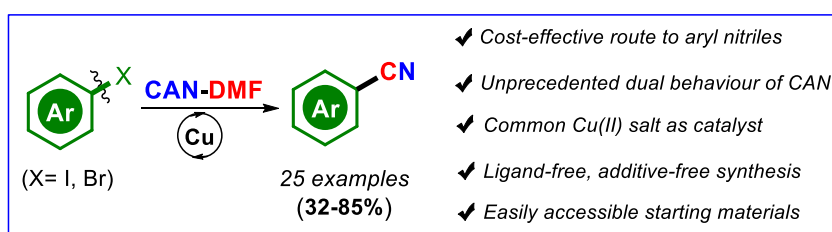


## Chapter 3

Organic &  
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PAPER

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19, 1344Revisiting the synthesis of aryl nitriles: a pivotal  
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**ABSTRACT:** This chapter discusses a cost-effective approach for the cyanation of aryl iodides/bromides with CAN–DMF as an addition to the existing pool of combined cyanation sources. The reaction is facilitated by the dual role of Ceric Ammonium Nitrate (CAN). Besides being an oxidant, CAN also acts as a source of nitrogen. The reaction is catalyzed by a readily available Cu<sup>II</sup> salt and the ability of CAN to generate ammonia in the reaction medium is utilized to eliminate the cumulative requirement of a nitrogen source, ligand, additive or toxic reagents. The mechanistic study suggests an evolution of CN<sup>−</sup> leading to the synthesis of a variety of aryl nitriles in moderate to good yields. The proposed mechanism is supported by controlled reactions and labeling experiment.

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## Chapter 3

### 3. Dual Role of Ceric Ammonium Nitrate in cyanation reaction.

#### 3.1 Introduction

As discussed in Chapter 1 and Chapter 2, Cu-catalyzed synthesis of benzonitrile and its derivatives occupy a significant domain of synthetic organic chemistry. Although other transition metals have also been utilized to mediate the process of cyanation, a plethora of cyanation processes have been efficiently catalyzed by Cu in its various homogeneous and heterogeneous modifications. This is on account of its economy and versatility [1-3]. The lethal effects caused by the stoichiometric use of metal cyanides and high temperature (approx. 150-250 °C) employed in the classical approaches of cyanation by Sandmeyer and Rosenmund-von Braun prompted the utilization of either indirect cyanide sources or *in situ* generated cyanide.

Apart from the recently established indirect cyanation sources discussed in Chapter 2, the extensive establishment of combination of sources of carbon and nitrogen to generate aryl nitriles are gaining increasing importance. The combination of  $\text{NH}_3(\text{aq})$ -DMF,  $\text{NH}_4\text{I}$ -DMF,  $\text{NH}_4\text{HCO}_3$ -DMSO,  $\text{NH}_4\text{HCO}_3$ -DMF, urea-DMSO,  $\text{CO}_2$ - $\text{NH}_3$  and  $\text{ClCF}_2\text{H}-\text{NaNH}_2$  are some standout examples (Figure 3.1). An ammonium salt is usually chosen as the nitrogen atom donor and the solvent (DMF/DMSO) behaves as the carbon source under the given reaction conditions. Cu-catalyst and an aerobic environment have been found necessary to bring about the necessary transformations and generate  $\text{CN}^-$  *in situ* [4]. In this regard, the cyanation of readily available aryl iodides/bromides with these combined-reagents enabled easy access to aryl nitriles. 4-(Trifluoromethyl)benzonitrile as a critical intermediate of the antidepressant 'Fluvoxamine' is readily synthesized from 4-chlorobenzotrifluoride on a ton-scale [5].

Known to participate as a one-electron oxidant in a number of carbon-carbon bond formation reactions, [6-9] the importance of Ceric Ammonium Nitrate (CAN) is highlighted in the pioneering works of Trahanovsky [10-13] and Heiba-Dessau [14-17]. Being the most extensively used Cerium(IV) reagent, the wide popularity of CAN is based on its easy handling, cost-effectiveness, high reduction potential value (+1.61 V vs. SHE), low toxicity and high solubility in many organic solvents [18].

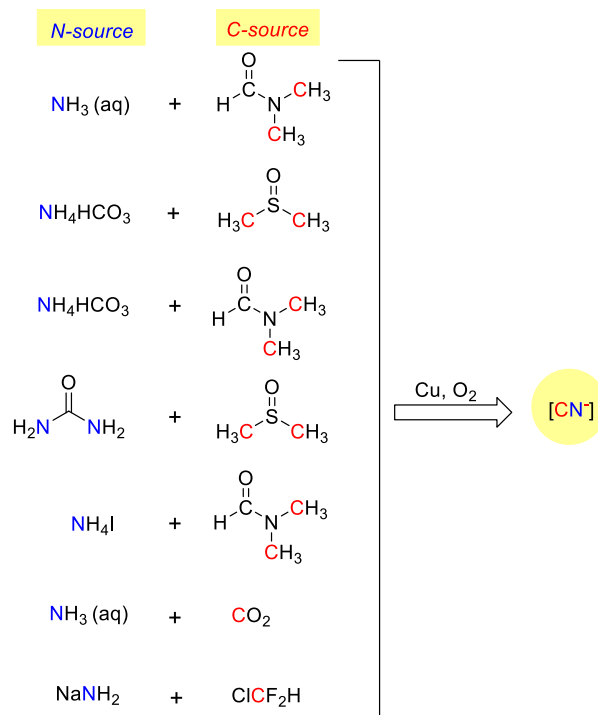


Figure 3.1 Combined sources of cyanation

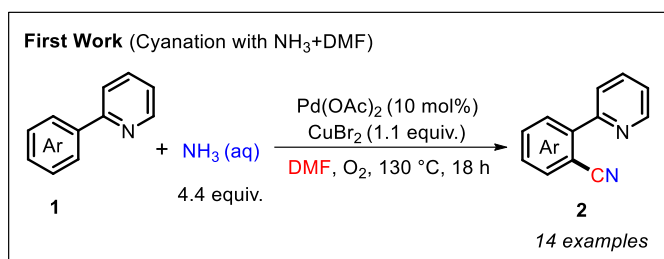
### 3.2 Background

The invention of combination sources of  $\text{CN}^-$  represents a significant paradigm shift from toxic metal-bound cyanide sources and the post-treatments associated with cyanation processes.

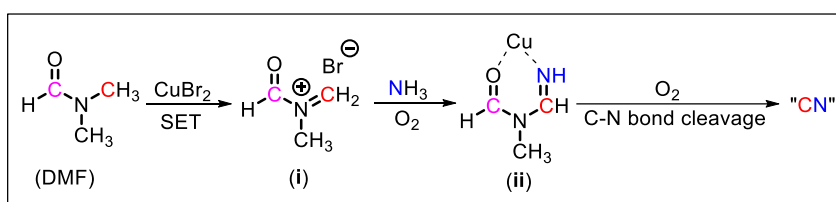
$\text{NH}_3(\text{aq})$  and DMF: In 2010, the research group of Chang pioneered the utilization of two readily available precursors i.e. ammonia and DMF as a combination of nitrogen source and carbon source respectively, to generate  $\text{CN}^-$  for cyanation [19]. Their application was showcased in a Pd-catalyzed cyanation of C–H bonds of 2-Phenylpyridine (**1**) (Scheme 3.1). While Cu played a role in the generation of  $\text{CN}^-$ , Pd was necessary for C–H bond activation of pyridines and both were found indispensable for the cyanation reaction. Labeling experiments were conducted for an insight into the plausible mechanism of release of  $\text{CN}^-$  from  $\text{NH}_3(\text{aq})$  and DMF. This was the first ever methodology that enabled synthesis of doubly labeled nitriles.

The mechanism of release of  $\text{CN}^-$ , as postulated in Chang's report, was initiated by a single electron transfer from Cu to form the iminium species (i) (Scheme 3.2). The iminium species forms the amidine intermediate (ii) on attack by  $\text{NH}_3$ , which can undergo C–N bond cleavage in an aerobic environment to release  $\text{CN}^-$  at the reaction

temperature. Thereafter, several reports were made with the combination source of cyanation.

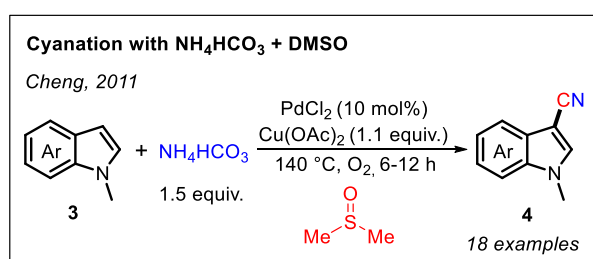


Scheme 3.1 First work on cyanation with combined source



Scheme 3.2 Mechanism of cyanation with the combination of ammonium and DMF

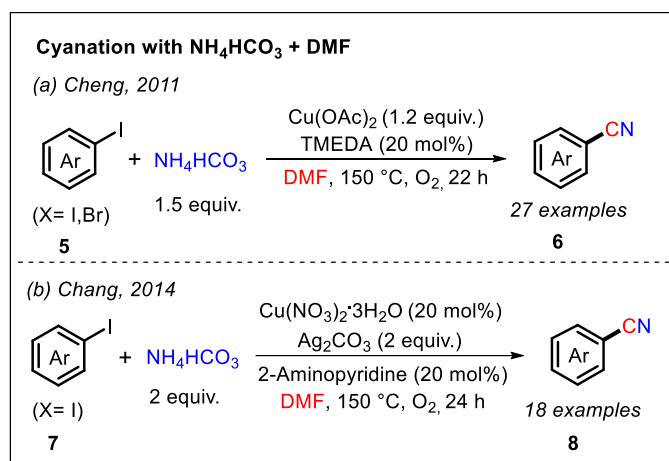
$\text{NH}_4\text{HCO}_3$  and DMSO: Soon after in 2011, the research group of Cheng reported another combination of  $\text{CN}^-$  and introduced DMSO and  $\text{NH}_4\text{HCO}_3$  as the carbon and nitrogen source respectively, for the cyanation of Indoles (**3**) (Scheme 3.3). *N*-methyl-1*H*-Indole-3-carbonitriles were obtained regioselectively in significantly shorter reaction times [20]. The methodology achieved cyanation with just 1.5 equivalents of the nitrogen source ( $\text{NH}_4\text{HCO}_3$ ) in contrast to 4.4 equivalents of  $\text{NH}_3$  in Chang's protocol [19].



Scheme 3.3 Cyanation with the combination of  $\text{NH}_4\text{HCO}_3$  and DMSO

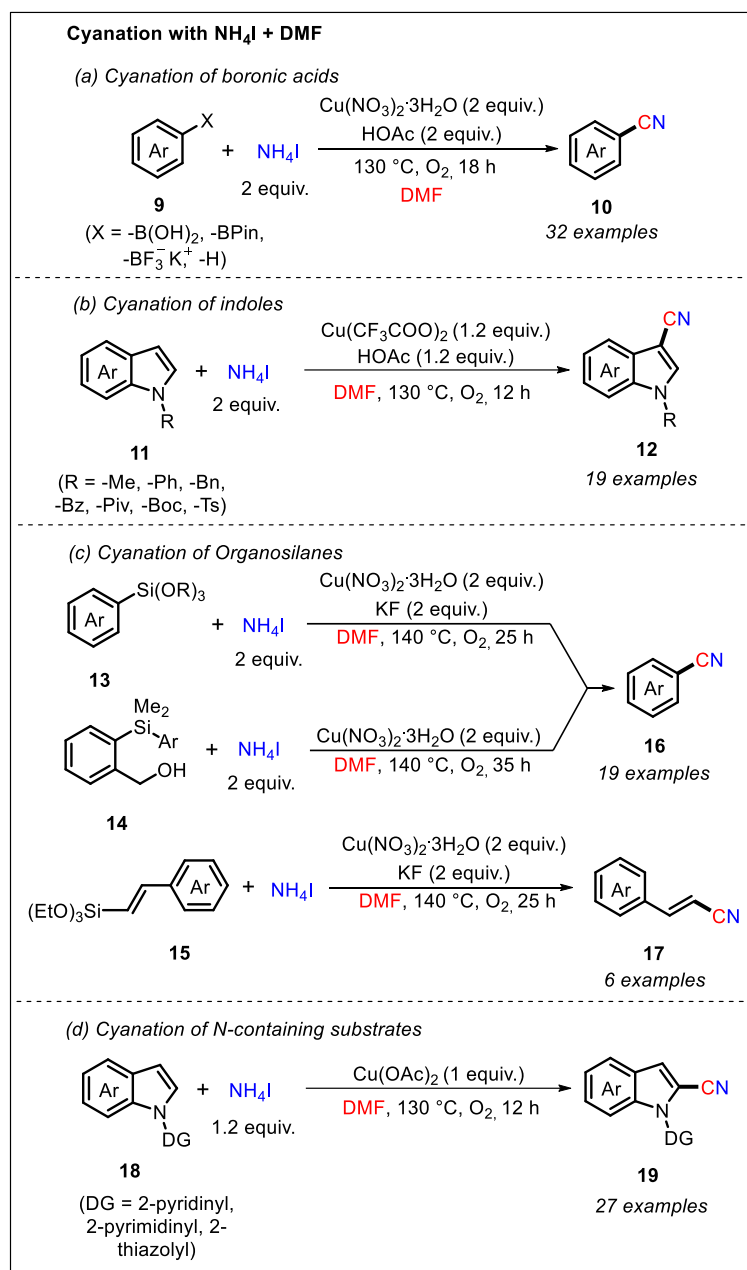
$\text{NH}_4\text{HCO}_3$  and DMF: Subsequently, the same research group of Cheng used  $\text{NH}_4\text{HCO}_3$  (nitrogen source) in combination with DMF to obtain benzonitriles from aryl iodides and bromides (**5**) (Scheme 3.4a). Although the protocol employed stoichiometric quantities of Cu-salt, it had the advantage of omitting Pd-metal and did not require a large excess of nitrogen source [21]. With the same combination, Chang's group envisioned the

synthesis of aryl nitriles but, with a catalytic amount of Cu (Scheme **3.4b**). They postulated that a suitable oxidant (here,  $\text{Ag}_2\text{CO}_3$ ) could bring about oxidation of the Cu(I)-species involved in the organometallic cycle and in return aid the reaction with catalytic amounts of Cu [22].

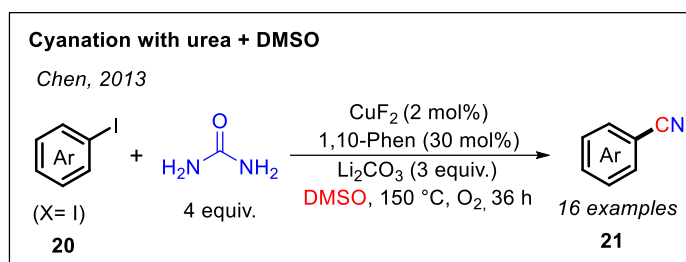


Scheme **3.4** Cyanation with the combination of  $\text{NH}_4\text{HCO}_3$  and DMF

$\text{NH}_4\text{I}$  and DMF: Another interesting combination source of cyanation was introduced by the Chang's research group to bring about cyanation of boronic acids (**9**) (Scheme **3.5a**) [23], indoles (**11**) (Scheme **3.5b**) [24], and organosilanes (**13**, **14** and **15**) (Scheme **3.5c**) [25]. Here,  $\text{NH}_4\text{I}$  and DMF were employed as the nitrogen and carbon source respectively which released  $\text{CN}^-$  under oxidative conditions. The corresponding iodination products were detected during mechanism study which affirmed that iodination took place initially in the reaction. Subsequent cyanation yielded the corresponding products under "Pd-free" reaction conditions. The study on cyanation of *N*-methylindoles was found contrary to the previous reports where a Pd-salt was deemed necessary for the cyanation of C-H bonds. The same combination source was utilized on another interesting approach to obtain selective 2-cyanoindoles (Scheme **3.5, d**). Other *N*-containing arenes like pyroles, carbazoles and 1-pyridinyl benzenes were also selectively cyanated with this methodology [26]. The reaction made use of efficient *N*-directing groups like pyrimidinyl, pyridinyl, pyrazolyl and thiazolyl for the selective C-2/C-1 cyanation. Study of reaction mechanism ruled out initial iodination and the primary role was played by the directing groups in anchoring Cu at the desired position of the *N*-containing arenes.

Scheme 3.5 Cyanation with the combination of  $\text{NH}_4\text{I}$  and DMF

**Urea and DMSO:** Another readily available and cheap precursor, urea was utilized in combination with DMSO as a safe cyanide source [27]. Zheng et al. utilized this for the cyanation of aryl iodides (Scheme 3.6). Although the reaction required catalytic amounts of Cu-metal, it employed large excess of urea and the base,  $\text{Li}_2\text{CO}_3$ . The mechanism of the reaction is still under investigation.



Scheme 3.6 Cyanation with the combination of urea and DMSO

### 3.3 Results and Discussion

In this chapter, we shall introduce another nitrogen atom donor i.e. Ceric ammonium nitrate (CAN). The ability of Ceric Ammonium Nitrate (CAN) to act as a nitrogen atom donor is discussed in addition to its utility as an oxidant. Together with DMF as a carbon source (and solvent), the two easily available precursors modulates into an efficient cyanating agent for aryl iodides/bromides. The presented methodology highlights a dual role of CAN and required no additives, no toxic reagents and involved ligand-free Cu(II) catalysis (Figure 3.2).

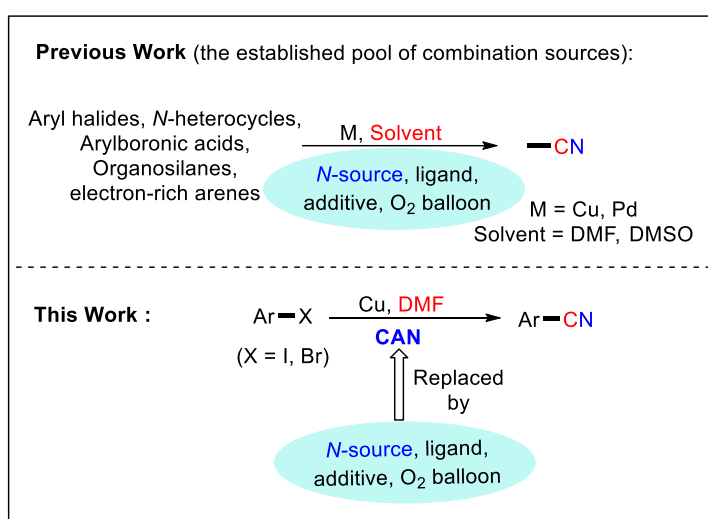


Figure 3.2 Representative work on cyanation with combination sources

Until the serendipity of the ability of CAN to act as a nitrogen source in the cyanation of an aryl halide moiety, our first efforts were put into investigating the oxidizing effect of CAN in the cyanation of 4-Iodoanisole with a different cyanation source. The reaction was catalyzed by 5 mol% of  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  and 10 mol% of 1,10-Phen. To our delight, a series of controlled reactions disclosed the ability of CAN to function as a cyanating agent in combination with the solvent. Henceforth, different reaction conditions were

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screened with 4-Iodoanisole (**22a**) as the model substrate and the summary of the observations are presented in Table **3.1** and Table **3.2**.

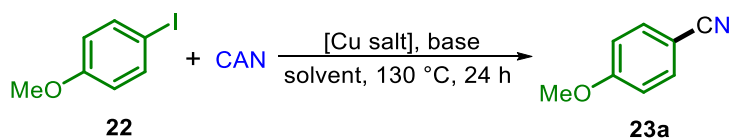
### 3.3.1 Optimization of reaction conditions

Table **3.1** displays screening results of different solvents, bases, Cu salts and ligands for the cyanation reaction with CAN. Consequently, the results of screening of optimal equivalents of CAN and amounts of the Cu-salt are presented in Table **3.2**.

With reaction temperature and time maintained at 130 °C and 24 h respectively, it was found that the reaction proceeded well in polar aprotic solvents such as CH<sub>3</sub>CN, DMSO, DMAc and DMF (Table **3.1**, entries **1-6**). Although CH<sub>3</sub>CN, DMSO and DMF have been utilized as sources of carbon, [19-30] it is evident from Table **3.1** that the highest yield of cyanated product (**23a**) was obtained in DMF (68%). The reaction, however, did not take place in non-polar solvents (Table **3.1**, entries **7** and **8**). Among the inorganic bases, K<sub>2</sub>CO<sub>3</sub> showed the best activity (75%), while organic bases like (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N and DABCO did not yield the desired cyanated product (Table **3.1**, entries **9-12**). Although both Cu(II) and Cu(I) salts catalyzed the reaction to afford product **23a** (Table **3.1**, entries **13-16**), the highest yield was obtained with Cu(OTf)<sub>2</sub> (75%). In addition, the employment of different ligands produced decent and similar yields (Table **3.1**, entries **17-20**). But the highest yield was obtained without the use of ligands (75%, Table **3.1**, entry **13**).

With optimized conditions from Table **3.1**, usage of the equivalents of CAN and amounts of Cu(OTf)<sub>2</sub> were screened to ascertain the final optimal reaction condition (Table **3.2**). A gradual increase in the yield of the desired product (**23a**) was observed with an initial increase in usage of CAN (until 2 equiv.) and then slowly decreased (Table **3.2**, entries **1-5**). The decrease in yield may be attributed to increase in the number of side products from greater amount of unreacted CAN left in the reaction medium. On the other hand, 30 mol% of Cu(OTf)<sub>2</sub> was sufficient to give the desired product in 85% yield (Table **3.2**, entries **6-9**). The amount of **23a** did not improve with a further increase in reaction time or temperature. Therefore, the final optimized reaction condition was fixed at 1.5 equiv. of CAN, 30 mol% of Cu(OTf)<sub>2</sub> in 4 mL DMF at 130 °C for 24 h (Table **3.2**, entry **8**).

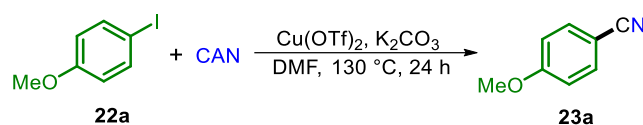


Table 3.1 Initial screening of reaction conditions.<sup>[a]</sup>

Entry	Solvent	Base	Cu-Salt	Yield <sup>[b]</sup> (%)
1	CH <sub>3</sub> OH	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	30
2	C <sub>2</sub> H <sub>5</sub> OH	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	NR
3	CH <sub>3</sub> CN	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	55
4	DMSO	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	65
5	DMAc	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	63
6	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	68
7	DCM	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	NR
8 <sup>[c]</sup>	Toluene	K <sub>2</sub> CO <sub>3</sub>	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	NR
9	DMF	NaOH	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	55
10	DMF	KO <sup>t</sup> Bu	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	62
11 <sup>[c]</sup>	DMF	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> N	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	Trace
12 <sup>[c]</sup>	DMF	DABCO	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O	Trace
<b>13</b>	<b>DMF</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>Cu(OTf)<sub>2</sub></b>	<b>75</b>
14	DMF	K <sub>2</sub> CO <sub>3</sub>	CuCl <sub>2</sub>	53
15	DMF	K <sub>2</sub> CO <sub>3</sub>	CuCl	73
16	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	67
17 <sup>[d]</sup>	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(OTf) <sub>2</sub>	56
18 <sup>[e]</sup>	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(OTf) <sub>2</sub>	72
19 <sup>[f]</sup>	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(OTf) <sub>2</sub>	74
20 <sup>[g]</sup>	DMF	K <sub>2</sub> CO <sub>3</sub>	Cu(OTf) <sub>2</sub>	70

<sup>[a]</sup>Reaction conditions: 4-Iodoanisole (**22a**, 1 mmol), CAN (1 equiv., 1 mmol), Cu-salt (0.1 mmol, 10 mol%), ligand (0.1 mmol, 10 mol%), base (1 equiv.), solvent (4 mL), 130 °C, 24 h; <sup>[b]</sup>Isolated yield based on 4-Iodoanisole, **22a**; <sup>[c]</sup>TLC analysis of the reaction mixture showed spot other than **23a**; <sup>[d],[e],[f],[g]</sup>2,2'-Bipyridyl, 1,10-Phen, 4,4'-Bipyridyl and L-Proline was used as ligands respectively; NR = no reaction.

Table 3.2 Effect of varying amounts of CAN and Cu(OTf)<sub>2</sub> for cyanation of aryl iodides and bromides.<sup>[a]</sup>



Entry	CAN (in equiv.)	Cu(OTf) <sub>2</sub> (in mol%)	Yield <sup>[b]</sup> (%)
1	1	10	75
2	1.5	10	77
3	2	10	78
4	2.5	10	76
5	3	10	76
6	1.5	15	80
7	1.5	20	83
<b>8</b>	<b>1.5</b>	<b>30</b>	<b>85</b>
9	1.5	40	83

<sup>[a]</sup>Reaction conditions: 4-Iodoanisole, **22a** (1 mmol), K<sub>2</sub>CO<sub>3</sub> (1 equiv., 1 mmol), DMF (4 mL), 130 °C, 24 h;

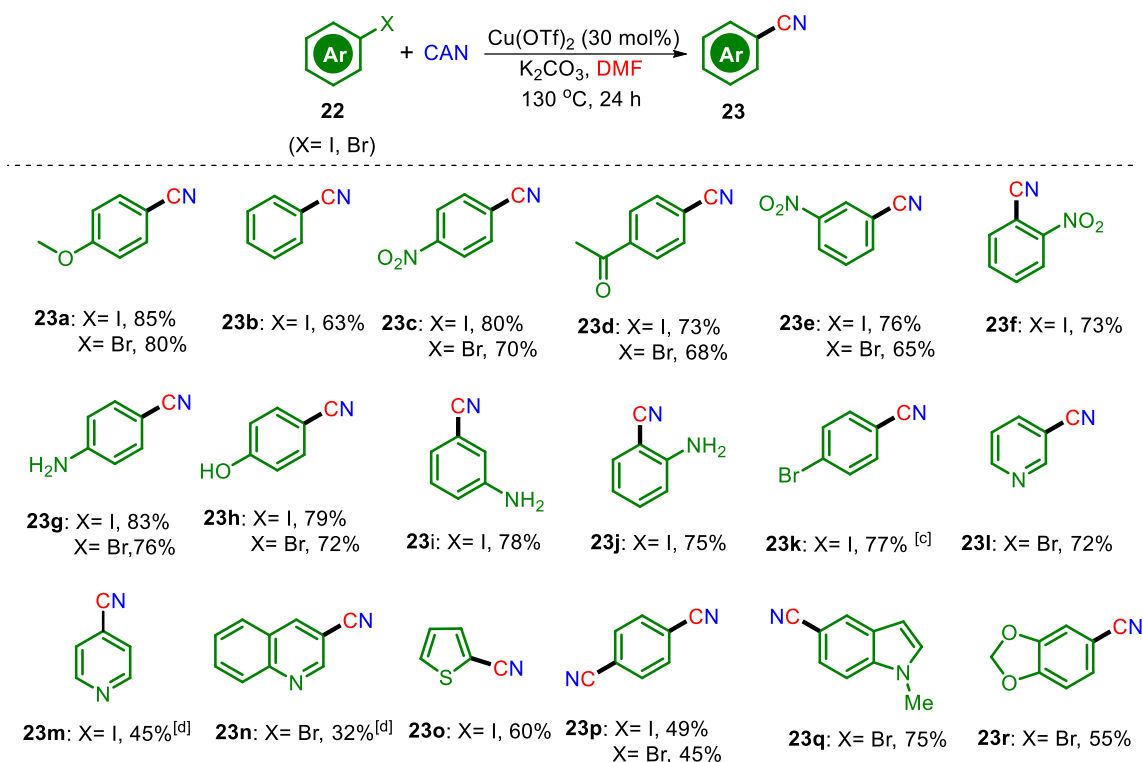
<sup>[b]</sup>Isolated yield based on 4-Iodoanisole (**22a**).

### 3.3.2 Substrate Scope Study

Post optimization, the substrate scope of cyanation reaction of aryl halides (iodides and bromides) with the combination of CAN-DMF as a new cyanation source was explored and the results are presented in Table 3.3. Various substituted aryl iodides and aryl bromides (**22**) reacted smoothly, producing the desired product in poor to good yields (32-85%). A significant range of electron-withdrawing and electron-donating groups were compatible with the optimized reaction condition. The Iodoarenes showed higher reactivity in comparison to bromobenzene derivatives. Electron-donating groups at *o*-, *m*- and *p*-positions of the aryl iodide/bromide yielded cyanated products with greater ease compared to that with electron-withdrawing groups. In addition, the reactivity of aryl iodides/bromides substituted at *o*- and *p*-positions were observed to be greater than that of the unsubstituted one (Table 3.3, **23b**) or with substitutions at the *m*-position (Table 3.3, **23e** and **23i**). In case of pyridines, cyanation took place relatively easily at the C-3 position (**23l**), than at the C-4 position (**23m**). Other heteroaromatic nitriles (Table 3.3, **23o**, **23q** and **23r**) were obtained in decent yields. Also,

terephthalonitrile was also obtained with the developed reaction condition (Table 3.3, 23p).

Table 3.3 Scope exploration of Cu<sup>II</sup>-catalyzed cyanation of aryl iodides and bromides with CAN–DMF.<sup>[a]</sup>



<sup>[a]</sup>Reaction conditions: Aryl halide, **22** (1 mmol), CAN (1.5 equiv.), Cu(OTf)<sub>2</sub> (30 mol%), K<sub>2</sub>CO<sub>3</sub> (1 equiv.), DMF (4 mL), 130 °C, 24 h (the reaction time was not optimized for each substrate); <sup>[c]</sup>4-Iodobenzonitrile was formed as a minor product, GC yield = 11%; <sup>[d]</sup>2 equiv. of CAN were used, 0.5 mmol reaction scale.

### 3.3.3. Mechanistic Study

The mechanistic study was initiated by a series of controlled experiments (Figure 3.3) [36]. As expected, the cyanated product, **23a** was not obtained without Cu (Figure 3.3, 5) but it was interesting to note that the desired product was also obtained with Pd(OAc)<sub>2</sub> (Figure 3.3, 1) and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (Figure 3.3, 2) in 50% and 35% yield respectively. The reaction did not proceed with other Ce–salt like CeCl<sub>3</sub>·7H<sub>2</sub>O salt, which does not have the ammonium counter ion (Figure 3.3, 6). This indicated that CAN is the nitrogen atom donor in the reaction medium and DMF alone could not bring about cyanation under the given reaction conditions. It was the carbon atom donor in reaction medium. The reaction did take place in the presence of (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, a previously

reported source of nitrogen in cyanation [20], but in lesser yield with the developed reaction conditions (Figure 3.3, 3). Thus, when a nitrogen source [CAN or (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>] was absent in the reaction medium, the desired product was not obtained (Figure 3.3, 7). The reaction yielded equally well when carried out under a nitrogen atmosphere (Figure 3.3, 4), which indicated the oxidizing behaviour of CAN, in addition to being a nitrogen source in the reaction medium. All the previously reported protocols employed an additional oxidant. In addition, the reaction does not give any product in the absence of K<sub>2</sub>CO<sub>3</sub>. To investigate that, the reaction was carried out with KCl and the desired product, **23a** was not obtained (Figure 3.3, 8).

*Labeling study:* Since several labeling experiments have already established the incorporation of the methyl carbon of DMF into the cyanated product, the present study further reinforces the observation. The labeling of the carbonyl carbon of DMF does not produce a <sup>13</sup>C-labeled cyanated product (Scheme 3.7), which strongly suggests that it is the methyl carbon and not the carbonyl carbon of DMF that was incorporated in the cyanated product.

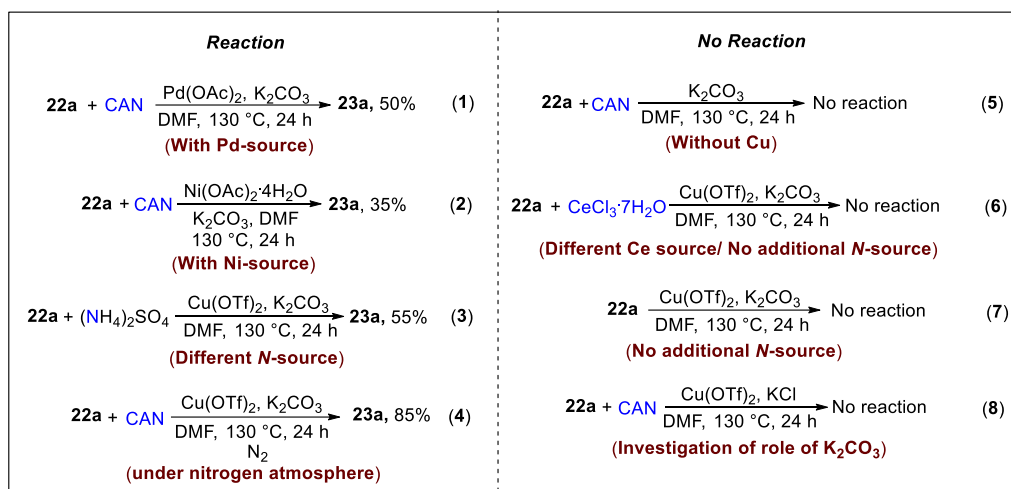
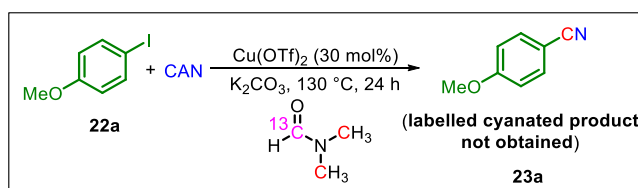


Figure 3.3 Controlled experiments for cyanation with CAN–DMF.



Scheme 3.7 Investigation of carbon source

### 3.3.4 Plausible Mechanism

From all the above observations, a plausible mechanism of cyanation with CAN-DMF is illustrated in Figure 3.4.

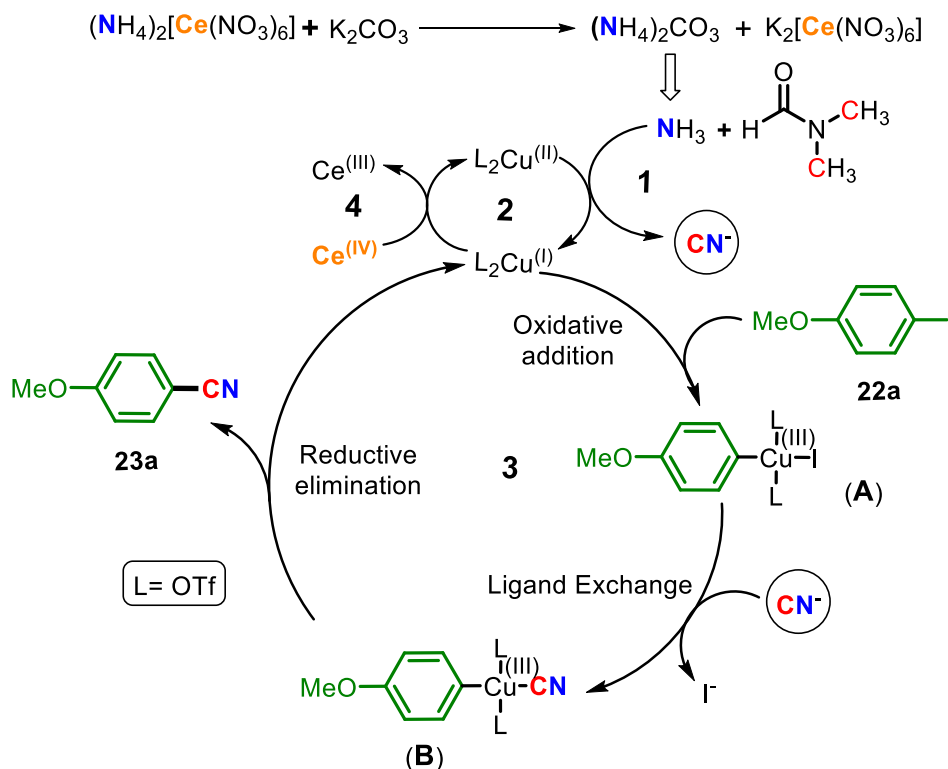


Figure 3.4 Plausible mechanism

Ceric Ammonium Nitrate (CAN) acts as a nitrogen-atom donor through the  $\text{NH}_4^+$  ions [31]. After loss of  $\text{NH}_4^+$  ions, the resulting Ce-complex was stabilized by the  $\text{K}^+$  ions from  $\text{K}_2\text{CO}_3$  in the reaction medium [32]. Subsequently,  $(\text{NH}_4)_2\text{CO}_3$  undergoes thermal decomposition at the reaction temperature to release  $\text{NH}_3$  during the reaction [33]. The released  $\text{NH}_3$  combines with DMF to generate the  $\text{CN}^-$  unit with a simultaneous reduction of  $\text{Cu}(\text{II})$  to  $\text{Cu}(\text{I})$  (Step 1 and 2). This is in accordance with Chang's report on combination sources of cyanation (as discussed above in section 3.2). On similar lines, when  $\text{KCl}$  was used instead of  $\text{K}_2\text{CO}_3$  (Figure 3.3, 8),  $\text{NH}_4\text{Cl}$  would have formed in the reaction medium which has a decomposition temperature higher than the reaction temperature and cannot release  $\text{NH}_3$  necessary to obtain the desired product. Hence, desired product was not obtained on using  $\text{KCl}$  in place of  $\text{K}_2\text{CO}_3$ . The released  $\text{CN}^-$  unit then enters the organometallic cycle at the stage of ligand exchange. The involvement of a  $\text{Cu}(\text{III})$  intermediate leads to the formation of the desired cyanated product, **23a**

through the processes of oxidative addition, ligand exchange and reductive elimination (Step 3). The Cu(I) species is re-oxidized to Cu(II) (catalyst regeneration) by the spontaneous reduction of Ce(IV) to Ce(III) (Step 4). The oxidizing behaviour of CAN in the reaction medium was supported by the XPS analysis of cerium ions after the reaction. XPS analyses of fresh CAN before use and crude reaction mixture after the reaction indicated the existence of both Cerium(III) ion (characteristic peaks at ca. 903.2, 899.5, 884.6 and 881.4 eV for  $\text{Ce}^{3+} 3d_{5/2}$ ) and cerium(IV) ion (characteristic peaks at ca. 915.4, 899.5, 897.9 and 881.4 eV for  $\text{Ce}^{4+} 3d_{5/2}$ ). However, the characteristic peaks of cerium(IV) ion (ca. 915.4, 899.5, and 897.9 eV) in the crude reaction mixture after the cyanation reaction seemed to relatively decrease in comparison to CAN before use (Figure 3.5, a vs. b). The generation of  $\text{CN}^-$  was also supported by a picrate paper test (as discussed in Chapter 2). The exact pathway of evolution of  $\text{CN}^-$  by CAN-DMF is still under investigation.

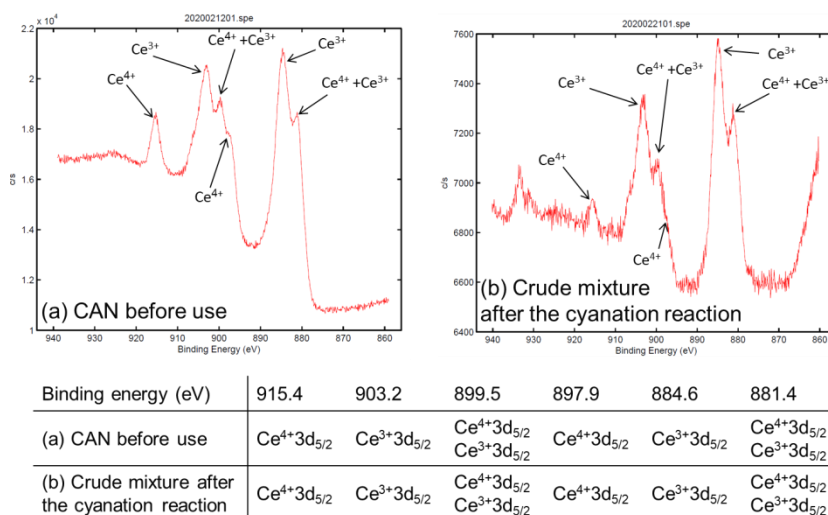


Figure 3.5 XPS Study of oxidation state of Cerium

### 3.3.5 Conclusion

We have developed a new route for the cyanation of readily available aryl iodides and bromides with the combination of CAN-DMF as the cyanation source. The methodology was applicable to a range of variously substituted aryl iodides/bromides in moderate to good yields. The wide scope of CAN was utilized to avoid toxic cyanation sources and additional employment of a nitrogen source or any other additives. Moreover, the disadvantages in the preparation and handling of modified metal catalysts was

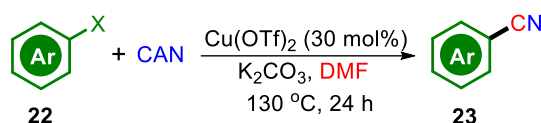
overcome by a simple, easily accessible Cu(II) salt in the developed protocol. We hope our study represents an important advancement in the field of cyanation and in overcoming some drawbacks associated with cyanation processes.

### 3.3.6 Experimental Section

#### 3.3.6.1 General Information

All the chemicals used for the reactions were procured commercially and used without further purification. The progress of the reaction was monitored through thin layer chromatography on Merck Kieselgel Silica gel 60F<sub>254</sub> plates using short wave UV light ( $\lambda=254$  nm). The products were purified by column chromatography using Silica gel (60-120 mesh and 100-200 mesh). The identification of the purified products was carried out by NMR (<sup>1</sup>H and <sup>13</sup>C) spectroscopy. The NMR spectra were recorded on a 400 MHz JEOL ECZ NMR spectrophotometer (400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C). Chemical shifts for both <sup>1</sup>H ( $\delta_H$ ) and <sup>13</sup>C ( $\delta_C$ ) NMR are assigned in parts per million (ppm) using TMS (0 ppm) as the internal reference and CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> as solvent (CDCl<sub>3</sub>:  $\delta_H$  = 7.25 ppm and  $\delta_C$  = 77.1 ppm; DMSO-*d*<sub>6</sub>:  $\delta_H$  = 2.5 ppm, DMSO-*d*<sub>6</sub> absorbed water = 3.3 ppm and  $\delta_C$  = 40.0 ppm). The multiplicities of the signals are assigned as: s=singlet, d=doublet, dd=doublet of doublet, t=triplet, br=broad and m=multiplet. The XPS analysis was carried out on ULVAC Quantera-SXM-GC.

#### 3.3.6.2 General experimental procedure for the synthesis of aryl nitriles (**23a-r**)

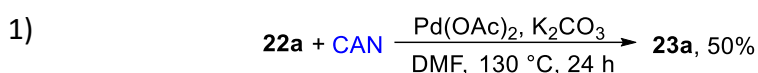


In a 50 mL oven-dried round-bottomed flask with a magnetic stirring bead, Copper(II) trifluoromethanesulfonate, Cu(OTf)<sub>2</sub> (30 mol%, 0.30 mmol, 0.108 g), CAN (1.5 equiv., 0.822 g), aryl halide (**22**, 1 mmol, 0.234 g) and K<sub>2</sub>CO<sub>3</sub> (1 equiv., 0.138 g) were taken in 4 mL DMF. The reaction flask was then fitted to a water condenser and stirred at 130 °C in a pre-heated oil bath under reflux conditions. After 24 h, TLC of the reaction was checked and the reaction mixture was extracted in ethyl acetate and washed with excess water to remove DMF. It was then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in a rotary evaporator. The product **23** was purified through column

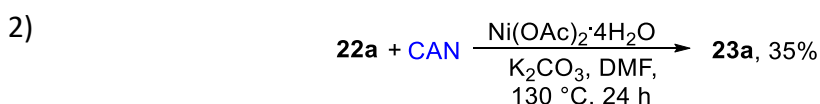
chromatography. Since all the reactions were carried out in a round-bottom flask fitted with a condenser, no extra precautionary measures were taken for the high reaction temperature. Further, the products were checked for the presence of Cu, if any, by ICP-AES. The general experimental procedure was followed for the synthesis of all the aryl iodides and bromides.

### 3.3.6.3 Experimental procedure for controlled reactions

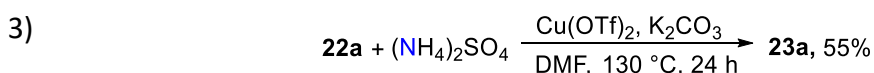
All the reactions were carried out in a 50 mL round-bottomed flask with a magnetic stirring bead fitted to a condenser (filled with water) and stirred at 130 °C in a pre-heated oil bath under reflux conditions for 24 hours.



Pd(OAc)<sub>2</sub> (30 mol%, 0.15 mmol, 0.034 g), CAN (1.5 equiv., 0.75 mmol, 0.411 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and K<sub>2</sub>CO<sub>3</sub> (1 equiv., 0.068 g) were taken in 2 mL DMF. After 24 h, the reaction was checked. The crude mixture was extracted in ethyl acetate, washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in a rotary evaporator. The product **23a** was purified through column chromatography and isolated in 50% yield.



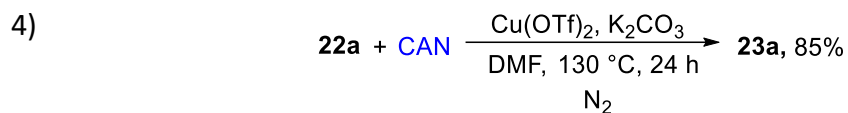
Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (30 mol%, 0.15 mmol, 0.039 g), CAN (1.5 equiv., 0.75 mmol, 0.411 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and K<sub>2</sub>CO<sub>3</sub> (1 equiv., 0.068 g) were taken in 2 mL DMF. After 24 h, the reaction was checked. The crude mixture was extracted in ethyl acetate, washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in a rotary evaporator. The product, **23a** was purified through column chromatography and was isolated in 35% yield.



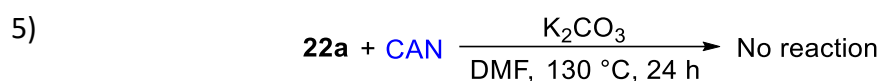
Cu(OTf)<sub>2</sub> (30 mol%, 0.15 mmol, 0.054 g), (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> (1.5 equiv., 0.75 mmol, 0.098 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and K<sub>2</sub>CO<sub>3</sub> (1 equiv., 0.068 g) were taken in 2 mL



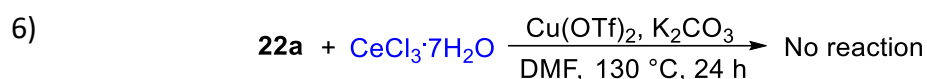
DMF. After 24 h, the reaction was checked. The crude mixture was extracted in ethyl acetate, washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in a rotary evaporator. The product, **23a** was purified through column chromatography and isolated in 55% yield.



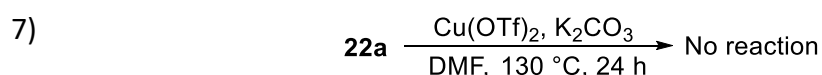
$\text{Cu(OTf)}_2$  (30 mol%, 0.15 mmol, 0.054 g), CAN (1.5 equiv., 0.4117 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and  $\text{K}_2\text{CO}_3$  (1 equiv., 0.068 g) were taken in 2 mL DMF and stirred under nitrogen atmosphere. After 24 h, the reaction was checked. The crude mixture was extracted in ethyl acetate, washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in a rotary evaporator. The product, **23a** was purified through column chromatography and isolated in 85% yield.



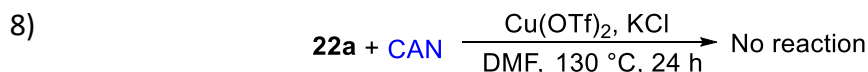
CAN (1.5 equiv., 0.4117 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and  $\text{K}_2\text{CO}_3$  (1 equiv., 0.068 g) were taken in 2 mL DMF. After 24 h, the reaction mixture was checked and the desired cyanated product, **23a** was not obtained.



$\text{Cu(OTf)}_2$  (30 mol%, 0.15 mmol, 0.054 g),  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (1.5 equiv., 0.75 mmol, 0.411 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and  $\text{K}_2\text{CO}_3$  (1 equiv., 0.068 g) were taken in 2 mL DMF. After 24 h, the reaction mixture was checked and the cyanated product, **23a** was not obtained.



$\text{Cu(OTf)}_2$  (30 mol%, 0.15 mmol, 0.054 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and  $\text{K}_2\text{CO}_3$  (1 equiv., 0.068 g) were taken in 2 mL DMF. After 24 h, TLC of the reaction was checked and the desired cyanated product, **23a** was not obtained.



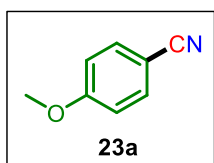
Cu(OTf)<sub>2</sub> (30 mol%, 0.15 mmol, 0.054 g), CAN (1.5 equiv., 0.4117 g), 4-Iodoanisole (**22a**, 0.5 mmol, 0.117 g) and KCl (1 equiv., 0.037 g) were taken in 2 mL DMF. After 24 h, TLC of the reaction was checked and the desired cyanated product, **23a** was not obtained.

#### 3.3.6.4 Sample Preparation for XPS analysis

In a 50 mL oven-dried round-bottomed flask with a magnetic stirring bead, Cu(OTf)<sub>2</sub> (30 mol%, 0.30 mmol, 0.108 g), CAN (1.5 equiv., 0.822 g), 4-Iodoanisole, **22** (1 mmol, 0.234 g) and K<sub>2</sub>CO<sub>3</sub> (1 equiv., 0.137 g) were mixed with 4 mL DMF. The reaction flask was then fitted to a condenser (filled with water) and stirred at 130 °C in a pre-heated oil bath under reflux conditions. After 24 h, the reaction mixture was concentrated using a rotary evaporator and then dried in vacuo at 80 °C. The resulting residue was analyzed by XPS.

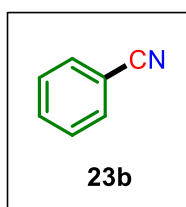
#### 3.3.7 NMR spectral analysis for aryl nitrile derivatives (**23a-r**).

##### 4-Methoxybenzonitrile (**23a**)

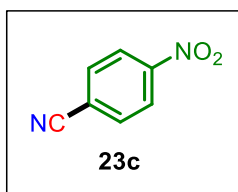


Synthesized from the general experimental procedure (from X=I, 85%, 113 mg and X=Br, 80%; 106 mg); obtained as a colourless solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> (ppm) 3.80 (s, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> (ppm) 56.2, 103.3, 115.6, 119.6, 134.6, 163.2. Spectroscopic data was consistent with literature [21].

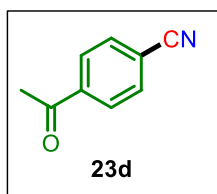
##### Benzonitrile (**23b**)



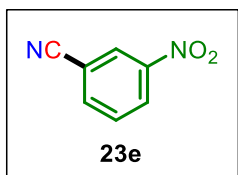
Synthesized from the general experimental procedure (from X=I, 63%, 71 mg); obtained as a colourless liquid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ<sub>H</sub> (ppm) 7.54 (t, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ<sub>C</sub> (ppm) 111.8, 119.3, 130.0, 132.7, 133.8. Spectroscopic data was consistent with literature [34].

4-Nitrobenzonitrile (**23c**)

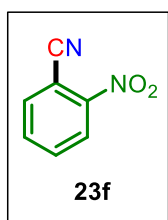
Synthesized from the general experimental procedure (from X=I, 80%, 118 mg and X=Br, 70%, 104 mg); obtained as a light yellow solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 8.13 (d, *J* = 8.0 Hz, 2H), 8.34 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 117.7, 117.8, 124.8, 134.6, 172.3. Spectroscopic data was consistent with literature [21].

4-Acetylbenzonitrile (**23d**)

Synthesized from the general experimental procedure (from X=I, 73%, 106 mg and X=Br, 68%, 97 mg); obtained as a colourless solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 2.59 (s, 3H); 7.96 (d, *J* = 8.0 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 27.5, 115.6, 118.7, 129.3, 133.2, 140.3, 197.9. Spectroscopic data was consistent with literature [21].

3-Nitrobenzonitrile (**23e**)

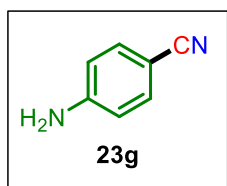
Synthesized from the general experimental procedure (from X=I, 76%, 113 mg and X=Br, 65%, 96 mg); obtained as a off white solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 7.84 (t, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.70 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 113.3, 117.5, 127.9, 128.5, 131.7, 139.0, 148.4. Spectroscopic data was consistent with literature [35].

2-Nitrobenzonitrile (**23f**)

Synthesized from the general experimental procedure (from X=I, 73%, 108 mg); obtained as a light yellow solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 7.93-7.98 (m, 2H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.35-8.38 (m, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 107.3, 116.1, 126.2, 135.0, 135.5, 136.3, 148.6. Spectroscopic data was

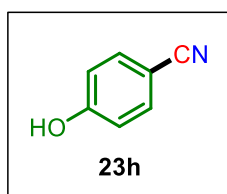
consistent with literature [35].

#### 4-Aminobenzonitrile (**23g**)



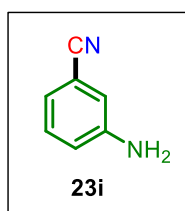
Synthesized from the general experimental procedure (from X=I, 83%, 98 mg and X=Br, 76%, 90 mg); obtained as a colourless solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 6.11 (br s, 2H); 6.56 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 95.9, 113.9, 121.2, 133.9, 153.5. Spectroscopic data was consistent with literature [34].

#### 4-Hydroxybenzonitrile (**23h**)



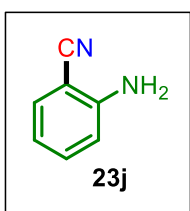
Synthesized from the general experimental procedure (from X=I, 79%, 94 mg and X=Br, 72%, 86 mg); obtained as a colourless solid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 6.86 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 10.61 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 101.4, 116.9, 120.0, 134.7, 162.1. Spectroscopic data was consistent with literature [21].

#### 3-Aminobenzonitrile (**23i**)



Synthesized from the general experimental procedure (from X=I, 78%, 92 mg); obtained as a yellow liquid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 5.56 (br s, 2H), 6.79-6.82 (m, 1H), 6.83 (s, 1H), 7.14 (t, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 111.9, 116.2, 118.9, 119.2, 120.0, 130.6, 150.0. Spectroscopic data was consistent with literature [36].

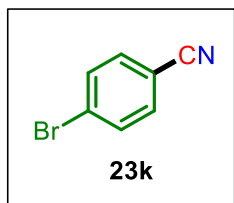
#### 2-Aminobenzonitrile (**23j**)



Synthesized from the general experimental procedure (from X=I, 75%, 89 mg); obtained as a yellow liquid, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  (ppm) 5.97 (br s, 2H), 6.54 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  (ppm) 93.8, 115.6, 116.4, 118.6,

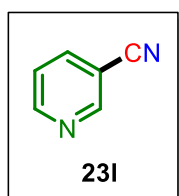
132.9, 134., 152.1. Spectroscopic data was consistent with literature [36].

#### 4-Bromobenzonitrile (**23k**)



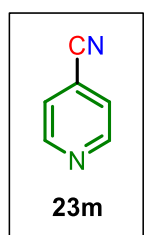
Synthesized from the general experimental procedure (from X=I, 77%, 140 mg); obtained as a colourless solid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  (ppm) 7.51 (d,  $J = 8$  Hz, 2H), 7.62 (d,  $J = 8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta_{\text{C}}$  (ppm) 111.0, 118.6, 128.0, 133.1, 134.6. Spectroscopic data was consistent with literature [21].

#### Pyridine-3-carbonitrile (**23l**)



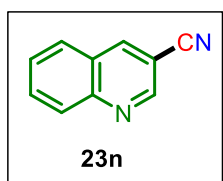
Synthesized from the general experimental procedure (from X=Br, 72%, 75 mg); obtained as a light yellow oil,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta_{\text{H}}$  (ppm) 7.59 (t,  $J = 8.0$  Hz, 1H), 8.28 (d,  $J = 8.0$  Hz, 1H), 8.82 (d,  $J = 8.0$  Hz, 1H), 8.99 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta_{\text{C}}$  (ppm) 109.7, 117.5, 124.6, 140.5, 152.9, 153.8. Spectroscopic data was consistent with literature [23].

#### Pyridine-4-carbonitrile (**23m**)

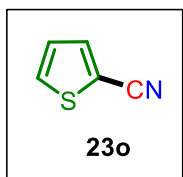


Synthesized from the general experimental procedure (from X=I, 45%, 23 mg); obtained as a colourless oil,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  (ppm) 7.43-7.45 (m, 2H), 8.69 (d,  $J = 8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  (ppm) 116.4, 120.3, 125.3, 150.7. Spectroscopic data was consistent with literature [34].

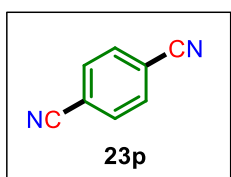
#### Quinoline-3-carbonitrile (**23n**)



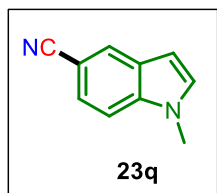
Synthesized from the general experimental procedure (from X=Br, 32%, 25 mg); obtained as a yellow oil,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  (ppm) 7.60 (t,  $J = 8.0$  Hz, 1H), 7.78-7.82 (m, 2H), 8.06 (d,  $J = 8.0$  Hz, 1H), 8.42 (s, 1H), 8.92 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  (ppm) 106.6, 117.2, 126.2, 128.3, 128.5, 129.8, 132.8, 141.5, 148.7, 149.7. Spectroscopic data was consistent with [37].

Thiophene-2-carbonitrile (**23o**)

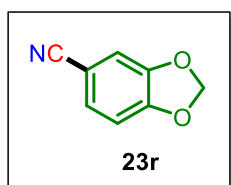
Synthesized from the general experimental procedure (from X=Br, 60%, 65 mg); obtained as a colourless liquid,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta_H$  (ppm) 7.23-7.25 (m, 1H), 7.91-7.92 (m, 1H), 8.03 (d,  $J = 8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta_C$  (ppm) 108.8, 115.0, 128.8, 135.4, 139.4. Spectroscopic data was consistent with literature [38].

Terephthalonitrile (**23p**)

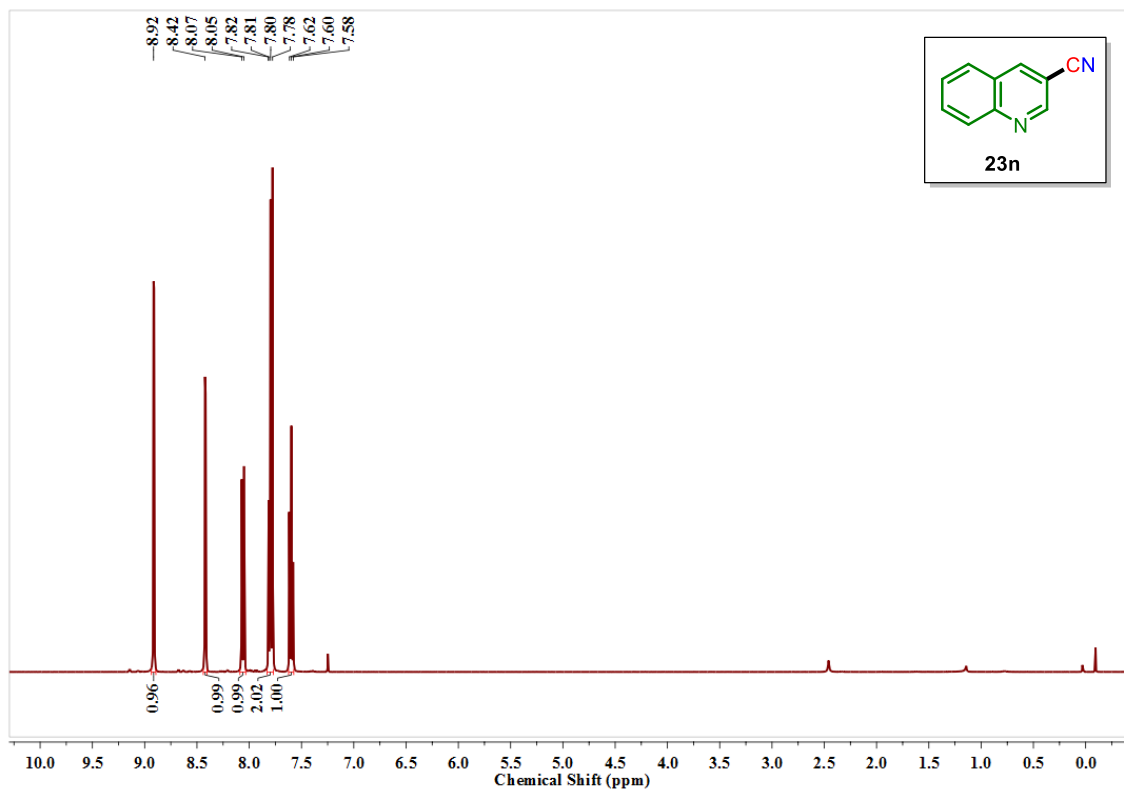
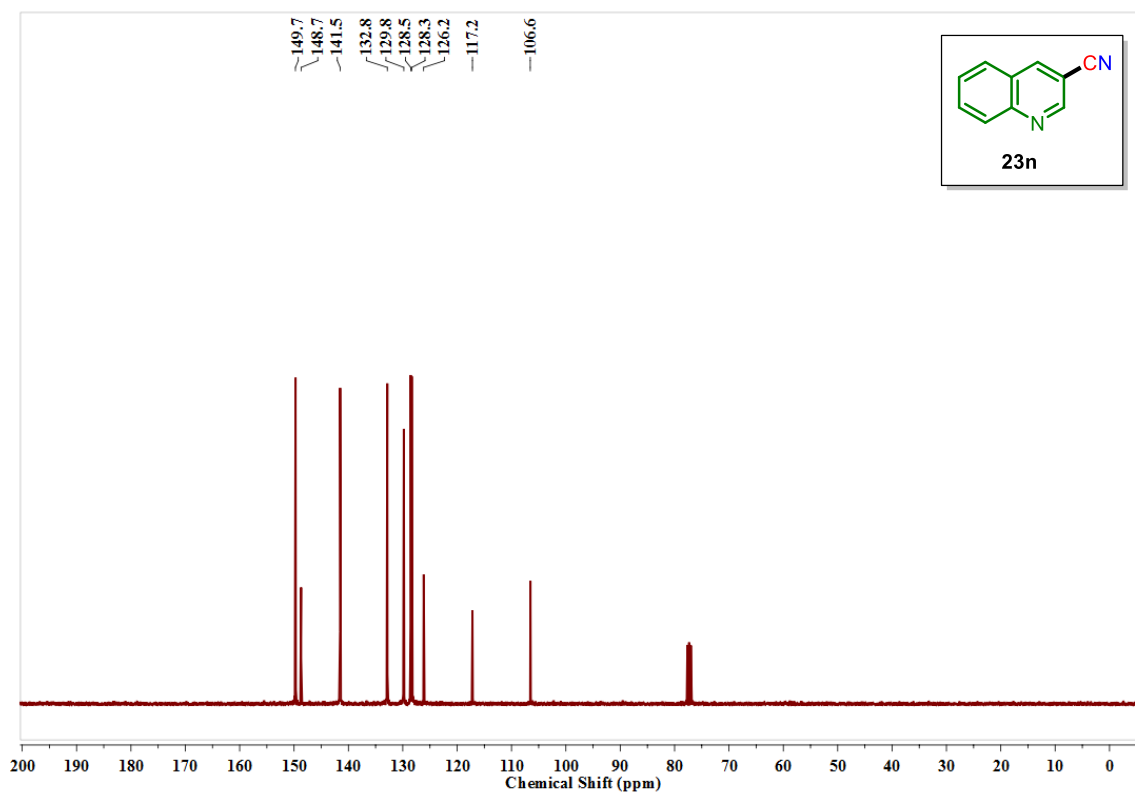
Synthesized from the general experimental procedure (from X=I, 49%, 63 mg; X=Br, 45%, 58 mg); obtained as a colourless solid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_H$  (ppm) 7.80 (s, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_C$  (ppm) 116.8, 117.0, 132.8. Spectroscopic data was consistent with literature [34].

1-Methyl-1*H*-indole-5-carbonitrile (**23q**)

Synthesized from the general experimental procedure (from X=Br, 75%, 117 mg); obtained as a yellow liquid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_H$  (ppm) 3.87 (s, 3H), 7.25 (d,  $J = 8.0$  Hz, 2H), 7.47 (d,  $J = 8$  Hz, 1H), 8.03 (s, 1H), 8.43-8.44 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_C$  (ppm) 33.0, 102.1, 110.2, 120.9, 124.2, 126.2, 128.1, 131.4, 138.1, 162.5. Spectroscopic data was consistent with literature [39].

Benzo[*d*][1,3]dioxole-5-carbonitrile (**23r**)

Synthesized from the general experimental procedure (from X=Br, 55%, 81 mg); obtained as a colourless solid,  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta_H$  (ppm) 6.13 (s, 2H), 7.06 (d,  $J = 8.0$  Hz, 1H), 7.35 (d,  $J = 8.0$  Hz, 1H), 7.38 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta_C$  (ppm) 103.0, 104.2, 109.9, 111.8, 119.4, 129.0, 148.3, 151.9. Spectroscopic data was consistent with literature [23].

**3.3.8 Representative  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of aryl nitrile derivatives**Figure 3.6  $^1\text{H}$  NMR spectrum of **23n** in  $\text{CDCl}_3$  (400 MHz, 298 K)Figure 3.7  $^{13}\text{C}$  NMR spectrum of **23n** in  $\text{CDCl}_3$  (100 MHz, 298 K)

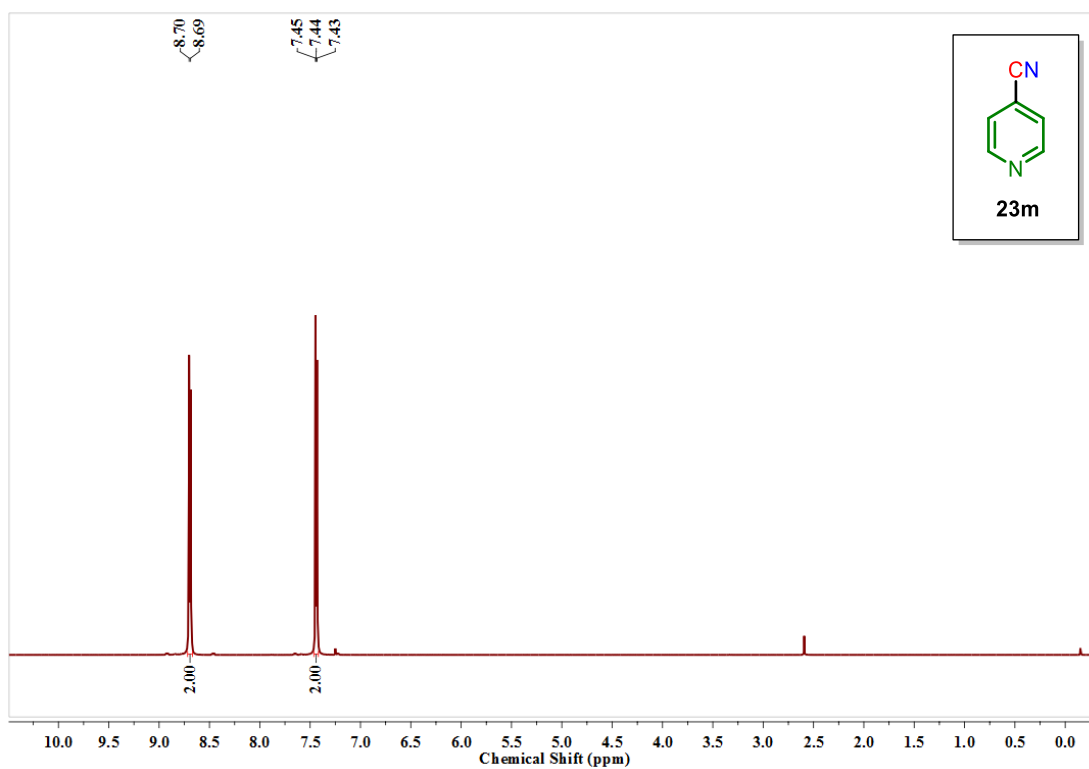


Figure 3.8  $^1\text{H}$  NMR spectrum of **23m** in  $\text{CDCl}_3$  (400 MHz, 298 K)

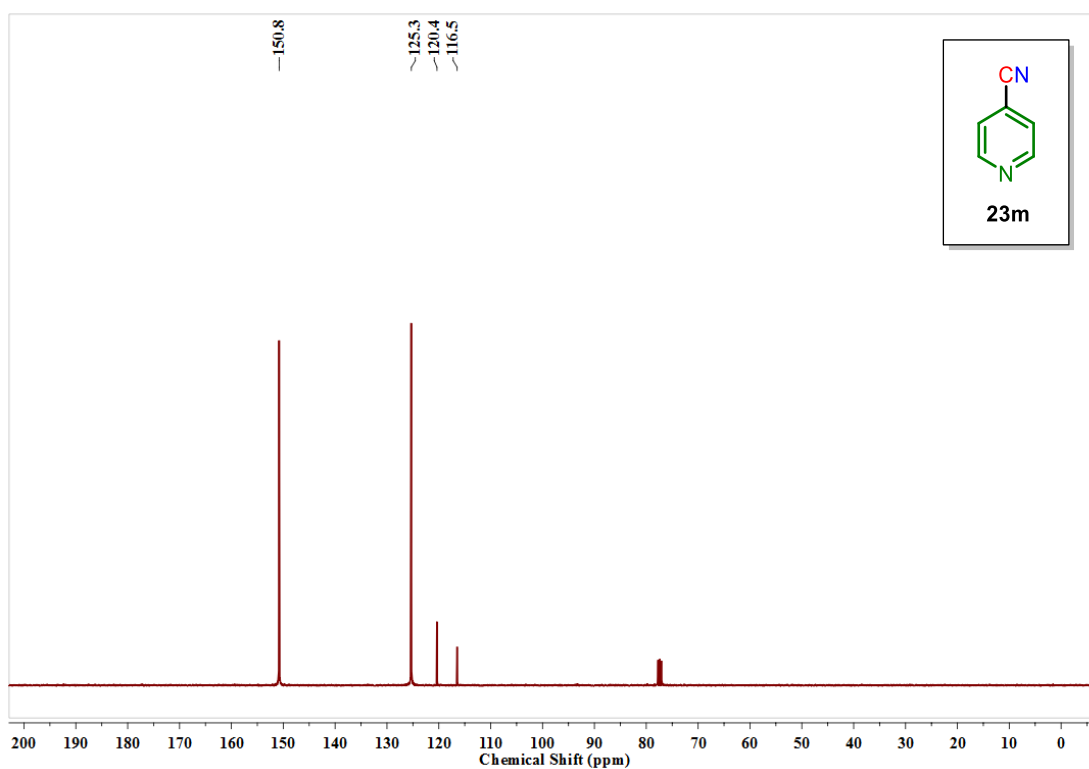


Figure 3.9  $^{13}\text{C}$  NMR spectrum of **23m** in  $\text{CDCl}_3$  (100 MHz, 298 K)



**3.4 Bibliography**

- [1] Wen, Q., Jin, J., Zhang, L., Luo, Y., Lu, P., and Wang, Y. Copper-Mediated Cyanation Reactions. *Tetrahedron Letters*, 55(7):1271-1280, 2014.
- [2] Yang, Y., and Buchwald, S. L. Copper-Catalyzed Regioselective ortho C-H Cyanation of Vinylarenes. *Angewandte Chemie International Edition*, 53(33):8677-8681, 2014.
- [3] Wu, Q., Luo, Y., Lei, A., and You, J. Aerobic Copper-Promoted Radical-Type Cleavage of Coordinated Cyanide Anion: Nitrogen Transfer to Aldehydes to Form Nitriles. *Journal of the American Chemical Society*, 138(9):2885-2888, 2016.
- [4] Wang, L., Shao, Y., and Cheng, J. Application of Combined Cyanide Sources in Cyanation Reactions. *Organic and Biomolecular Chemistry*, 19(40):8646-8655, 2021.
- [5] Anbarasan, P., Schareina, T., and Beller, M. Recent Developments and Perspectives in Palladium-Catalyzed Cyanation of Aryl Halides: Synthesis of Benzonitriles. *Chemical Society Reviews*, 40(10):5049-5067, 2011.
- [6] Hwu, J. R., Chen, K. L., Ananthan, S., and Patel, H. V. Ultrasonic Nitration of Allylsilanes by Use of Sodium Nitrite and Ceric Ammonium Nitrate. *Organometallics*, 15(2):499-505, 1996.
- [7] Gordon, K. H., and Balasubramanian, S. Exploring a Benzyloxyaniline Linker Utilizing Ceric Ammonium Nitrate (CAN) as a Cleavage Reagent: Solid-Phase Synthesis of *N*-unsubstituted  $\beta$ -lactams and Secondary Amides. *Organic Letters*, 3(1):53-56, 2001.
- [8] Nair, V., Nair, L. G., George, T. G., and Augustine, A. Cerium(IV) Ammonium Nitrate Mediated Addition of Thiocyanate and Azide to Styrenes: Expedient Routes to Phenacyl Thiocyanates and Phenacyl Azides. *Tetrahedron*, 56(38):7607-7611, 2000.
- [9] Bosman, C., D'Annibale, A., Resta, S., and Trogolo, C. Oxidation of Diphenyl Diselenide with Ceric Ammonium Nitrate: A Novel Route for Functionalization of Olefins. *Tetrahedron Letters*, 35(35):6525-6528, 1994.

- 
- [10] Trahanovsky, W. S., Young, L. B., and Brown, G. L. Oxidation of Organic Compounds with Cerium(IV). IV. Oxidation of Benzyl and Related Alcohols. *The Journal of Organic Chemistry*, 32(12):3865-3868, 1967.
- [11] Trahanovsky, W. S., and Young, L. B. Controlled Oxidation of Organic Compounds with Cerium(IV). II. The Oxidation of Toluenes. *The Journal of Organic Chemistry*, 31(6):2033-2035, 1966.
- [12] Syper, L. Partial Oxidation of Aliphatic Side Chains with Cerium(IV). *Tetrahedron Letters*, 7(37):4493-4498, 1966.
- [13] Trahanovsky, W. S., Young, M. G., and Nave, P. M. Oxidation of Organic Compounds with Cerium(IV). IX. Formation of 2-Methyltetrahydrofuran by Oxidation of 1-Pentanol. *Tetrahedron Letters*, 10(30):2501-2504, 1969.
- [14] Heiba, E. A. I., and Dessau, R. M. Oxidation by Metal Salts. VII. Syntheses Based on the Selective Oxidation of Organic Free Radicals. *Journal of the American Chemical Society*, 93(2):524-527, 1971.
- [15] Heiba, E. A. I., and Dessau, R. M. Oxidation by Metal Salts. VIII. Decomposition of Ceric Carboxylates in the Presence of Olefins and Aromatic Hydrocarbons. *Journal of the American Chemical Society*, 93(4):995-999, 1971.
- [16] Heiba, E. I., and Dessau, R. M. Oxidation by Metal Salts. IX. Formation of Cyclic Ketones. *Journal of the American Chemical Society*, 94(8):2888-2889, 1972.
- [17] Heiba, E. I., Dessau, R. M., and Rodewald, P. G. Oxidation by Metal Salts. X. One-Step Synthesis of Gamma-lactones from Olefins. *Journal of the American Chemical Society*, 96(26):7977-7981, 1974.
- [18] Nair, V., and Deepthi, A. Cerium(IV) Ammonium Nitrate a Versatile Single-Electron Oxidant. *Chemical Reviews*, 107(5):1862-1891, 2007.
- [19] Kim, J., and Chang, S. A New Combined Source of "CN" from *N,N*-dimethylformamide and Ammonia in the Palladium-Catalyzed Cyanation of Aryl C-H Bonds. *Journal of the American Chemical Society*, 132(30):10272-10274, 2010.
- [20] Ren, X., Chen, J., Chen, F., and Cheng, J. The Palladium-Catalyzed Cyanation of Indole C-H Bonds with the Combination of  $\text{NH}_4\text{HCO}_3$  and DMSO as a Safe Cyanide Source. *Chemical Communications*, 47(23):6725-6727, 2011.

- [21] Zhang, G., Ren, X., Chen, J., Hu, M., and Cheng, J. Copper-Mediated Cyanation of Aryl Halide with the Combined Cyanide Source. *Organic Letters*, 13(19):5004-5007, 2011.
- [22] Pawar, A. B., and Chang, S. Catalytic Cyanation of Aryl Iodides Using DMF and Ammonium Bicarbonate as the Combined Source of Cyanide: A Dual Role of Copper Catalysts. *Chemical Communications*, 50(4):448-450, 2014.
- [23] Kim, J., Choi, J., Shin, K., and Chang, S. Copper-Mediated Sequential Cyanation of Aryl C–B and Arene C–H Bonds Using Ammonium Iodide and DMF. *Journal of the American Chemical Society*, 134(5):2528-2531, 2012.
- [24] Kim, J., Kim, H., and Chang, S. Copper-Mediated Selective Cyanation of Indoles and 2-Phenylpyridines with Ammonium Iodide and DMF. *Organic Letters*, 14(15):3924-3927, 2012.
- [25] Wang, Z., and Chang, S. Copper-Mediated Transformation of Organosilanes to Nitriles with DMF and Ammonium Iodide. *Organic Letters*, 15(8):1990-1993, 2013.
- [26] Xu, S., Teng, J., Yu, J. T., Sun, S., and Cheng, J. Copper-Mediated Direct Cyanation of Heteroarene and Arene C–H Bonds by the Combination of Ammonium and DMF. *Organic Letters*, 21(24):9919-9923, 2019.
- [27] Zheng, K., Liu, B., Chen, S., and Chen, F. Copper-Catalyzed Cyanation of Aryl Iodide with the Combined Cyanide Source of Urea and DMSO. *Tetrahedron Letters*, 54(38):5250-5252, 2013.
- [28] Zhu, Y., Zhao, M., Lu, W., Li, L., and Shen, Z. Acetonitrile as a Cyanating Reagent: Cu-Catalyzed Cyanation of Arenes. *Organic Letters*, 17(11):2602-2605, 2015.
- [29] Xu, W., Xu, Q., and Li, J. Sandmeyer Cyanation of Arenediazonium tetrafluoroborate Using Acetonitrile as a Cyanide Source. *Organic Chemistry Frontiers*, 2(3):231-235, 2015.
- [30] Kou, X., Zhao, M., Qiao, X., Zhu, Y., Tong, X., and Shen, Z. Copper-Catalyzed Aromatic C-H Bond Cyanation by C-CN Bond Cleavage of Inert Acetonitrile. *Chemistry—A European Journal*, 19(50):16880-16886, 2013.
- [31] Li, Z., Huang, X., Chen, F., Zhang, C., Wang, X., and Jiao, N. Cu-Catalyzed Concise Synthesis of Pyridines and 2-(1H)-pyridones from Acetaldehydes and Simple Nitrogen Donors. *Organic Letters*, 17(3):584-587, 2015.

- 
- [32] Guillou, N., Louër, M., Auffrédic, J. P., and Louër, D. Two Polymorphic Forms of Ceric Potassium Nitrate,  $K_2Ce(NO_3)_6$ . *Acta Crystallographica Section C: Crystal Structure Communications*, 51(6):1029-1032, 1995.
- [33] Olszak-Humienik, M. On the Thermal Stability of Some Ammonium Salts. *Thermochimica Acta*, 378(1-2):107-112, 2001.
- [34] Ren, Y., Wang, W., Zhao, S., Tian, X., Wang, J., Yin, W., and Cheng, L. Microwave-Enhanced and Ligand-Free Copper-Catalyzed Cyanation of Aryl Halides with  $K_4[Fe(CN)_6]$  in Water. *Tetrahedron Letters*, 50(32):4595-4597, 2009.
- [35] Wu, Q., Luo, Y., Lei, A., and You, J. Aerobic Copper-Promoted Radical-Type Cleavage of Coordinated Cyanide Anion: Nitrogen Transfer to Aldehydes to Form Nitriles. *Journal of the American Chemical Society*, 138(9):2885-2888, 2016.
- [36] Dichiarante, V., Fagnoni, M., and Albin, A. Convenient Synthesis of Electron-Donating Substituted Benzonitriles by Photolysis of Phenyl Halides and Esters. *Chemical Communications*, (28):3001-3003, 2006.
- [37] Chatterjee, T., Dey, R., and Ranu, B. C. ZnO-Supported Pd Nanoparticle-Catalyzed Ligand- and Additive-Free Cyanation of Unactivated Aryl Halides using  $K_4[Fe(CN)_6]$ . *The Journal of Organic Chemistry*, 79(12):5875-5879, 2014.
- [38] Sawant, D. N., Wagh, Y. S., Tambade, P. J., Bhatte, K. D., and Bhanage, B. M. Cyanides-Free Cyanation of Aryl Halides using Formamide. *Advanced Synthesis & Catalysis*, 353(5):781-787, 2011.
- [39] Gerber, R., Oberholzer, M., and Frech, C. M. Cyanation of Aryl Bromides with  $K_4[Fe(CN)_6]$  Catalyzed by Dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}] palladium, A Molecular Source of Nanoparticles, and the Reactions Involved in the Catalyst-Deactivation Processes. *Chemistry—A European Journal*, 18(10):2978-2986, 2012.