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Recyclable bimetallic $CuMoO_4$ nanoparticles for C–N cross-coupling reaction under mild conditions†

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Herein we disclosed inexpensive copper(II) bimetallic $CuMoO_4$ nanoparticles for the C–N cross-coupling reaction of alkyl and aryl amines with haloarenes. The reaction proceeds under mild and ligand free conditions. The catalyst is recyclable and effective for a wide range of amines and haloarenes. Here, the efficiency of the Cu(II) catalyst is increased by doping molybdenum metal. The bimetallic nanoparticles are anticipated to proceed *via* normal oxidative addition and reductive eliminations.

Ullmann type[1] C–N cross-coupling reaction has been utilized for the synthesis of important intermediates during drug and natural product synthesis.[2] Hence, development of new methods for C–N bond formation is of great importance in pharmaceutical industry.[3] The reported catalysts for C–N cross-coupling are limited and made up of only either palladium or copper metal. Palladium[4,5] metal has been used extensively by Hartwig–Buchwald *et al.* using well defined phosphine ligands, whereas copper[6] metal is used along with carboxylate ligands. Subsequently, Ni,[7] Fe[8] and other metals[9] have been used for the above coupling reaction. The above reported catalyst involves the use of a phosphine ligand, chelating ligands, high temperature and harsh reaction conditions. So, chemists are constantly focusing on developing alternative heterogeneous catalysts, such as nanocatalysis,[10] keeping in mind constraints of solvent, temperature, *E*-factor, turn over frequency and turn over number and the cost of cross-coupling reactions.[11]

Our group has recently reported a heterogeneous and green CuO nano recyclable catalyst for C–N cross-coupling reaction. After closely looking at the reactivity and cost of the reaction process, copper[12] is the next best available cheap metal catalyst for a C–N cross-coupling reaction. Copper makes really a big difference in the C–N cross-coupling reaction in comparisons to an expensive palladium catalyst. Hence, the efficiency of low cost copper could be substantially increased by doping other metals.

The bimetallic $CuMoO_4$ nanoparticles are synthesized by the dropwise addition of aqueous ammonium molybdate solution to aqueous copper chloride dihydrate solution from room temperature to 80 °C. The resulting greyish green precipitate $CuMoO_4$ was characterized after sonication, centrifugation and drying (for details of synthesis and characterisation by SEM, EDX, IR, and XPS, see the ESI†).[13,17,18] In this context we have used a $CuMoO_4$ bimetallic nano catalyst with particle size <30 nm (see the ESI†), which has been found to be efficient for the C–N cross-coupling reaction.

At first, we investigated the reaction of aniline **2a** and iodobenzene **1a** for the C–N cross-coupling reaction of aniline with iodobenzene in the presence of 1.2 equivalent of a Cs_2CO_3 base and 2.6 mol% of catalyst at 90 °C in different solvents. The reaction in toluene and 1,4-dioxane solvents afforded 5–10% yield after 24 h (Table 1, entries 1 and 2); whereas changing the solvent to *t*-BuOH and acetonitrile afforded increased yield of 20–40% (Table 1, entries 3 and 4). DMF solvent provided an average yield of 65%; whereas DMSO solvent under similar conditions afforded C–N product **3a** in 86% yield after 24 h (Table 1, entry 6).

Furthermore, we screened different bases in DMSO solvent. Bases such as K_2CO_3 and KOH provided 25–55% yield, whereas *t*-BuOK provided 80% yield after 24 h (Table 1, entry 10). To understand the real catalytic process of the catalyst, reaction alone with Cs_2CO_3 (without $CuMoO_4$, Table 1, entry 12) and only $CuMoO_4$ (without Cs_2CO_3, Table 1, entry 13) did not afford any product. Similarly, the use of $CuCl_2{\cdot}2H_2O$ (Table 1, entry 14) or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (Table 1, entry 15) in the presence of Cs_2CO_3 underwent no reaction. The standardization of the reaction revealed that Scheme 1 was the best mild conditions for the cross-coupling of aniline with iodobenzene.

With the optimized conditions (Scheme 1), bromobenzene **1b** has been successfully coupled with aniline **2a** to afford 80% of the desired product **3a** after 24 h (Scheme 2, entry 1). Electron donating *p*-substituted 4-methoxyaniline (**2b**) was

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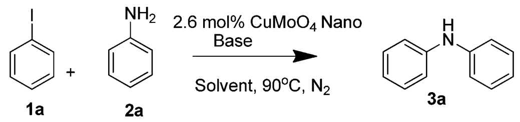
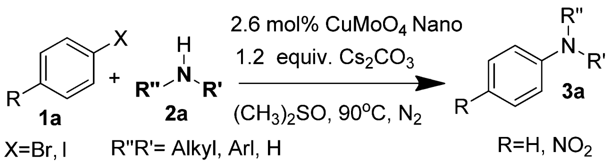
Table 1 Standardised reaction of aniline with iodobenzene

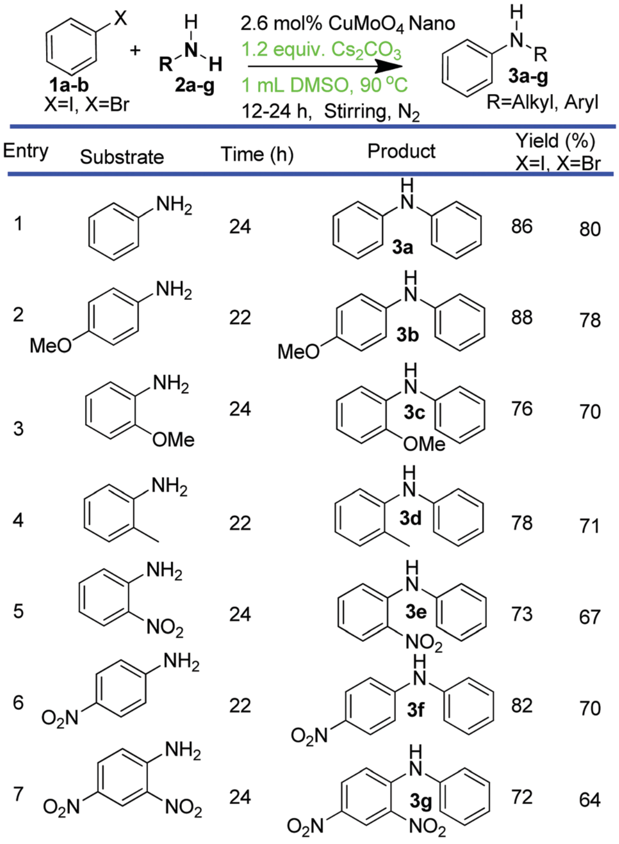


Sl no.	Solvent	Base	Temp. (°C)	Yield[a] (%)
1	Toluene	Cs_2CO_3	90	5[b]
2	1,4-Dioxane	Cs_2CO_3	90	10
3	*t*-BuOH	Cs_2CO_3	90	30
4	CH_3CN	Cs_2CO_3	90	40
5	DMF	Cs_2CO_3	90	65
6	DMSO	Cs_2CO_3	90	86
7	DMSO	Cs_2CO_3	85	82
8	DMSO	Pyridine	90	0
9	DMSO	K_2CO_3	90	25
10	DMSO	*t*-BuOK	90	80
11	DMSO	KOH	90	55
12	DMSO	Cs_2CO_3	90	0[c]
13	DMSO	—	90	0[d]
14	DMSO	Cs_2CO_3	90	5[e]
15	DMSO	Cs_2CO_3	90	0[f]

[a] Catalyst 2.6 mol% (3 mg), aniline (0.5 mmol), iodobenzene (0.55 mmol), base 1.2 equiv. were stirred for 24 h. [b] Isolated yield. [c] No catalyst. [d] No base. [e] $CuCl_2 \cdot 2H_2O$. [f] $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$.



Scheme 1 Standardised reaction conditions for C–N cross-coupling of amines with haloarenes.



Scheme 2 Reaction of primary amines with haloarene.

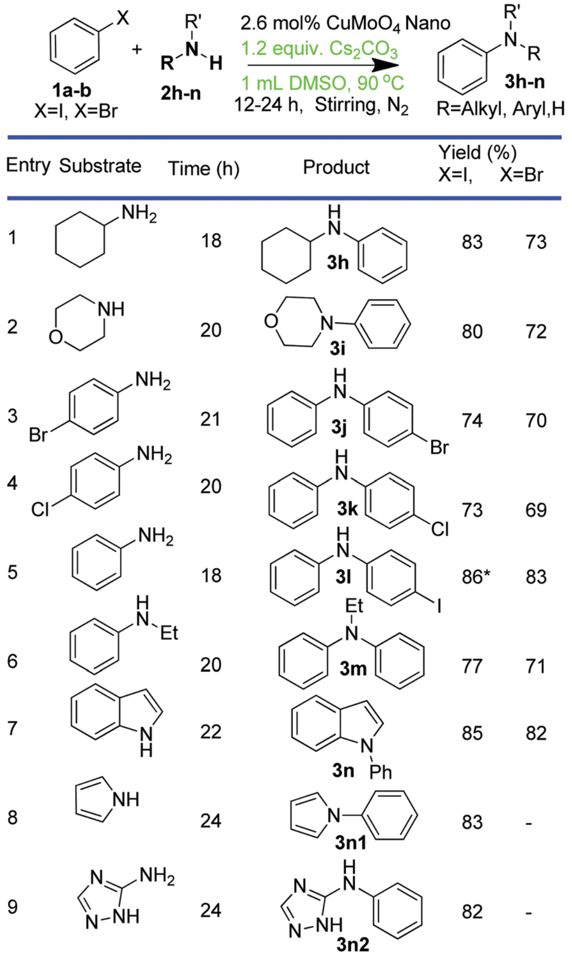
successfully coupled with iodo- and bromo-benzene with 78–88% product **3b** in comparison to its *ortho*-substituted substrates 2-methoxy aniline **2c** (Scheme 2, entry 3), whereas 2-methyl-aniline afforded 71–78% product **3d**. Electron withdrawing substrates such as 2-nitro, 4-nitro and 2,4-dinitro anilines **2e–g** have been successfully coupled with iodobenzene **1a** providing the corresponding product **3e–g** in 72–82% yield (Scheme 2, entries 5–7), whereas it afforded 64–70% yield with bromobenzene. The *ortho*-substituted substrates provided less yield with longer reaction than their *p*-substituted derivatives (Scheme 2).

To study the scope of the procedure, the reaction of other aliphatic amines (**2h–i**), secondary amines (**2i**, **2m**, **2n**), and halogen substituted aromatic amines (**2j–l**) was investigated (Scheme 3). Cyclohexylamine **2h** provided 83% yield of **3h**, whereas secondary aliphatic morpholine **2i** afforded 80% yield of **3i** in 20 h. Halogen-substituted aromatic amines such as 4-bromo, 4-chloro- and 4-iodo anilines were successfully coupled with iodo/bromo-benzene to afford 73–86% yield of **3j–l** without any side product (Scheme 3, entries 3–5). *N*-Ethylaniline (**2m**) afforded coupled product **3m** with iodobenzene **1a** in 77% yield and 71% yield with bromobenzene **1b**. Indole (**2n**) also underwent reaction with iodobenzene in 85% of product **3n** after 22 h (Scheme 3, entry 7). Heterocycles such as pyrrole and 1,2,3-triazole have been coupled to afford product **3n1–3n2** in 82–83% yield.

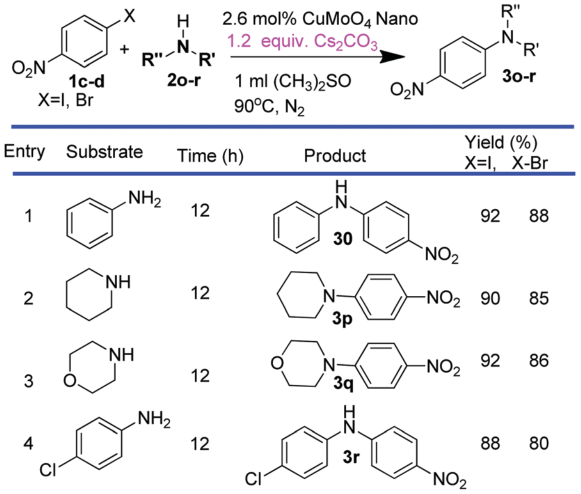
Next, we investigated the reactivity of some aromatic and aliphatic amines with electron withdrawing 4-nitroiodoarenes (**1c–d**) (Scheme 4). Under optimized conditions, 4-nitroiodo benzene **1c** afforded C–N cross-coupled product **3o** in 92% yield after 10 h, whereas 4-nitrobromobenzene **1d** gave 88% yield (Scheme 4). Secondary aliphatic amine piperdine has been coupled with 4-nitrohaloarenes **1c–d** in 85–90% yield after 12 h (Scheme 4, entries 2 and 3). Likewise, 4-chloroaniline was successfully coupled with **1c** and **1d** affording **3r** in 88% and 80% yields respectively. However, a benzyne product has not been observed by the reaction of amine **3o–r** with 4-nitrohalo benzenes **1c–d** (Scheme 4). Furthermore after completion of the reaction, the catalyst was recovered for subsequent fresh cycles. The catalyst was found to catalyze further cycles without loss of activity (see the ESI†). The XPS and IR spectra of the original and recycled catalyst remain the same. Also, ESI-HRMS spectra reveal no leaching of catalyst during the reaction (see the ESI†).

From Schemes 2–4, it is revealed that, under optimised conditions (Scheme 1) we did not find any product raised due to a benzyne mechanism. Reactivity of electron rich amines afforded more yield comparatively over electron withdrawing amines. Also, electron withdrawing haloarenes react faster than the general haloarenes. These trends suggest that the reaction might be occurring *via* oxidative addition followed by reductive elimination (Scheme 5).

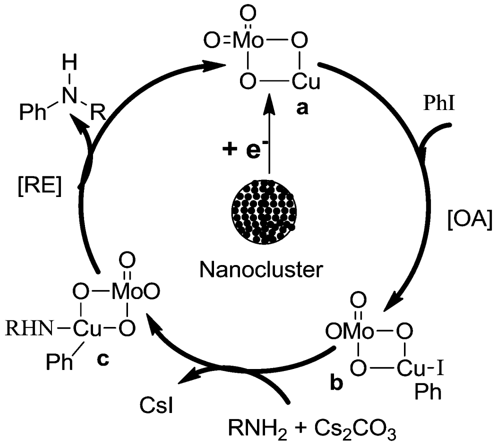
From, XPS and IR data, Cu^{2+} and Mo^{6+} are present along with Cu–O–Mo bonds (see the ESI†).[18] We believe that, in the



Scheme 3 Reaction of aliphatic-, secondary- and halogen substituted amines with haloarene; *1,4-diiodobenzene is used instead of iodobenzene.



Scheme 4 Reaction of amines with 4-nitrohalobenzene.



Scheme 5 Proposed mechanism by CuMoO$_4$ bimetallic nanoparticles.

CuMoO$_4$ nanocluster, molybdenum(VI) has a lower reduction potential (E = 0.11 mV) than copper(II) (E = 0.33 mV).[14] Hence, in the nanocluster, copper is believed to play an important role along with molybdenum. The electron rich nanocluster[15] is stabilised by DMSO solvent. The catalyst **a** undergoes oxidative addition of PhI to form precursor complex **b**. Subsequently it is converted to complex **c**[16] with amine and base. Further reductive elimination of the C–N cross-coupled product regenerates the catalyst **a** (Scheme 5). The positive charge developed at complex **b** and **c** is anticipated to be stabilized by the nanocluster.

Conclusions

In conclusion, we disclosed here new bimetallic CuMoO$_4$ nanoparticles developed for the first time for C–N cross-coupling of haloarenes with alkyl and aryl amines at 90 °C. The catalyst is highly efficient and recyclable. Here, the efficiency of the Cu(II) catalyst is increased by doping molybdenum metal. The CuMoO$_4$–DMSO–Cs$_2$CO$_3$ combination is found to afford C–N cross-coupling product in moderate to high yields under mild conditions. The catalyst is effective for a wide range of amines and haloarenes. Other applications along with a mechanistic study are under investigation in the laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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