbenzonitrile product was obtained in very low yield, along with 12 % 2-methylbenzaldehyde by-product that is from the oxidative dehydrogenation of the alcohol. The reaction with CuBr gave a similar result, while hardly any targeted product was obtained in the case of CuO. In addition, we tested the ability of several *N*-heterocyclic carbine-Cu catalysts (Figure 2), but the targeted product was obtained in only 2-7% yields. Fortunately, a combination of 1,10-phenanthroline (phen) and Cu_2O allowed 2-methylbenzonitrile to be obtained in a high yield (88%). Changing the ligand from 1,10-phenanthroline to 2,2′-bipyridine (bipy) or PPh_3 led to a significantly decrease in the yield of the targeted product. Of the screened Cu compounds, Cu_2O turned out to be the most effective one.

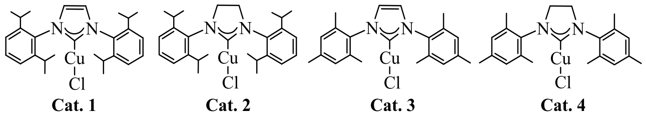
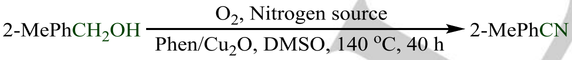


Figure 2. Several *N*-heterocyclic carbine-Cu catalysts.

After identifying an effective catalyst, we optimized other reaction conditions. We performed the reactions using $K_3Fe(CN)_6$ or KCN as the nitrogen source (Scheme 2), but the obtained yields were lower than that in the case of $K_4Fe(CN)_6$ (Figure 1), indicating that $K_4Fe(CN)_6$ was the optimal one among the screened nitrogen sources. As seen from Figure 3, the reaction was highly dependent on the type of the solvent. The use of toluene, tetrahydrofuran (THF), 1,4-dioxane and acetonitrile as the solvents gave the targeted product in 13-22% yields, while moderate yields were obtained in the case of *N*-methyl-2-pyrrolidone (NMP) and *N*,*N*-dimethylformamide (DMF). Of the screened solvents, dimethyl sulfoxide (DMSO) was the most effective. It is noteworthy that the main by-product was 2-methylbenzaldehyde in most cases, whereas the use of THF was an exception where 48% 2-methylbenzoic acid by-product was observed. In addition, a small amount of 2-methylbenzamide was produced in the case of DMSO.



$$\text{2-MePhCH}_2\text{OH} \xrightarrow[\text{Phen/Cu}_2\text{O, DMSO, 140 °C, 40 h}]{\text{O}_2\text{, Nitrogen source}} \text{2-MePhCN}$$

Nitrogen source: 0.6 equiv $K_3Fe(CN)_6$ Yield: 72%

Nitrogen source: 2 equiv KCN Yield: 13%

Scheme 2. Reaction of 2-methylbenzyl alcohol using different cyanide sources. (reaction conditions: 0.5 mmol substrate, nitrogen source, 0.075 mmol Cu_2O, 0.5 mmol phen, 2 mL DMSO, 2 MPa O_2, 40 h, 140 °C).

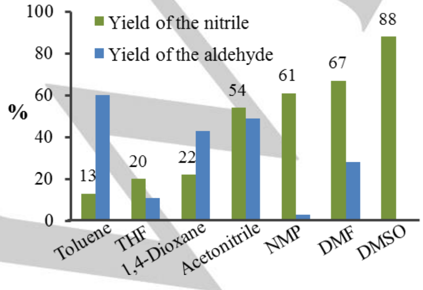


Figure 3. Effect of the solvent on the reaction (reaction conditions: 0.5 mmol 2-methylbenzyl alcohol, 0.3 mmol $K_4Fe(CN)_6$, 0.075 mmol Cu_2O, 0.5 mmol phen, 2 mL solvent, 2 MPa O_2, 40 h, 140 °C).

Subsequently, the effect of the oxygen pressure on the reaction was investigated (Figure 4). Hardly any targeted product was obtained in the absence of oxygen, which revealed that oxygen played an important role in the reaction. The reaction under 0.1 MPa oxygen gave the targeted product in 5% yield. The yield of the targeted product increased continuously with elevating the oxygen pressure from 0.1 to 2 MPa, while the yield become slightly lower when the oxygen pressure increased from 2 MPa, suggesting that 2 MPa was the optimum pressure. It is worth noting that excessively high oxygen pressure would lead to the formation of 2-methylbenzamide. For example, no 2-methylbenzamide was observed in the case of 1.5 MPa oxygen, whereas the reaction with 1.5 MPa oxygen gave 2-methylbenzamide in 8% yield.

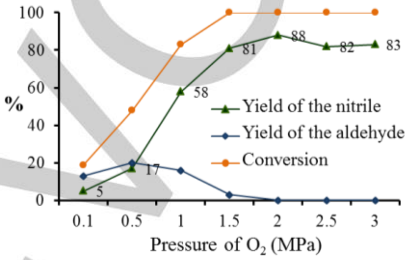


Figure 4. Effect of O_2 pressure on the reaction (reaction conditions: 0.5 mmol 2-methylbenzyl alcohol, 0.3 mmol $K_4Fe(CN)_6$, 0.075 mmol Cu_2O, 0.5 mmol phen, 2 mL DMSO, 2 MPa O_2, 40 h, 140 °C).

A series of representative benzyl alcohols were tested to explore the scope and generality of this reaction. As shown in Table 1, various benzyl alcohols underwent the transformation to give the targeted product in moderate to high yields, along with benzamide or benzaldehyde by-products. The presence of electron-donating groups bonded to the benzene ring decreased the yields of the targeted products, but increased the conversion of substrates. For example, 4-bromobenzyl alcohol was converted to 4-bromobenzonitrile in 81% yield with 95% conversion (Table 1, entry 1), while the same condition allowed 4-methoxybenzyl alcohol to be converted to the targeted product in 49% yield with 100% conversion (Table 1, entry 2). It is worth noting that the transformation of 4-methoxybenzyl alcohol gave by-products such as 4-methoxybenzaldehyde, 4-methoxybenzoic acid and so on from oxidation of the alcohol in as high as 51% total yield. These results indicate that the presence of electron-donating groups is beneficial for dehydrogenation of the alcohol to the aldehyde, but would decrease the reactivity of the substrate in the step of conversion of the aldehyde to the targeted product. So we had to increase the reaction temperature to 140 °C in the case of the benzyl alcohols with electron-donating groups (Table 1, entries 3-6). It is worth noting that the presence of electron-withdrawing group would increase the yield of benzamide by-products. For instance, the reaction of the benzyl alcohols with alkoxy or amino groups gave only 1-4% benzamide by-products, whereas this kind of by-products were obtained in as high as 10-21% yields in the case of using 4-fluorobenzyl alcohol, 4-chlorobenzyl alcohol and 3,4-dichlorobenzyl alcohol as the substrates. Interestingly, although 2-methylbenzyl alcohol had a bigger steric hindrance around the reactive site than 4-methylbenzyl alcohol, it was converted to the targeted product in higher yield than the latter, due to the formation of larger amount of 4-methylbenzamide by-product in the case of 4-methylbenzyl alcohol (Table 1, entry 12 vs 13), which suggested that the steric

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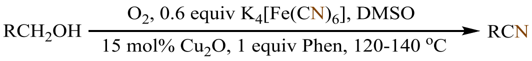
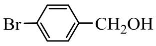
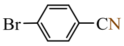
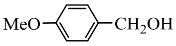
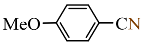
hindrance would restrain the formation of the amide by-product. 1-naphthalenemethanol was a good substrate and gave the nitrile product in 91% yield (Table 1, entry 16), but the reaction of 9-anthracenemethanol gave the targeted product in only 52% yield (Table 1, entry 17). The reaction of 4-pyridinemethanol also proceeded well, but the obtained main product was 4-pyridinecarboxamide (Table 1, entry 18). Interestingly, 2-furanmethanol was converted to 2-furoic acid rather than the nitrile product (Table 1, entry 19). In addition, the present method was efficient for the conversion of cinnamic alcohol to 3-phenylacrylonitrile, and the nitrile product was obtained in 81% yield (Table 1, entry 20).

Table 1. Conversion of various alcohols to aromatic nitriles.[a]



$$\text{RCH}_2\text{OH} \xrightarrow[\text{15 mol\% Cu}_2\text{O, 1 equiv Phen, 120-140 °C}]{\text{O}_2\text{, 0.6 equiv K}_4[\text{Fe(CN)}_6]\text{, DMSO}} \text{RCN}$$

Entry	Substrate	Product[b]	Yield (%)[c]
1[e]			81
2[e]			49[d]
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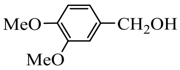
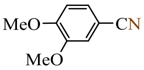
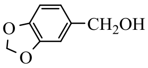
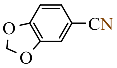
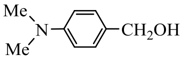
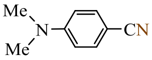
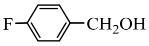
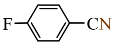
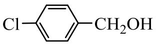
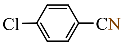
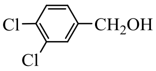
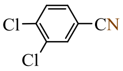
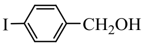
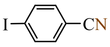
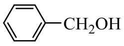
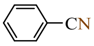
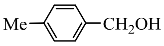
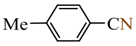
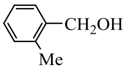
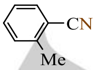
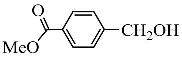
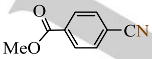
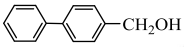
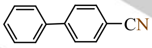
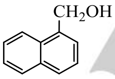
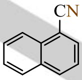
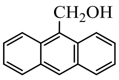
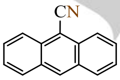
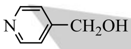
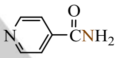
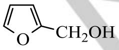
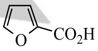
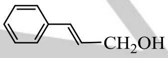
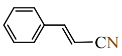
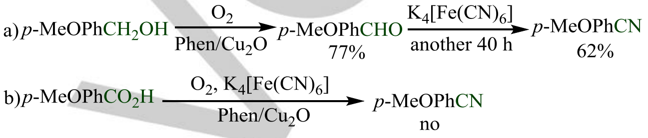
4			68
5			62
6			80
7[f]			85[d]
8[f]			81[d]
9[e]			74
10[e]			86
11[g]			72[d]
12[e]			80[d]
13			88[d]
14			63
15			80
16[g]			91
17[g]			52
18			75
19[e]			64
20			81

[a] Reaction conditions: 0.5 mmol 2-methylbenzyl alcohol, 0.3 mmol $K_4Fe(CN)_6$, 0.075 mmol Cu_2O, 0.5 mmol phen (1,10-phenanthroline), 2 mL DMSO, 2 MPa O_2, 40 h, 140 °C. [b] Determined by ^{1}H-NMR and ^{13}C-NMR. [c] Isolated yield. [d] The yield was determined by GC with an internal standard. [e] 120 °C. [f] 0.05 mmol Cu_2O, 120 °C. [g] 0.1 mmol Cu_2O, 120 °C.

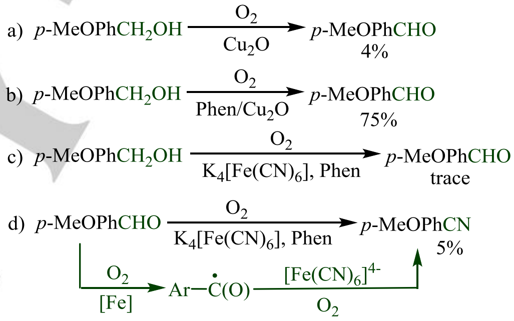
Subsequently, several control experiments were performed to gain insight into the reaction mechanism. As shown in Scheme 3a, 4-methoxybenzyl alcohol underwent the oxidative dehydrogenation to give the aldehyde product in 77% yield in the absence of $K_4[Fe(CN)_6]$, and the reaction between the aldehyde and $K_4[Fe(CN)_6]$ went well under our condition. These results indicate that the present transformation is a stepwise reaction where oxidative dehydrogenation of the alcohol to the aldehyde is followed by conversion of the aldehyde to the nitrile. A small amount of 4-methoxybenzoic acid by-product was observed under our conditions, hence it was possible that the present reaction underwent the formation, decarboxylation and cyanation of 4-methoxyphenylacetic acid, but this possibility was ruled out based on the following result: The present condition did not allow 4-methoxyphenylacetic acid to be converted to the nitrile product (Scheme 3b).



$$\text{a) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{Phen/Cu}_2\text{O}]{\text{O}_2} \underset{77\%}{p\text{-MeOPhCHO}} \xrightarrow[\text{another 40 h}]{\text{K}_4[\text{Fe(CN)}_6]} \underset{62\%}{p\text{-MeOPhCN}}$$

$$\text{b) } p\text{-MeOPhCO}_2\text{H} \xrightarrow[\text{Phen/Cu}_2\text{O}]{\text{O}_2\text{, K}_4[\text{Fe(CN)}_6]} \underset{\text{no}}{p\text{-MeOPhCN}}$$

Scheme 3. Control experiments for the investigation on the intermediates (for the reaction conditions, see Scheme S1 in the supporting information).



$$\text{a) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{Cu}_2\text{O}]{\text{O}_2} \underset{4\%}{p\text{-MeOPhCHO}}$$

$$\text{b) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{Phen/Cu}_2\text{O}]{\text{O}_2} \underset{75\%}{p\text{-MeOPhCHO}}$$

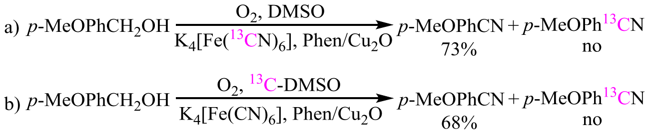
$$\text{c) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{K}_4[\text{Fe(CN)}_6]\text{, Phen}]{\text{O}_2} \underset{\text{trace}}{p\text{-MeOPhCHO}}$$

$$\text{d) } p\text{-MeOPhCHO} \xrightarrow[\text{K}_4[\text{Fe(CN)}_6]\text{, Phen}]{\text{O}_2} \underset{5\%}{p\text{-MeOPhCN}}$$

$$p\text{-MeOPhCHO} \xrightarrow[{[\text{Fe}]}]{\text{O}_2} \text{Ar}\text{—}\dot{\text{C}}\text{(O)} \xrightarrow[\text{O}_2]{[\text{Fe(CN)}_6]^{4-}} p\text{-MeOPhCN}$$

Scheme 4. Control experiments for the mechanistic investigation (for the reaction conditions, see Scheme S2 in the supporting information).

Afterwards, we wanted to clarify the roles of Cu_2O, 1,10-phenanthroline (phen) and $K_4[Fe(CN)_6]$ in the step of the oxidative dehydrogenation of the alcohol. The dehydrogenation hardly occurred in the presence of O_2/Cu_2O (Scheme 4a), while an addition of phen resulted in the formation of 75% 4-methoxybenzaldehyde (Scheme 4b). These results suggest that phen is indispensable in this step, which is possibly attributed to that phen can effectively disperse the hardly soluble Cu_2O to form the catalytically active species by its coordination to Cu species. In addition, the effect of phen as the ligand on the electronic configuration of Cu species is one of the main reasons. As shown in Scheme 4c, the dehydrogenation hardly occurred in the absence of Cu_2O, revealing that phen/Cu_2O played the role of the catalyst in the step of the conversion of the alcohol to the aldehyde. Interestingly, when Cu_2O was absent, 5% 4-methoxybenzonitrile product was formed (Scheme 4d), which revealed that 4-methoxybenzaldehyde could directly react with $K_4[Fe(CN)_6]$.



$$\text{a) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{K}_4[\text{Fe}(^{13}\text{CN})_6]\text{, Phen/Cu}_2\text{O}]{\text{O}_2\text{, DMSO}} \underset{73\%}{p\text{-MeOPhCN}} + \underset{\text{no}}{p\text{-MeOPh}^{13}\text{CN}}$$

$$\text{b) } p\text{-MeOPhCH}_2\text{OH} \xrightarrow[\text{K}_4[\text{Fe(CN)}_6]\text{, Phen/Cu}_2\text{O}]{\text{O}_2\text{, }^{13}\text{C-DMSO}} \underset{68\%}{p\text{-MeOPhCN}} + \underset{\text{no}}{p\text{-MeOPh}^{13}\text{CN}}$$

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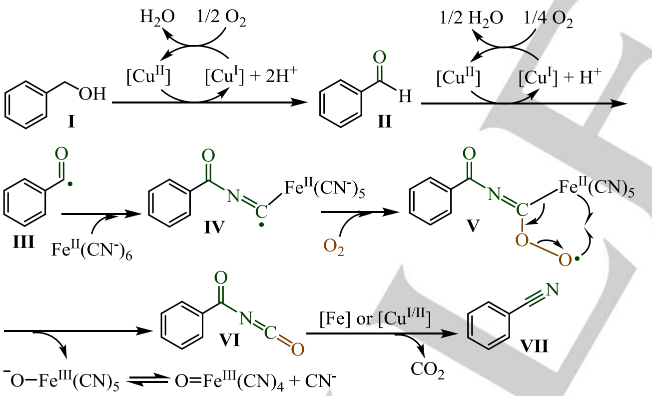
Scheme 5. C^{13}-labelling experiments (for the reaction conditions, see Scheme S3 in the supporting information).

Next, we performed several control experiments to clarify where the carbon atom of the cyano group in the nitrile product came from. When either $K_4[Fe(^{13}CN)_6]$ or ^{13}C-DMSO was used, no ^{13}C-labelled product was formed (Scheme 5), which revealed that both $K_4[Fe(CN)_6]$ and DMSO did not provide the carbon to the nitrile product, thus it was reasonable that the carbon atom of the cyano group was from the alcohol under our condition. In addition, the nitrogen atom came obviously from $K_4[Fe(CN)_6]$ because no other compound apart from this reagent contained the nitrogen atom in the reaction system. These results revealed that $K_4[Fe(CN)_6]$ underwent the complete cleavage of the C≡N triple bond in the present reaction.

At last, we put forward a plausible mechanism with benzyl alcohol as the representative substrate based on the observation above and previous literatures.[13,14] As shown in Scheme 6, the alcohol **I** undergoes firstly the oxidative dehydrogenation to give the aldehyde **II** under the catalysis of 1,10-phenanthroline/Cu_2O, which be followed by the formation of acyl radical **III** from Cu-catalyzed oxidation via the single electron transfer. The acyl radical **III** reacts with $Fe^{II}(CN^{-})_6$ to give the Fe^{II}-bonded carbon-centered radical **IV**. Then the reaction between the radical **IV** and the oxygen molecule gives benzoyl isocyanate **VI**. Finally, a carbon dioxide molecule is eliminated from the benzoyl isocyanate **VI** to give benzonitrile product. It is worth noting that transition metals catalyzed conversion of benzoyl isocyanate to benzonitrile has been reported in previous literatures,[13,17] but the mechanism pathway for this step cannot be clarified at the present stage.



Scheme 6. Proposed pathway for the present reaction.

Conclusion

In conclusion, we found an effective catalyst for the conversion of benzyl alcohols into aromatic nitriles with $K_4[Fe(CN)_6]$ as the nitrogen source via the complete cleavage of the C≡N triple bond, which avoided the consumption of stoichiometric Cu salts in previous reports.[13,14] A series of alcohols including benzyl alcohols and cinnamic alcohol underwent the present transformation to provide the targeted products in moderate to high yields. The present method was compatible with various groups, e.g. alkyl, alkoxy, fluoro, bromo, chloro, methoxycarbonyl and *N,N*-dimethylamino group. To our knowledge, this is the first example for using a catalytic amount of transition metal salts to enable the nitrogen transfer from cyanide anion to the aldehydes or the alcohols. Compared with previous methods for synthesis of aromatic nitriles from benzyl alcohols with ammonia,[7] sodium azide[8] or $TMSN_3$[10] as the nitrogen source, the present method has an advantage of using readily available and less toxic nitrogen source.

Experimental Section

1. General comments

All procedures for the cyanation were carried out in a 40 mL stainless steel autoclave lined with Teflon. *N*-heterocyclic carbine-Cu catalysts were synthetized based on previous literature.[16] All commercially available chemicals were used directly as purchased without further purification unless otherwise stated. GC-MS spectra was recorded on an Agilent 6890/5973N gas chromatography-mass spectrometry instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz instrument. Gas chromatography analyses were performed on a Varian CP-3800 instrument with a FID detector and a CP-WAX 57CB FS capillary chromatographic column.

2. General procedure for Cu_2O-catalyzed conversion of benzyl alcohols into aromatic nitriles

To a stainless steel autoclave lined with Teflon, 0.5 mmol substrate, 0.3 mmol $K_4Fe(CN)_6$, 0.5 mmol 1,10-phenanthroline, Cu_2O (0.05, 0.075 or 0.1 mmol) and 2 mL DMSO were added. Then the reactor was filled with 2 MPa oxygen, and was heated under magnetic stirring at 120 or 140 °C for 40 h. Once the reaction time was reached, the mixture was cooled to room temperature, diluted with 5 mL ethyl acetate, filtered via a Celite pad, and washed with 10 mL ethyl acetate. The organic phase was washed with 6 mL water, dried with anhydrous sodium sulfate and concentrated in vacuum. GC analysis provided the GC yields of the products with an internal standard. In addition, the crude product from another parallel experiment was purified by column chromatography, and identified by ^{1}H-NMR and ^{13}C-NMR.

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Keywords: Cuprous oxide • Aromatic nitriles• Benzyl alcohols • Catalysis • Potassium ferrocyanide

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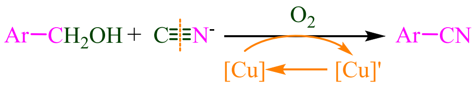

A catalytic method was firstly developed for the nitrogen transfer from cyanide anion to the alcohols via the complete cleavage of the C≡N triple bond using Phen/Cu_2O as the catalyst. The present condition allowed various benzyl alcohols to be smoothly converted into aromatic nitriles in moderate to high yields.

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