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Catalytic cyanation of aryl iodides using DMF and ammonium bicarbonate as the combined source of cyanide: a dual role of copper catalysts†

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Cu(II)-catalyzed cyanation of aryl iodides has been developed using DMF and ammonium bicarbonate as the combined source of cyanide. It is assumed that copper is involved both in the generation of "CN" units from DMF–ammonia and in the cyanation of aryl halides. A range of electron-rich and fused (hetero)aryl iodides underwent cyanation resulting in moderate to good yields.

Nitrile is a ubiquitous building unit used in synthetic chemistry, and it can readily be converted to various functional groups such as aldehydes, amides, amines, amidines, tetrazoles, or other carboxy variants.[1] Nitriles are also present in diverse natural products and industrially important compounds such as pharmaceuticals, agrochemicals, and dyes.[2] Sandmeyer[3] and Rosenmund-von Braun[4] reactions are the classical methods for the introduction of cyano groups, in which CuCN is employed as a cyanating agent in stoichiometric amounts. Procedures based on transition metals[5] including Pd, Ni, or Cu species also serve as attractive and economical synthetic routes to the preparation of nitriles. In this approach, the anionic cyanide sources used include NaCN,[6] KCN,[7] $Zn(CN)_2$,[8] and $K_4[Fe(CN)_6]$.[9] A major drawback of this process is the requirement of toxic cyanating agents along with the formation of metal wastes in a stoichiometric amount. This issue has recently been addressed in a new approach that employs non-metallic organic precursors bearing a cyano unit in their molecular structure.[10] These organo precursors include acetone cyanohydrine,[11] TMSCN,[12] acetonitrile,[13] malononitrile,[14] benzyl cyanide,[15] benzyl thiocyanate,[16] phenyl cyanate,[17] DDQ,[18] AIBN,[19] ethyl isocyanate,[20] *tert*-butyl isocyanide,[21] *N*-cyanobenzimidazole,[22] cyanogen bromide,[23] or *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS).[24]

On the other hand, in the past few years, an additional research direction for cyanation has been scrutinized by utilizing organic compounds that generate "CN" units *in situ*. For instance, Yu *et al.* reported the Cu-mediated cyanation of aryl C–H bonds using nitromethane as a cyano precursor.[25] In this regard, we discovered that the cyano unit "CN" can be generated *in situ* from the combined source of DMF and aqueous ammonia under copper-mediated oxidative conditions for the cyanation of the aryl C–H bond using a palladium catalyst.[26a] An isotope study disclosed that the carbon atom of -CN comes from the dimethyl amino group of DMF and the nitrogen atom originates from ammonia. Subsequently, NH_4I and DMF were also utilized as the combined source of cyanide in the cyanation of aryl boronic acids and electron-rich arenes,[26b] indoles[26c] and organosilanes.[26d] In this case, ammonium iodide plays a dual role as an iodinating reagent as well as the nitrogen source of the "CN" unit. Although our cyanation approach was proved to be unique and versatile, one of the main drawbacks was the requirement of more than stoichiometric amounts of copper species in each procedure.

Some additional elegant cyanation approaches have also been reported by others by employing DMF,[27] formamide[28] or analogous combined sources[29] to produce the cyano group *in situ*. Again, the main limitation of the above-mentioned procedures is the use of more than stoichiometric amounts of copper species. This led us to investigate the development of a cyanation method, being *catalytic in copper*.[30] Herein, we describe our preliminary results of the Cu-catalyzed cyanation of aryl iodides using NH_4HCO_3 and DMF as the combined source of "CN" units.

We initiated our studies by examining a catalytic reaction of *p*-iodoanisole (**1a**) using NH_4HCO_3 and DMF as the combined source of "CN" units using $Cu(NO_3)_2{\cdot}3H_2O$ (20 mol%). We envisioned that the key to success would be the choice of a suitable oxidant, and therefore, a wide range of oxidants were screened (see the ESI† for details). We were pleased to observe that Ag_2CO_3 worked as an effective oxidant under the initial catalytic conditions (Table 1, entry 1). It was also found that a sub-stoichiometric amount of silver species could facilitate cyanation under an O_2 atmosphere using 10 mol% of copper(II) nitrate (entry 2). While the reaction was best performed at 150 °C, lowering the reaction temperature resulted in a decreased product yield (entry 3). Various silver salts such as Ag_2O, AgOAc and AgOTf were less effective when compared to Ag_2CO_3 (entries 4–6). In addition, copper species (*e.g.* CuI or $CuSO_4$) other

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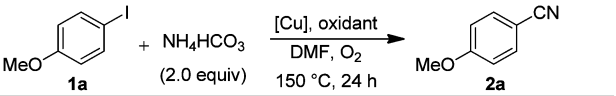
Table 1 Optimization of reaction conditions[a]



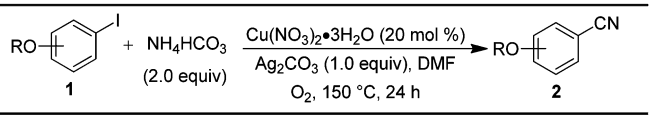
Entry	[Cu] (mol%)	Oxidant (equiv.)	Yield[b] (%)
1	$Cu(NO_3)_2{\cdot}3H_2O$ (20)	Ag_2CO_3 (1.5)	85
2	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	Ag_2CO_3 (0.4)	80(76)[c]
3	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	Ag_2CO_3 (0.4)	66[d]
4	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	Ag_2O (0.4)	67
5	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	AgOAc (0.4)	44
6	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	AgOTf (0.4)	62
7	CuI (10)	Ag_2CO_3 (0.4)	26
8	$CuSO_4$ (10)	Ag_2CO_3 (0.4)	16
9	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	Ag_2CO_3 (0.4)	50[e]
10	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	Ag_2CO_3 (0.4)	9[f]
11	—	Ag_2CO_3 (0.4)	0
12	$Cu(NO_3)_2{\cdot}3H_2O$ (10)	—	16

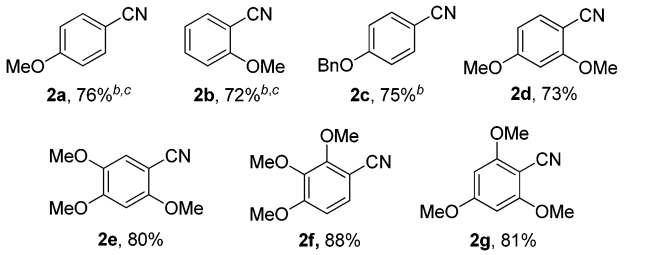
[a] Reaction conditions: **1a** (0.3 mmol), NH_4HCO_3 (2.0 equiv.), oxidant, and [Cu] in DMF (1.5 mL) under an O_2 balloon at 150 °C. [b] ^1H NMR yield (internal standard: 1,1,2,2-tetrachloroethane). [c] Isolated yield in parentheses. [d] Run at 140 °C. [e] Under an air atmosphere. [f] Under a N_2 atmosphere.

than $Cu(NO_3)_2{\cdot}3H_2O$ displayed significantly reduced reactivity (entries 7 and 8). When the reaction was carried out under an air or nitrogen atmosphere, the desired product **2a** was obtained in 50% and 9% yields, respectively, suggesting that O_2 plays an important role in this transformation (entries 9 and 10). As predicted, cyanation did not take place in the absence of copper species (entry 11). Cyanation was observed to be catalytic only in the presence of Ag_2CO_3 (entry 12). In addition, although different carbon sources were tested, they were much less effective for catalytic cyanation under otherwise identical conditions: DMSO (<5%), *N*,*N*-dimethylacetamide (DMA, 22%), *N*-methyl-2-pyrrolidone (NMP, 11%) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU, 27%) (see the ESI† for details).

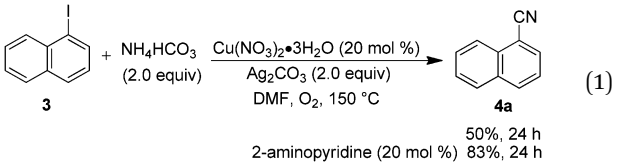
With the optimized catalytic conditions in hand, we next investigated the substrate scope of electron-rich aryl iodides (Table 2). The reaction proceeded efficiently with *o*-iodoanisole to furnish the corresponding nitrile **2b** in 72% yield using 10 mol% of $Cu(NO_3)_2{\cdot}3H_2O$ and 0.4 equiv. of Ag_2CO_3. *p*-Benzyloxyiodobenzene underwent cyanation with 67% yield, but the yield of **2c** was further improved to 75% by employing 1.0 equiv. of Ag_2CO_3. Aryl iodides bearing multiple substituents were also examined, and it

Table 2 Cu-catalyzed cyanation of electron-rich aryl iodides[a]





[a] Reaction conditions: **1** (0.3 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (20 mol%), NH_4HCO_3 (2.0 equiv.), Ag_2CO_3 (1.0 equiv.) in DMF (1.5 mL) under an O_2 balloon at 150 °C for 24 h. [b] $Cu(NO_3)_2{\cdot}3H_2O$ (10 mol%). [c] Ag_2CO_3 (40 mol%).



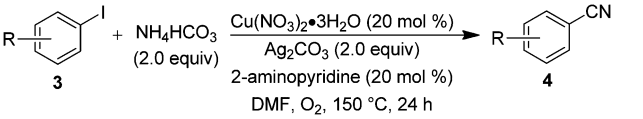
(1)

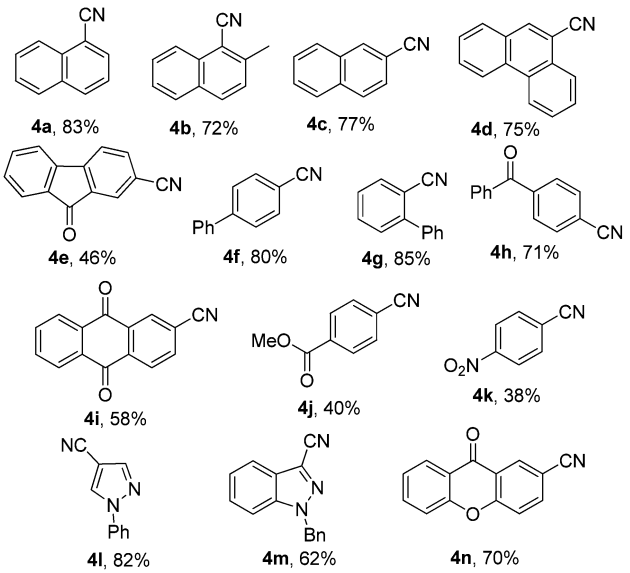
was found that the reaction efficiency was still maintained high using these substrates (**2d**–**2g**). However, cyanation of aryl bromides did not occur under the present conditions.

We subsequently scrutinized the cyanation of electronically neutral or deficient (hetero)aryl iodides. When the above optimal conditions were applied to 1-iodonaphthalene (**3**) as a model substrate, cyanation was observed to be sluggish, leading to only moderate product yield [**4a**, 50%, eqn (1)]. As a result, we decided to search for any accelerating effects of certain suitable external ligands. After screening various monodendate and bidentate nitrogen ligands (see the ESI† for details), it was found that 2-aminopyridine displayed the highest ligand effects in the presence of an excess amount of silver species.

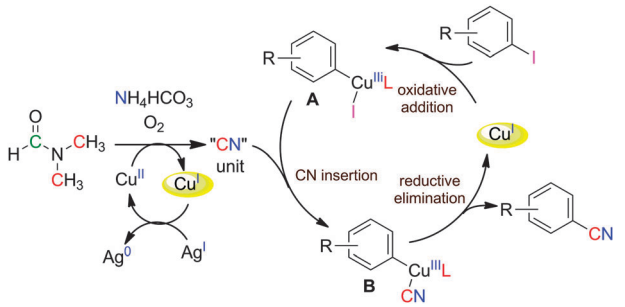
The new cyanation conditions containing an external ligand, 2-aminopyridine, were subsequently applied to a wide range of pertinent substrates (Table 3). The reaction of fused aryl iodides took place smoothly to afford the corresponding nitriles in good yields (**4a**–**4d**). 2-Iodofluorenone was reacted under the present conditions to deliver **4e** in moderate yield. Aryl iodides substituted with a phenyl group at different positions were cyanated without difficulty (**4f**–**4g**). *p*-Iodobenzophenone and 2-iodoanthraquinone underwent the desired cyanation in acceptable yields (**4h** and **4i**, respectively). However, the reaction of aryl iodides bearing an ester

Table 3 Cu-catalyzed cyanation of various aryl iodides[a]





[a] Reaction conditions: **3** (0.3 mmol), NH_4HCO_3 (2.0 equiv.), $Cu(NO_3)_2{\cdot}3H_2O$ (20 mol%), Ag_2CO_3 (2.0 equiv.), 2-aminopyridine (20 mol%) in DMF (1.5 mL) under an O_2 balloon at 150 °C for 24 h.

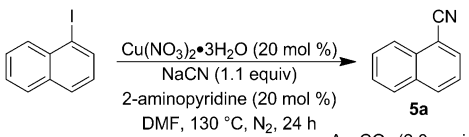


Scheme 1 Plausible mechanism for the catalytic cyanation.

or nitro group proceeded with moderate efficiency (**4j–4k**). In addition, heteroaryl substrates containing pyrazole, indazole and xanthone underwent cyanation in satisfactory yields (**4l–4n**).

A mechanistic proposal for the current catalytic cyanation is outlined in Scheme 1. While Cu(II) species is involved in the *in situ* generation of "CN" from DMF and NH_4HCO_3, as in the case of our previous stoichiometric procedures,[26] it is now postulated that silver salt reoxidizes the resultant Cu(I) species under oxidative conditions. Copper-catalyzed cyanation of aryl iodides with cyanide involving a Cu(III) intermediate[31] has already been well studied,[7–9] and it would be reasonable to assume that our current reaction also follows a similar pathway, implying that the copper catalyst plays a dual role being involved in both catalytic cycles.

In order to gain a mechanistic insight, control experiments were also carried out. When 1-iodonaphthalene was subjected to the reaction conditions containing NaCN (1.1 equiv.), but in the absence of NH_4HCO_3, 1-naphthylnitrile (**5a**) was produced in high yield (78%) under a N_2 atmosphere [eqn (2)]. More interestingly, cyanation also took place smoothly even in the absence of Ag_2CO_3. These results suggest that, as shown in the above proposal, both O_2 and Ag_2CO_3 are crucial in the first stage of "CN" generation from NH_4HCO_3 and DMF.



(2)

In summary, we developed the Cu-catalyzed cyanation of aryl iodides using DMF and NH_4HCO_3 as the combined source of cyanide. Copper is believed to play a dual role in both the catalytic generation of "CN" and the subsequent cyanation process. This catalytic procedure was successfully applied for the cyanation of electron-rich and fused aryl iodides. Ligand accelerating effects were observed in the reaction of electron-deficient (hetero)aryl iodides.

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