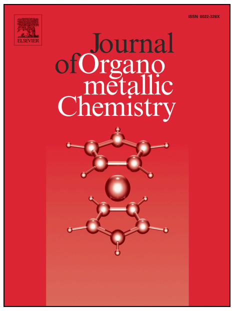

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CNT-CuO catalyzed C–N bond formation for N-arylation of 2-phenylindoles

Jeongah Lim, Ji Dang Kim, Hyun Chul Choi,* Sunwoo Lee*

Department of Chemistry, Chonnam National University, 77 Yongbong-rog, Buk-gu, Gwangju 61186, Republic of Korea

Corresponding author. Tel: +82-62-530-3492 (H. C. Choi), +82-62-530-3385 (S. Lee), Fax: +82-62-530-3389,

E-mail : chc12@chonnam.ac.kr (H. C. Choi). sunwoo@chonnam.ac.kr(S. Lee).

Abstract

Carbon nanotube–copper oxide (CNT–CuO) nanocomposites were prepared by depositing CuO nanoparticles onto functionalized CNT surfaces. The structure and elemental content of CNT–CuO were characterized using transmission electron microscopy, X-ray diffraction, and Auger electron spectroscopy. The prepared CNT-CuO was subsequently employed as a catalyst for the coupling reaction of 2-phenylindole with aryl iodides to provide the desired *N*-aryl 2-phenylindoles in good yields.

Keywords : CuO-CNT; C-N bond formation; arylamination; 2-phenylindole; recyclable catalyst

Indole is one of the most important heterocycles in pharmaceutical chemistry, leading to the development of many marketed drugs and promising drug candidates comprising an indole nucleus.[1] Owing to their important applications, many examples of the *N*-arylation of indoles have been reported over the past decades.[2] Among them, Buchwald-Hartwig aryl amination, which is the palladium-catalyzed coupling reaction of aryl halides and amine, is the most powerful method for the synthesis of *N*-arylated heterocyclic compounds including indoles.[3] Although this method provides a variety of arylated amines in good yields and high functional group tolerance, it presents several limitations including the high cost of the palladium catalyst and requirement of a ligand. To address these issues, impressive progress has been made in the aryl amination methodology during the last decades. For example, inexpensive first-row metals such as cobalt,[4] zinc,[5] nickel,[6] and copper[7] have been employed as catalysts. However, the use of such homogeneous catalytic systems lead to environmental problems. To address these issues, heterogeneous catalytic systems are continuously being developed and applied to metal-catalyzed aryl aminations.[8] Notably, heterogeneous catalytic systems are considered as green chemical systems as they address waste issues derived from the purification process.[9] However, to the best of our knowledge, a heterogeneous copper catalytic system for the *N*-arylation of 2-phenylindoles has not been reported to date. The 1,2-diaryl-1H-indole moiety is a key structure of bioactive molecules such as antiestrogen,[10] and antiprion[11] compounds. Thus, 2-arylindoles have been readily prepared via Pd-catalyzed arylation.[12,13] However, the employed palladium catalyst is expensive and this synthetic process usually requires a ligand.

To address these issues, we focused on the development of an environmentally friendly method for the *N*-arylation of 2-phenylindoles, paying particular attention to two factors: the employment of a copper catalyst known to be insensitive to catalyst poisoning caused by the strong coordination ability of the heteroatom and the development of a heterogeneous copper catalyst. Herein, we report the preparation of a recyclable copper catalyst and its application to C–N bond formation of aryl iodide and 2-phenylindole.

To achieve our goals, we propose a simple and effective process for the preparation of carbon nanotube–copper oxide (CNT–CuO) nanocomposites using functionalized CNTs as an efficient recyclable catalyst for the C–N coupling reaction.

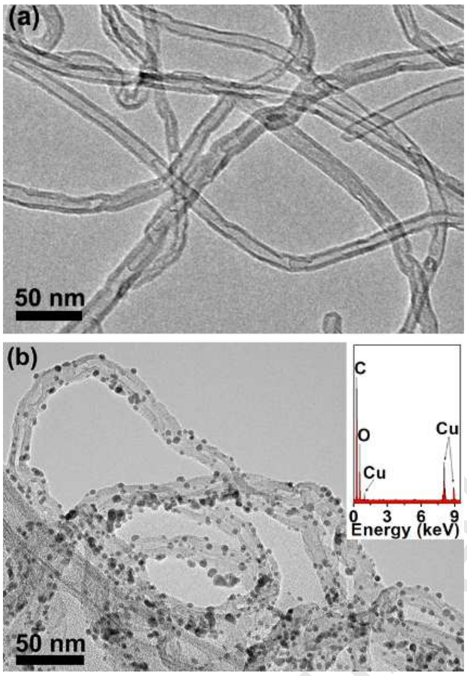


Figure 1. (a) Transmission electron micrograph of the pristine carbon nanotubes (CNTs) and (b) transmission electron micrograph of the prepared carbon nanotube–copper oxide (CNT–CuO), with the corresponding energy-dispersive X-ray (EDX) spectrum (inset).

Figure 1(a) illustrates the overall morphology of the pristine CNTs: the multi-walled tubular structures comprise outer diameters in the range 5–10 nm and lengths of several hundreds of nanometers. All the tubes present clean surfaces. Figure 1(b) displays a typical transmission electron micrograph of a CNT–CuO catalyst in which the nanoparticles are densely dispersed on the surfaces of the individual CNTs and isolated nanoparticles are not observed (average particle size, ~4.6 nm). The corresponding energy-dispersive X-ray (EDX) spectrum presented peaks corresponding to the C, O, and Cu elements [Fig. 1(b)], signaling the presence of Cu-based nanoparticles on the CNTs.

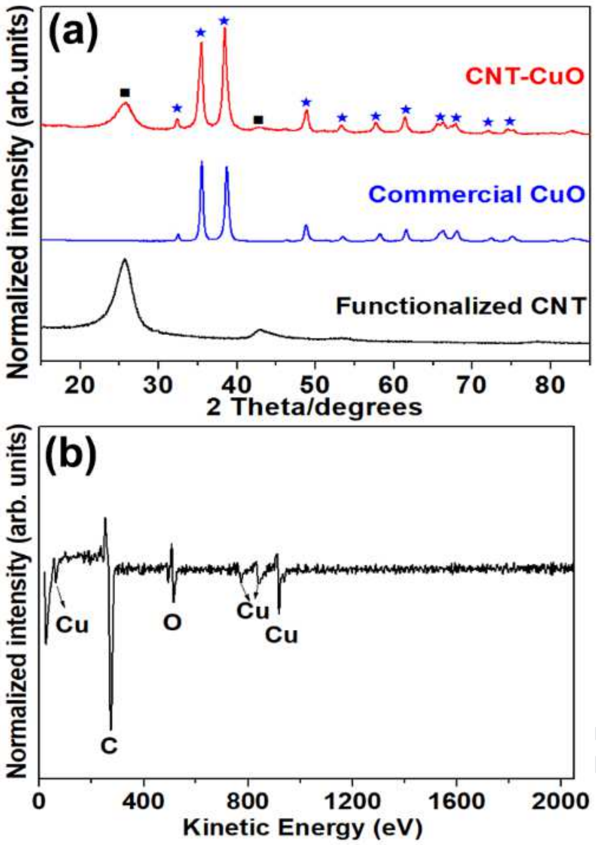


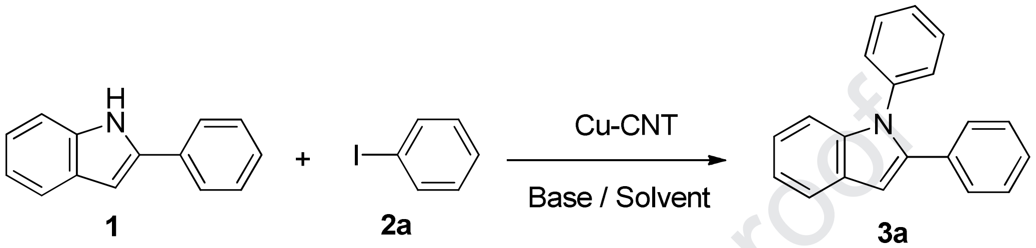
Figure 2. (a) Powder X-ray diffraction (XRD) patterns of the functionalized carbon nanotube (CNT), CNT–copper oxide (CuO), and commercial CuO and (b) Auger spectrum of CNT–CuO.

Figure 2(a) displays the powder X-ray diffraction (XRD) patterns of the functionalized CNT (black), CNT–CuO (red), and commercial CuO (blue, monoclinic structure). The pristine CNTs presented two peaks at 25.7 and 43° corresponding to the (002) and (101) planes of graphite, respectively. For the CNT–CuO sample, distinct diffraction peaks appeared at $2\theta = 35.6$ and 38.7°, respectively, corresponding to the (002) and (111) reflection planes of monoclinic CuO. These observations reconfirmed that the monoclinic CuO nanoparticles were effectively deposited onto the functionalized CNT surface. The Cu content (~9.2%) of CNT-CuO was estimated from the Auger peak areas [Fig. 2(b)] and corrected according to the tabulated sensitivity factors.

We next evaluated the CNT-CuO catalytic activity in the C-N coupling reaction. We selected

2-phenylindole and iodobenzene as the standard substrates and employed 5 mol% CNT-CuO based on the copper content.

Table 1. Optimal condition for the coupling reaction with 1 and 2a using carbon nanotube–copper oxide (CNT–CuO).[a]



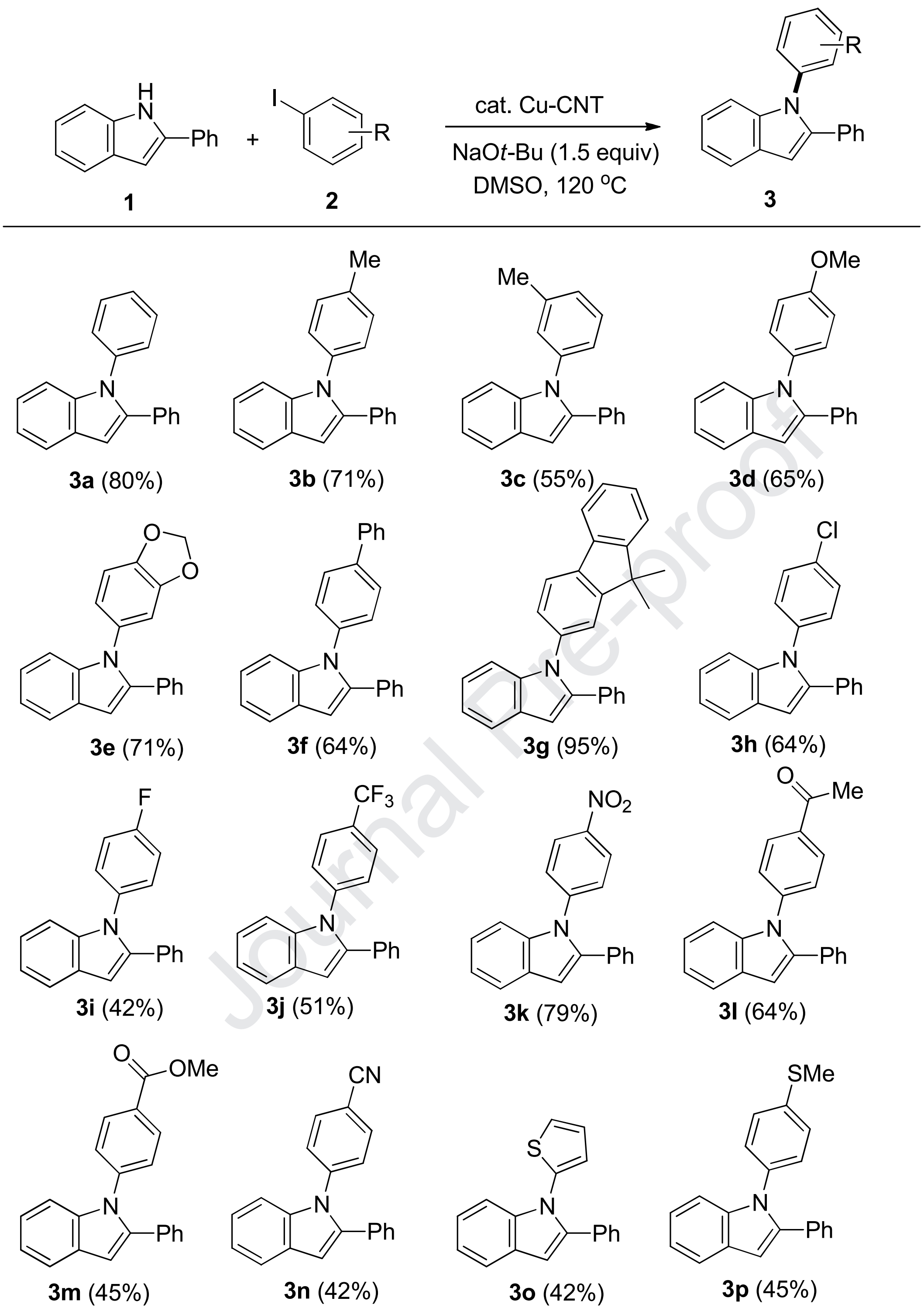
Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	K_3PO_4	CH_3CN	80	-
2	K_3PO_4	dioxane	80	-
3	K_3PO_4	toluene	120	8
4	K_3PO_4	DMF	120	30
5	K_3PO_4	DMSO	120	37
6	Cs_2CO_3	DMSO	120	42
7	NaOH	DMSO	120	41
8	NaOtBu	DMSO	120	81
9	KOtBu	DMSO	120	77
10	NaHMDS	DMSO	120	4
11	KHMDS	dioxane	120	10

[a]Reaction conditions: **1** (0.3 mmol) and **2a** (0.3 mmol) were reacted with a base (0.45 mmol) in the solvent (1.0 mL). [b]Yields were determined via gas chromatography with an internal standard.

To evaluate the solvent conditions, the reaction was first conducted with K_3PO_4 under various solvents. The results revealed that CH_3CN and 1,4-dioxane were not suitable solvents (entries 1 and 2). When the reaction was conducted with toluene, DMF, and DMSO, the desired product **3a** was formed in 8%, 30%, and 37% yields, respectively (entries 3–5, respectively). Selecting the best solvent (DMSO), we next evaluated different bases at 120 °C. The reactions with Cs_2CO_3 and NaOH afforded **3a** in 42% and 41% yields, respectively (entries 6 and 7). Among the strong bases, NaO^tBu afforded the best result, producing the desired product in 81% yield (entry 8), while the other bases produced inferior results (entries 9–11).

With the optimal conditions in hand, we next evaluated various substituted aryl iodides for the coupling reaction of 2-phenylindole. As expected, **3a** was successfully isolated in 80% yield from the reaction with 1 and iodobenzene. Methyl substituted aryl iodides such as *para*- and *meta*-tolyl iodides afforded the product in 71% and 55% yields, respectively. The alkoxy substituted aryl iodides presented good yields in the formation of the corresponding indoles **3d** and **3e**. Thus, 4-iodo-1,1’-biphenyl and 2-iodo-9,9-dimethyl-9H-fluorene furnished the corresponding **3f** and **3g** in 64% and 95% yields, respectively, while aryl iodides comprising a halogen group produced **3h**, **3i**, and **3j** in acceptable yields. The 4-nitro- and 4-acetyl-substituted aryl iodides coupled with **1** to afford **3k** and **3l**, respectively, in good yields. Cs_2CO_3 was employed as a base for aryl iodides comprising base-sensitive ester and nitrile functional groups; these reactions afforded the desired product **3m** and **3n** in 45% and 42% yields, respectively. 2-Iodothiophene and 4-iodophenyl methyl sulphide also provided the desired product **3o** and **3p** with moderate yields. In most cases, we found that 2-phenyl indole still remained even though aryl iodides were added more than one equivalents.

Scheme 1. Coupling reactions of 2-phenylindole with aryl iodide[a]

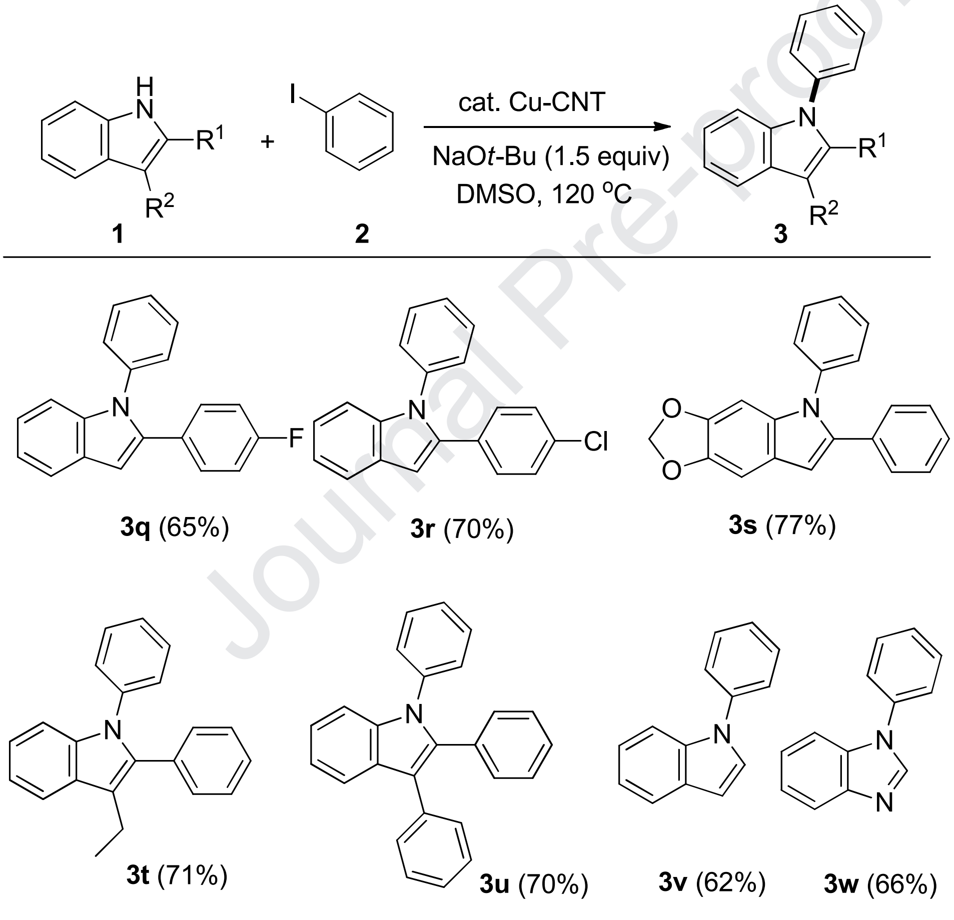


[a]Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), and CNT-CuO (5 mol%) were reacted with NaOt-Bu (3.0 mmol) in DMSO (6.0 mL) at 120 °C for 12 h. The numbers in parenthesis represent the isolated yields.

We expanded this method to the coupling reactions of iodobenzene with the substituted 2-arylindoles, indole and benzimidazole. The results are summarized Scheme 2. 2-(4-

Fluorophenyl)indole, 2-(4-chlorophenyl)indole, 6-phenyl-5*H*-[1,3]dioxolo[4,5-f]indole, 3-ethyl-2-phenylindole, and 2,3-diphenylindole afforded the corresponding products **3q**, **3r**, **3s** **3t**, and **3u** in 65%, 70%, 77%, 71%, and 70% yields, respectively. In addition, when indole and benzimidazole reacted with iodobenzene, the desired product **3v** and **3u** were formed in 62% and 66% yields, respectively.

Scheme 2. Coupling reactions of substituted 2-arylindoles[a]



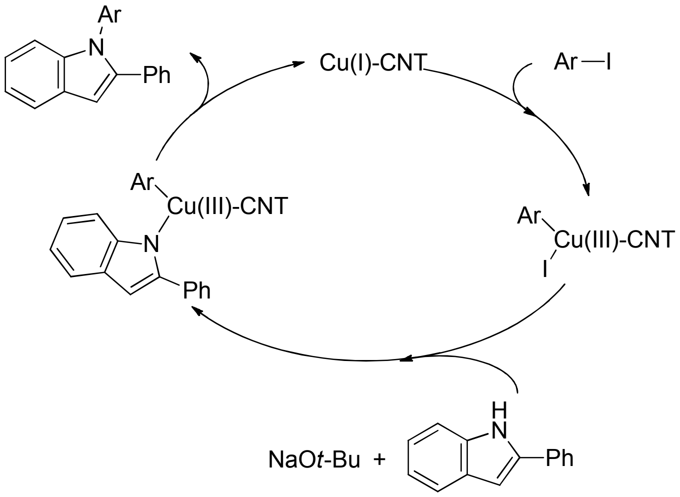
[a]Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), and CNT-CuO (5 mol%) were reacted with NaOt-Bu (3.0 mmol) in DMSO (6.0 mL) at 120 °C for 12 h. The numbers in parenthesis represent the isolated yields.

The potential recyclability of CNT-CuO was next explored in the cross-coupling reaction of iodobenzene and indole. The reaction was conducted in DMSO solvent at 120 °C for 12 h.

After cooling to 25 °C, the reaction mixture was worked up with water and the organic products were extracted with ethyl acetate. Subsequently, the yield was determined by gas chromatography. The precipitated CNT-CuO catalyst in the water phase was collected by filtration and subsequently washed with water and ethyl acetate. The recovered CNT-CuO was transferred to a new reaction vial containing fresh 2-phenylindole and iodobenzene. This process was repeated until the product yield began to decrease significantly. The results revealed that the CNT-CuO catalyst system afforded the product in 80% yield for five recycle. [1st run: 80%, 2nd run: 79%, 3rd run: 82%, 4th run: 78%; 5th run: 80%]

Based on the previous report and our results [14], we next proposed the reaction pathway illustrated in Scheme 2. CuO-CNT might be reduced to Cu(I) which is the active catalyst species in this reaction system because Cu(I) species was found in the XRD analysis after the completion of reaction [See Supporting Information]. Thus, aryl iodide was oxidatively added to the copper catalyst to form the arylated copper complex. The 2-phenylindole reacted with the base and subsequently substituted the iodide of the arylated copper complex **A** to afford the copper complex **B**. Finally, reductive elimination afforded the desired product. It was noteworthy that Cu(I) species was found in the XRD analysis after the completion of reaction [See Supporting Information].

Scheme 2. Proposed reaction pathway.



In summary, we prepared a CNT–CuO nanocomposite and used it as a catalyst for the cross-coupling reaction of aryl iodide and 2-phenylindole. The best yield was observed when 5 mol% CNT-CuO was employed with NaOt-Bu as the base. A variety of aryl iodide compounds were coupled with 2-phenylindole to afford the corresponding *N*-arylated 2-phenylindoles in good yields. The results revealed that the synthesized catalyst could be reused fivefold and showed good activity.

Experimental Section

Preparation of CNT-CuO

Functionalized CNTs were prepared according to the previously reported surface thiolation method.[15] The acid-treated CNTs were subsequently dispersed in tetrahydrofuran (THF), after which a NaSH aqueous solution was added to produce thiol groups on their surfaces. In this study, a CNT–CuO catalyst can be facile prepared by thermal oxidation of Cu nanoparticles deposited onto functionalized CNTs. In brief, Cu nanoparticles were first synthesized by a sol-gel method. Copper chloride ($CuCl_2$) and sodium borohydride ($NaBH_4$) were used as the metal precursor and reducing agent, respectively. The obtained Cu nanoparticles were added to the functionalized CNT solution under 24 h stirring. Finally, the

CNT–CuO catalysts were obtained by centrifugation, washed with DI water, and dried in air at 150 °C overnight.

The transmission electron micrographs were obtained using an FEI TECNAI-F20 transmission electron microscope equipped with a CM-200 EDX at 200 kV. The powder XRD patterns obtained from the CNT–CuO nanoparticles were recorded using an X'Pert-PRO high-resolution X-ray diffractometer (PANalytical, Almelo, Netherlands) with Cu Kα ($\lambda = 1.5406$ Å) radiation. Auger electron spectroscopy (AES) was performed using a PHI 700 scanning Auger nanoprobe with an incident electron energy of 10 keV.

CNT-CuO catalyzed N-arylation of 2-phenylindole

CNT-CuO (0.01 mmol), aryl iodide (0.2 mmol), 2-phenylindole (0.2 mmol), and NaO*t*-Bu (0.3 mmol) in DMSO were placed in a reaction vial and stirred at 120 °C for 12 h. The reaction mixture was washed with water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and evaporated. The crude reaction mixture was purified by column chromatography on silica gel.

Acknowledgement

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Highlights

- Carbon nanotube-copper oxide (CNT-CuO) nanocomposites were prepared by depositing CuO nanoparticles onto functionalized CNT surfaces
- CNT-CuO was employed as a catalyst for *N*-arylation of 2-phenyl indoles and showed good yields.
- CNT-CuO catalyst was reused for five times with good activity