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A copper-mediated oxidative *N*-cyanation reaction†

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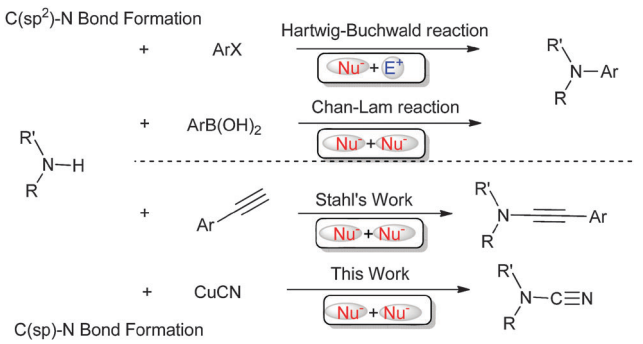
Copper-promoted *N*-cyanation of aliphatic *sec*-amine by CuCN is achieved *via* oxidative coupling. This procedure employs O_2 as a clean oxidant. Notably, sulfoximines and 1,1,3,3-tetramethylguanidine also worked well in this procedure. Thus, it represents a key progress in the C–N bond formation reaction as well as in the cyanation reaction.

Amine and its derivatives serve as nucleophiles owing to their inherent properties in the transition-metal-catalyzed C–N bond formation reaction.[1] The C_{sp^2}–N bond coupling includes the reaction between a nitrogen nucleophile and a C_{sp^2}–X unit as an electrophile, typified by the Hartwig–Buchwald reaction (Scheme 1),[2] as well as the oxidative coupling of nitrogen nucleophile with another aromatic nucleophile, such as the Chan–Lam reaction (Scheme 1).[3] However, less attention has been paid to the construction of the C_{sp}–N bond. Among the sp-hybridized carbon reaction partners, terminal alkynes and cyanides are likely the most abundant chemicals. Therefore, the oxidative coupling is probably the most straightforward strategy leading to the C_{sp}–N bond formation.[4]



Scheme 1 The C–N bond formation reaction.

In this respect, the oxidative coupling of alkynes with N-containing compounds was developed by Stahl and Bolm, respectively (Scheme 1).[5] To the best of our knowledge, such a strategy has never been applied in the coupling of cyanides with amines, which affords cyanamides. Importantly, the cyanamide core is an important pharmacophoric substructure and is widely found in several bioactive molecules.[6] Moreover, cyanamides serve as cyanide sources,[7] ligands[8] and versatile building blocks in the synthesis of amidines, guanidines,[9] and heterocycles[10] *via* cycloaddition.

However, sharply in contrast with the well-developed transition-metal-catalyzed C–CN bond formation reaction,[11] to date, the efficient method for the construction of N–CN bond is limited to the nucleophilic cyanation of amines by XCN (X = halo).[12] For tertiary amines, it was known as the von Braun reaction[13] BrCN is highly toxic and sensitive to moisture. Herein, we report an efficient *N*-cyanation of aliphatic *sec*-amine, sulfoximine and 1,1,3,3-tetramethylguanidine using CuCN as the cyanation source under mild conditions.

Initially, Bn_2NH (**1a**) was selected as the model substrate to optimize the reaction conditions. Initial success was achieved by using 0.05 mmol of Cu_2O and 0.6 mmol of *N,N,N,N*-tetramethyl ethylene diamine (TMEDA) under O_2 in CH_3CN at 50 °C, producing the *N*-cyanation product in 35% yield (Table 1, entry 1). Following this promising result, other copper(I) and (II) sources, such as CuO, $CuBr_2$, $CuCl_2$, $Cu(OAc)_2$ and CuI were tested in the procedure and found to promote the cyanation reaction to some extent (Table 1, entries 2–6). To our delight, $CuBr_2$ and $CuCl_2$ gave the *N*-cyanation product in 55% and 54% yields, respectively (Table 1, entries 3 and 4). At 100 °C, no cyanation product was isolated (Table 1, entry 3). In DCM, the yield decreased to 29% and no reaction took place in toluene (Table 1, entries 7 and 8). Intriguingly, in the presence of Na_2SO_4, the reaction was further increased to 78% (Table 1, entry 9). The possibility of Na_2SO_4 acting as the drying reagent was ruled out, as adding 10 equivalents of water did not inhibit the reaction. Replacing TMEDA with bipy and DABCO resulted in no reaction or low yield, indicating that TMEDA may not solely act as the ligand (Table 1, entry 9). The employment of CsF, NaOH decreased the yield (Table 1, entries 10 and 11). No cyanation reaction took

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Table 1 Optimization of reaction conditions[a]

Entry	Catalyst	Solvent	Additive	Yield (%)
1	Cu_2O	MeCN	—	35
2	CuO	MeCN	—	40
3	$CuBr_2$	MeCN	—	55(<1)[b]
4	$CuCl_2$	MeCN	—	54
5	$Cu(OAc)_2$	MeCN	—	40
6	CuI	MeCN	—	31
7	$CuBr_2$	Toluene	—	<1
8	$CuBr_2$	DCM	—	29
9	$CuBr_2$	MeCN	Na_2SO_4	78(<5)[c](<1)[d,e]
10	$CuBr_2$	MeCN	CsF	73
11	$CuBr_2$	MeCN	NaOH	50
12	—	MeCN	Na_2SO_4	65

[a] Reaction conditions: **1a** (0.3 mmol), CuCN (0.6 mmol), Cu catalyst (0.05 mmol), TMEDA (0.6 mmol), additive (0.6 mmol), and 3 mL of indicated solvent, O_2, 50 °C, 12 h. [b] 100 °C. [c] Bipy, no TMEDA. [d] DABCO, no TMEDA. [e] No TMEDA.

place in the absence of CuCN, indicating CH_3CN did not serve as the cyanation source. In the absence of $CuBr_2$, the cyanation product was isolated in 65% yield, indicating the CuCN could promote the cyanation reaction (Table 1, entry 12).

With the optimized reaction conditions in hand, the substrate scope of *sec*-amine was also studied, as shown in Fig. 1.

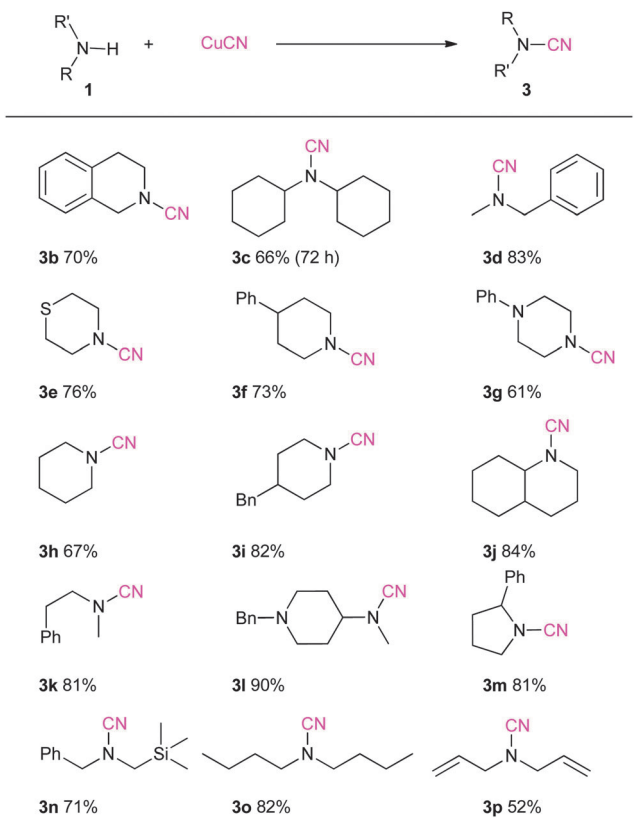


Fig. 1 The oxidative cyanation of *sec*-amine by CuCN. [a] All reactions were run with **1** (0.3 mmol), CuCN (0.6 mmol), Na_2SO_4 (0.6 mmol), $CuBr_2$ (0.05 mmol), TMEDA (0.6 mmol), and 3 mL of CH_3CN, O_2, 50 °C, 12 h.

It turned out that the cyclic *sec*-amine ran smoothly under the standard conditions to provide the *N*-cyanation products in good to excellent yields (*e.g.* **3b**, **3e–3j** and **3m**). Meanwhile, the acyclic analogues also worked well in this reaction (*e.g.* **3c**, **3d**, **3k**, **3l**, and **3n–3p**). For example, dibutyl amine provided the cyanation product **3o** in 82% yield. Particularly, diallylamine worked under the procedure, delivering the target product **3p** in 52% yield. However, this procedure did not tolerate the aromatic amine very well. For example, *N*-methyl aniline provided the desired product in low yield because of the significant homocoupling side reaction leading to N–N bond formation.[14] Similarly, diphenyl amine did not work under the standard procedure. Disappointingly, primary aliphatic amines, such as benzylamine and butylamine failed to take part in the cyanation reaction.

The substrate scope was not only limited to *sec*-amine and sulfoximine could also run smoothly under the standard procedure leading to *N*-cyano sulfoximines as potential insecticides (Fig. 2).[15] This procedure is applicable for both aryl alkyl sulfoximine and the diaryl analogues. For example, (*S*-methylsulfonimidoyl)benzene derivative provided the *N*-cyanation product **4a** in 76% yield. Particularly, sulfonimidoyldibenzene produced the cyanation product **4d** in 91% yield. Indeed, this method provided a fundamentally different pathway to access *N*-cyano sulfoximines.[16] Notably, 1,1,3,3-tetramethylguanidine also took part in the *N*-cyanation reaction in 78% yield (**4f**).

To increase the practicality, a 20 mmol scale reaction was conducted and **3d** was isolated in a comparable 77% yield.

More experiments were conducted to gain some insight into the reaction. Firstly, UV spectrum was tested (see ESI†), indicating TMEDA acted as the ligand in the catalytic cycle.[17] However, heating the combination of TMEDA (0.05 mmol), $CuBr_2$ (0.05 mmol), amine (0.3 mmol) and CuCN (0.6 mmol) under 50 °C provided trace of the desired product. The cyanation reaction took place well only by adding an additional 2.0 equivalents of TMEDA to the reaction mixture. This result indicated that TMEDA also played other roles in the reaction, most probably as a base. Lei reported the dual role of TMEDA in

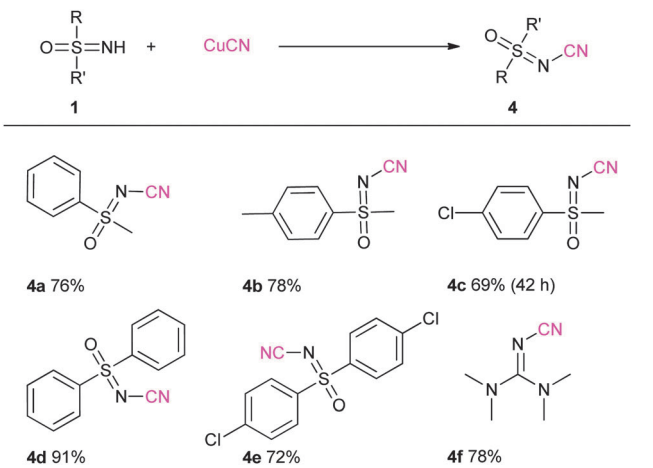
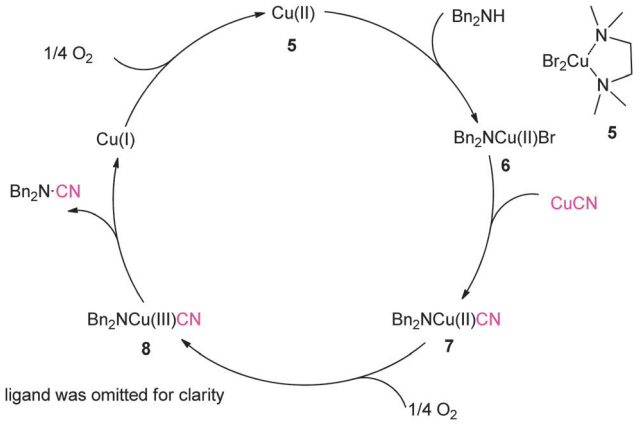


Fig. 2 The oxidative cyanation of sulfoximine and guanidine by CuCN. [a] All reactions were run with **1** (0.3 mmol), CuCN (0.6 mmol), Na_2SO_4 (0.6 mmol), $CuBr_2$ (0.05 mmol), TMEDA (0.6 mmol), and 3 mL of CH_3CN, O_2, 50 °C, 12 h.



Scheme 2 Proposed mechanism.

copper-mediated oxidative coupling of the terminal alkyne.[18] Secondly, the ratio of the consumed O_2 and the *N*-cyanation product was tested and found to be nearly 1 : 2 (see ESI†). Finally, the XPS study confirmed that the valence of copper was (II) after the reaction.[19]

Based on the above experiments and earlier reported literature, the proposed mechanism was outlined in Scheme 2.

Initially, the ligand exchange between the Cu(II) catalyst coordinated by TMEDA and Bn_2NH forms a copper(II) species **6**. Then, the reaction between **6** and CuCN produces another Cu(II) species **7** *via* the second ligand exchange. Then the intermediate **7** is oxidized to a Cu(III) species **7** by O_2. Finally, the reductive elimination of **8** delivers the final *N*-cyanation product, along with a Cu(I) species. The Cu(I) species is oxidized by O_2 to regenerate the Cu(II) catalyst. However, the role of Na_2SO_4 is not clear in the current stage.

In conclusion, we have developed a copper-mediated oxidative *N*-cyanation of *sec*-amine, sulfoximine and 1,1,3,3-tetramethylguanidine by CuCN. This procedure employed O_2 as a clean terminal oxidant. Thus, it provided a practical approach to access cyanamides and *N*-cyano sulfoximines.

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