

Short communication

Nano cobalt-copper ferrite catalyzed regioselective α -C(sp³)-H cyanation of amines: Secondary, tertiary, and drug molecules

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ABSTRACT

Oxidative cyanation of sp^3 C-H bonds at the α position of amines was achieved using $CoCuFe_2O_4$ as a catalyst and NaCN as an inexpensive cyanide source at room temperature.

$CoCuFe_2O_4$ was found to be an active catalyst for Csp [3]-Csp coupling, efficiently delivering valuable α -aminonitriles from tertiary/secondary amines in good yields. The corresponding products were obtained with high selectivity toward α position. In addition, functional group tolerance offered the opportunity for application in late-stage functionalization of biologically active molecules. This transformation proceeds conveniently on a gram-scale, and the catalyst can be reused for several runs with consistent catalytic activity.

1. Introduction

Regioselective C-H bond functionalization has attracted great attention and has become a popular research topic in organic synthesis [1]. C-H bonds are ubiquitous in organic compounds. Therefore, direct functionalization of such bonds represents chemical transformations in a single step by displacement of a hydrogen atom with an efficient atom economy and unlocks the opportunity to access a new scope of products inaccessible through the standard chemistries. In fact, the CDC (cross-dehydrogenative coupling) reactions effectively shorten the synthetic routes [2]. In this regard, achieving selectivity among different C-H bonds remains a challenging issue. Regioselectivity is strictly controlled by bond strength and secondarily by the steric hindrance. Consequently, sp^3 C-H bonds adjacent to a heteroatom or a functional group are often more reactive toward functionalization.

Regarding this fact, the transformation of amines into the corresponding α -functionalized compounds is valuable. In this class, α -amino nitriles are of great importance.

These compounds have proven to be important synthetic intermediates as they can be easily transformed into other functional groups [3] such as α -amino acids and alkaloids [4]. In addition, these compounds can be easily hydrogenated to useful compounds like 1,2-diamines [5].

On the other hand, owing to the interesting and specific structural feature of α -amino nitriles, they are categorized as bifunctional compounds possessing an amino and a nitrile group, located at the same

carbon atom which shows dual reactivity acting as both nucleophile and electrophile.

Traditional methods for synthesis of such frameworks were three-component Strecker reactions of carbonyl, amine, and cyanide [6]. Another approach toward their synthesis includes reductive Strecker reactions through the cyanation of amides and lactams [7].

However, the formation of methylformanilide [8] and *N*-methyl-aniline [9] as by-products, derived from the oxidation of tertiary amine, is the major shortcoming associated with the practical applications of this route.

Therefore, finding efficient methods for the synthesis of these structural motifs is of great importance. Oxidative cyanation of amines is an important alternative strategy for constructing α -aminonitriles.

In 2008, Murahashi and co-workers published Ru-catalyzed α -amino synthesis via oxidative cyanation of amines [10]. Subsequently, Sain introduced a vanadium-based catalyst for oxidative cyanation of tertiary amines with molecular oxygen in the presence of sodium cyanide and acetic acid to afford the corresponding α -aminonitriles [11]. High-valent rhenium(V) complex-catalyzed synthesis of α -amino nitriles by oxidative cross-dehydrogenative reaction was reported by Zhou and co-workers in 2013 [12] (Scheme 1).

However, these methods suffer from the drawbacks of tedious recovery and non-recycling ability of the catalyst and the use of precious metals such as ruthenium and rhenium.

Previously, we reported the activation of para C-H bond in tertiary amines (C(sp²)-H activation). In continuation of our works in C-H bond

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3. Result and discussion

CoCuFe₂O₄ nanoparticles were prepared using the co-precipitation method according to our previously reported procedure [16]. Characterization data of the catalyst are given in the supporting information. The catalyst was characterized using various physicochemical techniques including AAS, SEM, VSM, XRD, EDS, XPS, and FT-IR analysis. Atomic absorption spectroscopy analysis of the catalyst showed that the amount of Co and Cu are 5.2 wt% and 10 wt%, respectively.

Encouraged by the good performance of cobalt-copper ferrite on activation of C(sp)-H bond [17], we investigated its application in C(sp³)-H bond activation via oxidative cyanation of amines.

As shown in Table 1, we chose *N,N*-dimethylaniline as a model substrate to explore the suitable conditions toward sp³C-H cyanation. Initial trials showed that the reaction proceeded to give the desired product in a moderate yield when NaCN was used as the cyanation reagent, H₂O₂ as an oxidant, and CH₃OH/HOAc as a solvent at room temperature.

Solvent screening showed that changing the solvent from methanol to another solvent, such as DMF/HOAc, DMSO/HOAc, EtOH/HOAc, EtOAc/HOAc, H₂O/HOAc, Aceton/HOAc, and CH₃CN/HOAc, is less effective in the system (Table 1, entries 1–8). Inspired by the work of Rueping and co-workers [18], in an effort to improve the yields of the reaction, we speculated that AcOH as additive may aid the reaction. The role of acetic acid can be attributed to the liberation of HCN in the presence of NaCN. Therefore, acetic acid acts as a co-catalyst in this transformation. A controlling experiment in the absence of HOAc was done indicating that the addition of acetic acid was crucial to ensure good conversion.

Further investigation of the reaction conditions revealed that changing the reaction temperature to 40 °C and 60 °C did not improve the transformation (Table 1, entries 9–10). Therefore, room temperature

was selected as an optimized reaction temperature as selectivity was found to be lower at higher temperatures with the formation of an intricate mixture of by-products.

Next, different CN sources were screened. K₃[Fe(CN)₆], malononitrile, and DMF/NH₃ were found to be ineffective for the reaction, and no product was detected. NH₄HCO₃ afforded an 18% isolated yield (Table 1, entries 11–14).

Then, our studies focused on the effect of various oxidants on the model reaction (Table 1, entries 15–18). TBHP was the best oxidant in terms of conversion and reaction time. Other tested oxidants such as O₂, oxon, di-tert-butyl peroxide (DTBP), and benzoyl peroxide proved to be unfavorable in the system. In the absence of oxidant, the yield of reaction product dropped significantly.

To optimize the amount of required catalyst for this transformation, the model reaction was repeated in the presence of 2.5 and 10 mol% of CoCuFe₂O₄ nanoparticles (Table 1, entries 20–21). Gratifyingly, the experiment results showed that high yield is achieved when 5 mol% of CoCuFe₂O₄ was used as a catalyst. A series of background reactions were conducted to gain insights into the importance of each reaction parameter for reactivity. In the absence of catalyst, a low amount (14%) of the desired compound was obtained, suggesting that the transformation is indeed driven by a transition metal-based catalyst (Table 1, entry 22).

By switching the catalyst to various spinel ferrites including NiFe₂O₄, CoFe₂O₄, and CuFe₂O₄ under the described experimental conditions, lower yields were achieved. For Fe₃O₄ as a catalyst, poor yield was obtained (12%) even after 24 h (Table 1, entries 23–26).

These observations established the synergetic effect between metals in cobalt-copper ferrite that improves its catalytic activity. In fact, the introduction of another catalytically active metal into the ferrite lattice can expand the scope of accessible reactions - in this case, the oxidative CDC of Csp³ carbons.

Table 1
Results of optimization experiments^a.

Entry	Solvent	Temp. (°C)	Cyanide source	Oxidant	Catalyst/mol%	Yield ^b (%)
1	CH ₃ OH/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	54
2	DMF/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	–
3	DMSO/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	–
4	EtOH/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	49
5	EtOAc/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	40
6	H ₂ O/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	trace
7	Aceton/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	34
8	CH ₃ CN/HOAc (4:1)	RT	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	50
9	CH ₃ OH/HOAc (4:1)	40	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	52
10	CH ₃ OH/HOAc (4:1)	60	NaCN	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	50
11	CH ₃ OH/HOAc (4:1)	RT	CH ₂ (CN) ₂ /KOtBu	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	–
12	CH ₃ OH/HOAc (4:1)	RT	K ₃ [Fe(CN) ₆]	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	–
13	CH ₃ OH/HOAc (4:1)	RT	NH ₄ HCO ₃	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	15
14	CH ₃ OH/HOAc (4:1)	RT	DMF/NH ₃	H ₂ O ₂ (35%)	CoCuFe ₂ O ₄ /5	–
15 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	CoCuFe₂O₄/5	89
16 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	DTBP	CoCuFe ₂ O ₄ /5	31
17 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	Benzoyl peroxide	CoCuFe ₂ O ₄ /5	25
18 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	Oxon	CoCuFe ₂ O ₄ /5	30
19 ^c	CH ₃ OH	RT	NaCN	TBHP(70%)	CoCuFe ₂ O ₄ /5	15
20 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	CoCuFe ₂ O ₄ /2.5	69
21 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	CoCuFe ₂ O ₄ /10	90
22 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	–	12
23 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP (70%)	Fe ₃ O ₄ /5	16
24 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	NiFe ₂ O ₄ /5	70
25 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	CoFe ₂ O ₄ /5	69
26 ^c	CH ₃ OH/HOAc (4:1)	RT	NaCN	TBHP(70%)	CuFe ₂ O ₄ /5	67

^a Reaction conditions: *N,N*-dimethylaniline (0.5 mmol), CN source(0.6 mmol), oxidant (1.25 mmol), solvent (2 mL), 6 h.

^b Isolated yield.

^c 2.5 h.

Thus, the optimized reaction conditions for α -cyanation of *N,N*-dimethylaniline are $\text{CoCuFe}_2\text{O}_4$ (5 mol%) in MeOH/HOAc using NaCN as cyanide source and TBHP as oxidant at room temperature for 2.5 h (Table 1, entry 15).

To generalize the protocol developed, a variety of tertiary/secondary amines were used as the substrate for oxidative cyanation under optimized reaction conditions. The results of these experiments are presented in Table 2.

Results showed that aromatic substrates bearing electron-donating groups were found to be more reactive as compared to the substrates having electron-withdrawing groups.

For *N*-methylisatin, *N*-methylimidazole, *N*-ethyl-*N*-phenylbenzamide, and 4-(4-methyl-thiobenzoyl)-morpholine, the starting materials remained intact even after 24 h and under temperatures up to 50 °C. This observation proved that the presence of free ion pair of nitrogen atoms is vital for this transformation, and in substrates whose ion pair of nitrogen is involved in the resonance, the corresponding amino nitrile cannot be formed. The reactions of cyclic amine such as piperidine derivative proceeded well and afforded the corresponding α -amino nitriles in good yields.

Steric hindrance also seems to have an effect on the results. For example, the reaction of bulky tribenzylamine afforded the expected product in 47% yield (Table 2, entry 11).

N,N-Dimethylbenzylamine, as an unsymmetrical amine, underwent a regioselective oxidative cyanation in the methyl group rather than in the methylene carbon of the benzyl group to furnish the desired product in 53% yield (Table 2, entry 10).

Comparing entries 1 and 13 revealed that tertiary amines are more reactive toward this C–C coupling rather than secondary amines.

It is worth mentioning that in all cases, the $\alpha\text{-C}(\text{sp}^3)\text{-H}$ bond of amine is cleaved and functionalized under the present reaction conditions.

To demonstrate the applicability of this catalytic system, we shifted our focus toward the late-stage functionalization of pharmaceutical molecules (Table 3). For this purpose, biologically active molecules such as nicotine as an alkaloid and two known drugs (repaglinide and rivastigmine) were selected.

Repaglinide, a drug with an unprotected acid functionality, provided the $\text{C}\alpha\text{-H}$ cyanation product in the highest yield in this series.

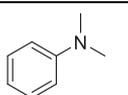
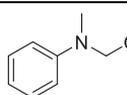
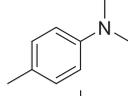
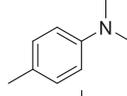
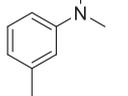
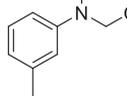
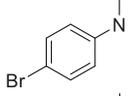
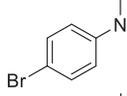
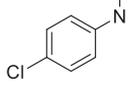
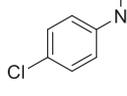
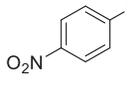
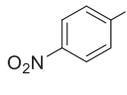
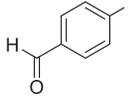
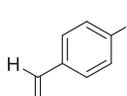
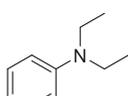
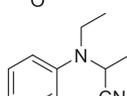
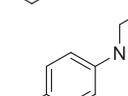
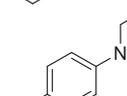
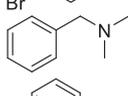
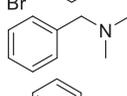
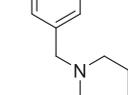
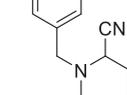
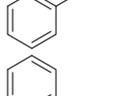
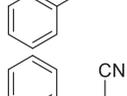
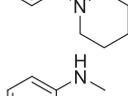
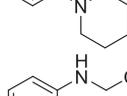
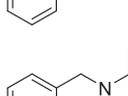
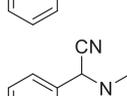
For nicotine, a molecule with different available α -protons for substitution, C–H cyanation selectively occurred at the pyrrolidine ring and no methyl cyanation was observed. In fact, the reaction took place at the less hindered carbon.

Rivastigmine as an aliphatic acyclic tertiary amine underwent the $\text{C}\alpha\text{-H}$ cyanation in relatively low yields under our conditions. In fact, introducing the CN unit on drug molecules could develop the drug biological functionality [3]. Nitrile is a strong hydrogen bond acceptor and may improve solubility and alter the biological function of the molecule by modulating the interactions with a diverse range of bioactive receptors. As the nitrile segment is smaller than bromine and iodine, it has better contact with amino acids locating at the active site. Apart from the mentioned features, the nitrile group is a key component for molecular recognition and could be transferred into other valuable and practical functional groups.

We then focused on demonstrating the synthetic utility of the catalytic system on a large scale. The scalability of the procedure was explored by the reaction of *N,N*-dimethylaniline and NaCN under the optimized reaction conditions on 10 mmol scale (Scheme 2). Results indicate that $\text{CoCuFe}_2\text{O}_4$ catalytic system has the potential to be employed for large scale synthesis of α -amino nitriles in high yields.

In terms of industrial applications, the recyclability of the catalyst is a very important factor. To check the reusability of the catalyst, the oxidative cyanation of *N,N*-dimethylaniline was investigated under the optimized reaction conditions. At the end of the reaction, the catalyst was easily separated by an external magnet, washed with EtOH, dried, and reused for consecutive reaction runs. This process was repeated 5 times, and each time, the isolated yield was calculated exactly. Fig. 1

Table 2
Scope of the oxidative α -cyanation catalyzed by $\text{CoCuFe}_2\text{O}_4$.^a

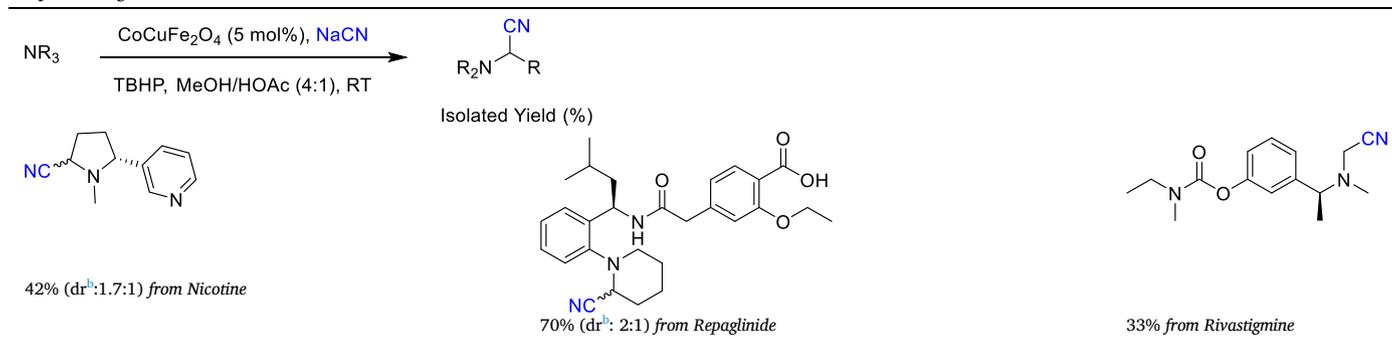
Entry	Reactant	Product	Yield ^b (%)
1			89
2			88
3			85
4			77
5			71
6			29
7			41
8			86
9			62
10			53
11			47
12			80
13			78
14			49

^a Reaction conditions: substrate (0.5 mmol), NaCN (0.6 mmol), TBHP (1.25 mmol), $\text{CH}_3\text{OH}/\text{HOAc}$ (2 mL), $\text{CoCuFe}_2\text{O}_4$ (5 mol%), at room temperature, 2.5 h.

^b Isolated yield.

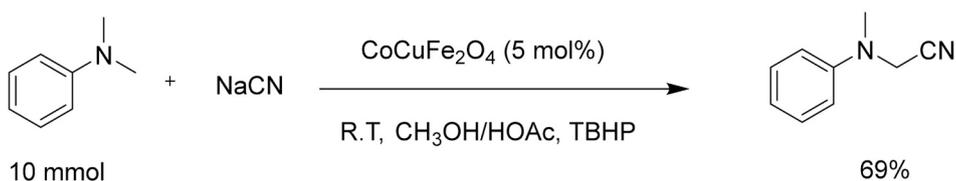
clearly indicates the efficient recycling of the catalyst without any significant loss in catalytic activity. Furthermore, to ascertain the leaching of the catalyst, the filtrates were subjected to ICP analysis; no metal could be observed, therefore establishing that the catalyst is truly a

Table 3
Scope of drug substrate^a.



^a Reaction conditions: as described in Table 2.

^b Diastereomeric ratio was identified by ¹H NMR in a crude mixture.



Scheme 2. Examining scalability of the reaction.



Fig. 1. The recyclability of CoCuFe₂O₄ in the cyanation reaction of *N,N*-dimethyl aniline.

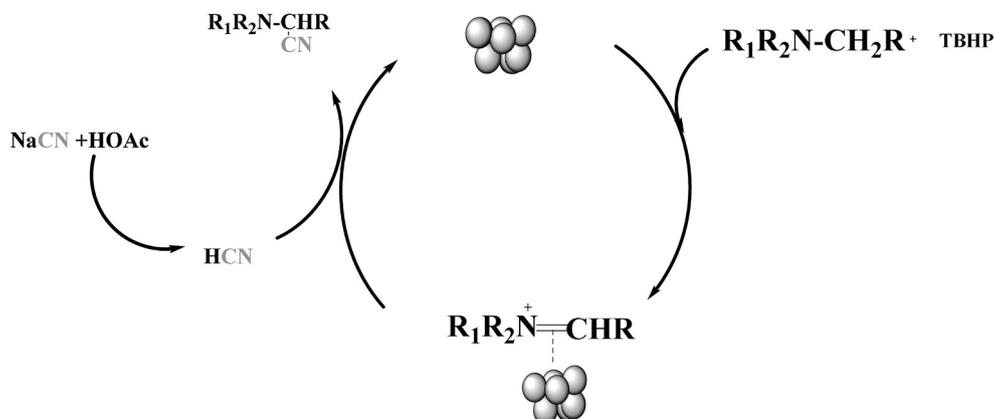
heterogeneous one without noteworthy leaching of metal nanoparticles.

Although significant developments on mixed metal spinel ferrite catalyzed cross-coupling reactions have been achieved, the mechanism of such reactions is still under-explored. To gain some insights into the

reaction mechanism, an experiment (*N,N*-dimethyl aniline as a substrate) in the presence of a radical scavenger TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxy) led to the formation of desired α -aminonitrile in 63% yield under the standard reaction conditions. The results ruled out the radical pathway and suggest that an intermediate free-radical species does not appear to be involved in this system.

Analogous to the existing reports [19–20], along with the obtained results through conducting controlling experiments, a rational mechanism for this reaction was proposed.

The first step involves the abstraction of a hydrogen atom from the amine with the help of TBHP and CoCuFe₂O₄ to give iminium ion intermediate as shown in Scheme 3. The in-situ generation of HCN (generated from NaCN and acetic acid) and its subsequent attack on the activated iminium ion intermediate yields the corresponding α -aminonitrile. The catalyst surface is regenerated by the action of the oxidant with the catalyst, which leads to desorption of the product molecules, thereby favoring further oxidation.



Scheme 3. Plausible reaction mechanism.

4. Conclusion

To date, the most challenging aspect in the area of regioselective C—H activation is C(sp³)-H functionalization. This study showed the unlocking reactivity of ubiquitous C(sp³)-H bonds by smart molecular design and employment of CoCuFe₂O₄ as a catalyst. Under the optimized reaction conditions, C—H bond cyanation of variety of tertiary/secondary amines with selectivity for the α position was achieved and the corresponding α-amino nitriles were formed in high yields in the presence of NaCN as a cyanating source. By this methodology, different families of α-amino nitriles have been prepared. Remarkably, this protocol prompted us to introduce the cyano group in known drugs and alkaloid, which is another attractive feature of this catalytic system.

In fact, this is a valuable alternative to the Strecker synthesis of α-amino nitriles, avoids the use of pre-functionalized starting material, and thus serves as a valuable and straightforward synthetic strategy.

In this report, constructing C(sp³)-CN bonds was done at room temperature. Hence, the required energy and time for the reaction minimized in this method compared to previously report oxidative cyanation reactions. In addition, employing nano cobalt copper ferrite as an inexpensive magnetic heterogeneous catalyst is another important benefit of this study.

Declaration of Competing Interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.catcom.2020.106211>.

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