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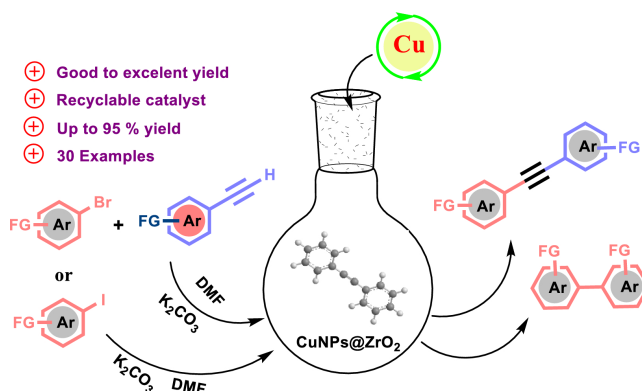
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Abstract Cu nanoparticles ($\text{CuNPs}@ZrO_2$) supported on ZrO_2 were synthesized using a one-step co-precipitation process, and their application in C–C coupling reactions was investigated. The catalyst was characterized using XRD, XPS, SEM, TEM, and TGA techniques. The prepared catalyst was used for the Sonogashira cross-coupling reaction of aryl bromides with phenyl-acetylene in the presence of K_2CO_3 in DMF at 110 °C, which resulted in di-substituted alkynes with good to excellent yields. The protocol was also extended for the Ullmann coupling reaction of aryl iodide under similar reaction conditions, yielding the desired products with good to excellent yields without homo-coupling. Interestingly, unlike other copper catalysts, the present catalyst worked under air and did not require an inert atmosphere to prevent alkyne. This catalytic system is versatile, tolerant, and significantly cheaper than the “traditional” Pd-catalyzed Sonogashira cross-coupling of terminal alkynes with aryl halides. The catalyst could be reused for five catalytic cycles with no significant change in the product yield. All of these characteristics make our prepared $\text{CuNPs}@ZrO_2$ catalyst quite suitable for the gram-scale synthesis of biaryls and alkynes, with a simple workup.

Graphical Abstract:



Keywords (separated by '- ') CuNPs - ZrO_2 - Ullmann coupling - Sonogashira coupling - Recyclability

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ZrO₂ Supported Cu Nanoparticles for Sonogashira and Ullmann Coupling Reactions Under Palladium-Free Conditions

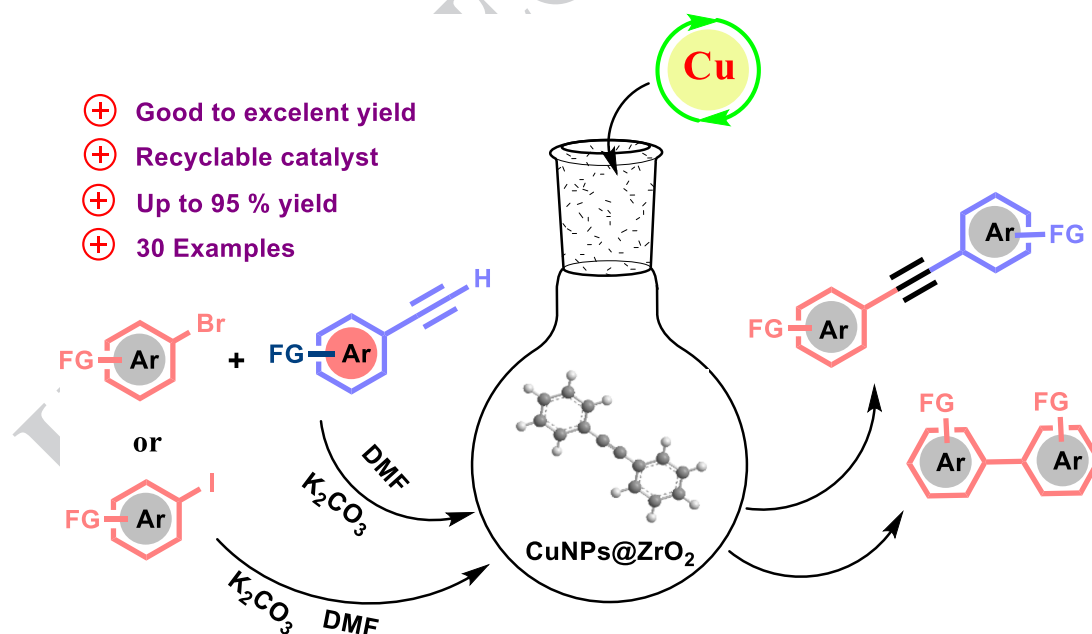
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Abstract

Cu nanoparticles (CuNPs@ZrO₂) supported on ZrO₂ were synthesized using a one-step co-precipitation process, and their application in C–C coupling reactions was investigated. The catalyst was characterized using XRD, XPS, SEM, TEM, and TGA techniques. The prepared catalyst was used for the Sonogashira cross-coupling reaction of aryl bromides with phenylacetylene in the presence of K₂CO₃ in DMF at 110 °C, which resulted in di-substituted alkynes with good to excellent yields. The protocol was also extended for the Ullmann coupling reaction of aryl iodide under similar reaction conditions, yielding the desired products with good to excellent yields without homo-coupling. Interestingly, unlike other copper catalysts, the present catalyst worked under air and did not require an inert atmosphere to prevent alkyne. This catalytic system is versatile, tolerant, and significantly cheaper than the “traditional” Pd-catalyzed Sonogashira cross-coupling of terminal alkynes with aryl halides. The catalyst could be reused for five catalytic cycles with no significant change in the product yield. All of these characteristics make our prepared CuNPs@ZrO₂ catalyst quite suitable for the gram-scale synthesis of biaryls and alkynes, with a simple workup.

Graphical Abstract



Keywords CuNPs · ZrO₂ · Ullmann coupling · Sonogashira coupling · Recyclability

Extended author information available on the last page of the article

1 Introduction

Transition metal-catalyzed cross-coupling reactions are versatile tools for constructing C–C bonds and play an indispensable role in organic synthesis [1]. Owing to their incomplete d-orbitals, transition metals are extensively used in catalysis, which makes them easily accept and donate electrons to other atoms or molecules during the catalytic cycle. Over the past four decades, several transition metals have been used as catalysts in various organic reactions due to their profitable catalytic properties [2–12]. Palladium-catalyzed Sonogashira and Ullmann coupling reactions are particularly powerful, versatile, and popular tools for the selective construction of aryl alkynes and biaryl compounds. These compounds serve as the most substantial structural intermediates in the synthesis of natural products, agrochemicals, polymers, and pharmaceuticals [13, 14]. The Sonogashira reaction involves the cross-coupling reaction between an aryl halide (Cl, Br, I) or triflate (OTf) and a terminal acetylene.

In traditional methodologies, palladium metal complexes are used along with Cu-salts as a co-catalyst, under harsh thermal conditions, in the presence of excess organic bases and excessive ligands (Scheme 1) [15–20]. Over the past few decades, several efforts have been made to modify catalytic systems, such as Pd-catalytic systems without Cu, Fe, Ni, or Cu-complexes without Pd, and copper as catalysts with various ligands, under harsh reaction conditions [19, 21–25]. Despite their effectiveness, the methodologies used in palladium-catalyzed Sonogashira coupling reactions have several drawbacks. One of them is the use of expensive Pd catalysts, which increases the possibility of losing the catalyst at the end of the catalytic cycle. Moreover, palladium metal is toxic, limiting its application in bioactive compounds and, thus, reducing the potential for industrial-scale organic transformations. [26, 27] These issues create economic and ecological barriers to the development of palladium-catalyzed Sonogashira coupling reactions.

In modern synthetic chemistry, it is important to consider various aspects such as toxicity, recyclability, and the need for palladium-free catalytic systems. These factors present a significant challenge for synthetic organic chemists [28, 29]. To overcome these challenges, one solution

is to use a cheaper metal catalyst in place of palladium, which offers a smart and effective catalytic route [30, 31]. Recently, more attention has been paid to copper-based alternative catalysts due to their less harmfulness, easy commercial availability at a reasonable cost, admiring reactivity compared with heavier late d-block metals, and ecological and operational simplicity. [32–37]

The use of catalytic processes for carbon–carbon bond forming coupling reactions is an important aspect of industrial chemistry. A cost-effective and environmentally-friendly approach to this process is the use of heterogeneous and ligandless catalytic methods, which allow for easy separation, recovery, and recyclability [38–42]. This method also eliminates the risk of ligand contamination in the final product. To meet these demands, a supported heterogeneous Cu-catalyst for the C–C coupling reaction is an ideal solution.

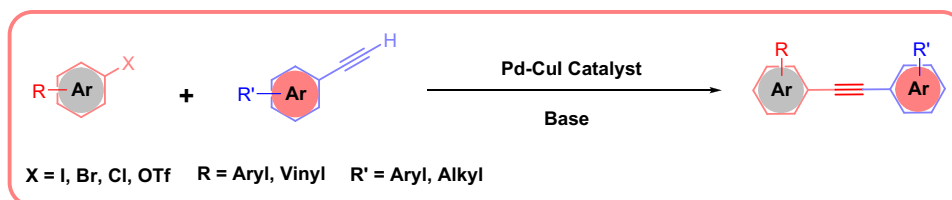
In line with our work to develop various catalysts for different organic transformations [43–47], we report the synthesis and characterization of CuNPs supported on ZrO₂ (CuNPs@ZrO₂) in this article. This catalyst can efficiently facilitate ligandless Sonogashira and Ullmann coupling reactions, making it an excellent choice for industrial applications. (Fig. 1).

2 Results and Discussion

2.1 Catalyst Preparation

The CuNPs supported on ZrO₂ (CuNP_S@ZrO₂) catalyst were prepared by the co-precipitation method (Fig. 1). Initially, 0.05 M aqueous solutions of Cu(NO₃)₂·3H₂O and Zr(NO₃)₃·3H₂O were mixed in a beaker and precipitated using 0.2 M aqueous potassium carbonate at room temperature. The precipitate was aged further for 6 h at room temperature. The obtained precipitate was separated by filtration and washed with deionized water to remove the traces of inorganic impurities. The resultant precipitate was dried in a static air oven at 373 K for 8 h and further calcined at 673 K for 4 h. Finally, the calcined material was reduced under H₂ pressure to afford the desired CuNP_S@ZrO₂ catalyst [48]. ICP–AES analysis of CuNP_S@ZrO₂ showed that anchored CuNPs content on CuNP_S@ZrO₂ catalyst was found to be 0.025 mmol g⁻¹.

Scheme 1. General representation of Pd-Cu-catalyzed Sonogashira reaction



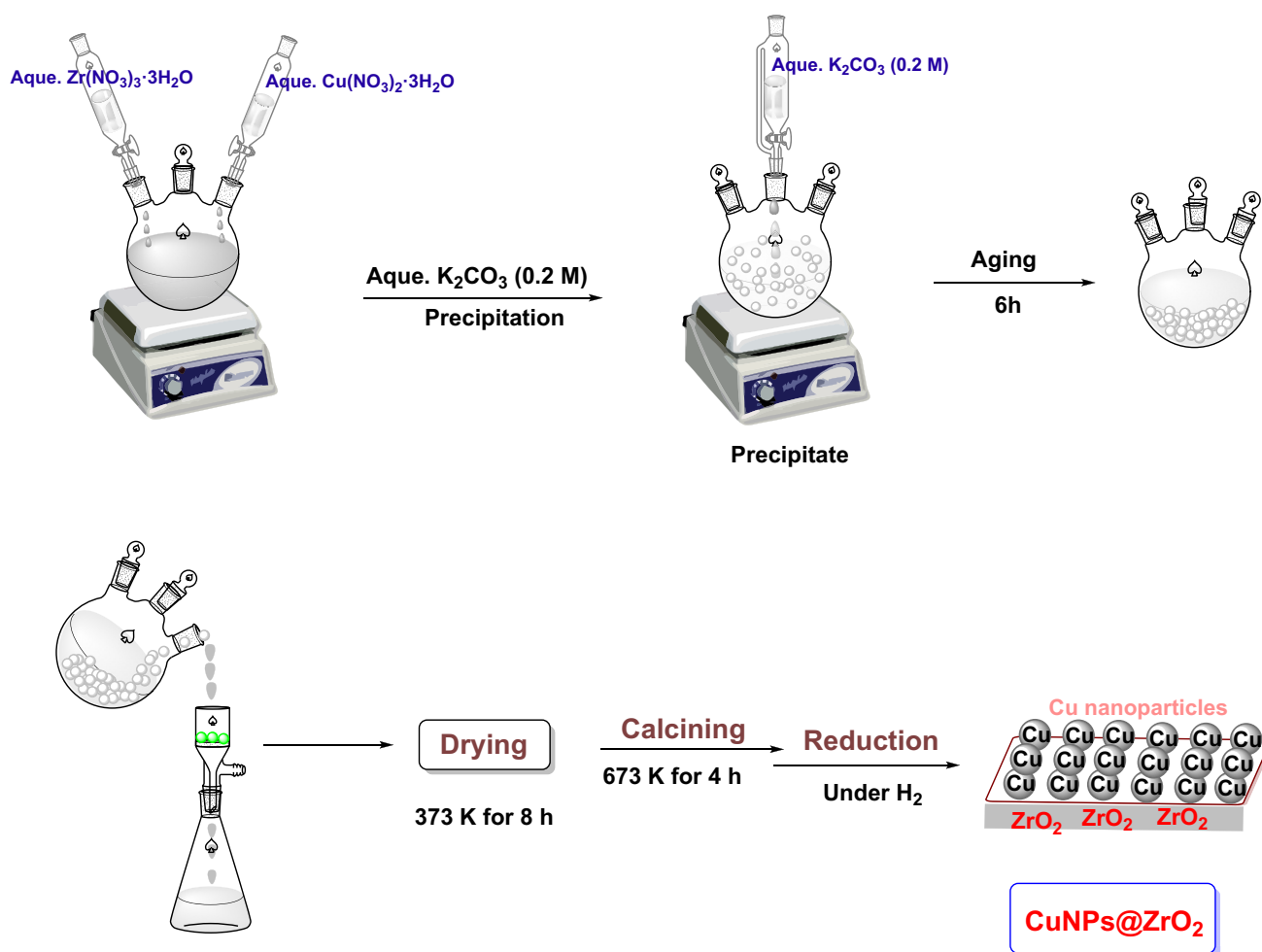


Fig. 1 Synthetic strategy used for the making CuNPs@ZrO₂ catalyst

107 2.2 Catalyst Characterization

108 After the successful preparation of the catalyst, our next
 109 effort was focused on the characterization of the resulting
 110 catalyst, which would be used as the heterogeneous cata-
 111 lyst in the Sonogashira and Ullmann coupling reactions. To
 112 further verify the presence and amount of the CuNPs on
 113 the support, the obtained CuNPs@ZrO₂ catalyst was char-
 114 acterized using SEM-EDS, TEM, XRD, TGA, and XPS
 115 techniques.

116 2.3 Surface Characterization of the Prepared 117 Catalysts

118 The morphology of the catalyst was studied by SEM and
 119 TEM analysis. SEM images show the two-dimensional planar
 120 structure with heavy crumpling features of the CuNPs@
 121 ZrO₂ (Fig. 1b and 2a). The SEM images confirmed the depo-
 122 sition of CuNPs on the surface of ZrO₂ material, and most
 123 of them are almost uniform in shape [49].

2.4 EDS Spectrum

Qualitative analysis of the elements present in the CuNPs@
 ZrO₂ complex was carried out by taking the EDS spectrum
 of the catalyst at random points on the surface (Fig. 3). The
 formation of the CuNPs@ZrO₂ catalyst was confirmed by
 detecting the Cu species using dispersive X-ray spectroscopy
 (EDS). This implies that a large amount of CuNPs was
 successfully anchored on the entire surface of ZrO₂.
 Additionally, EDS mapping of the CuNPs@ZrO₂ catalyst
 confirmed a well-defined distribution of Cu metal on the
 surface of the ZrO₂.

2.5 HR-TEM Analysis

The precise size mapping of the CuNPs was carried out by
 HR-TEM analysis. The TEM analysis images of the pre-
 pared catalyst (Fig. 4a) showed that the average diameter
 of the CuNPs was about 30–100 nm with a thin size distri-
 bution fresh catalyst. This is also a close agreement with

Fig. 2 SEM images of CuNPs@ZrO₂ catalyst

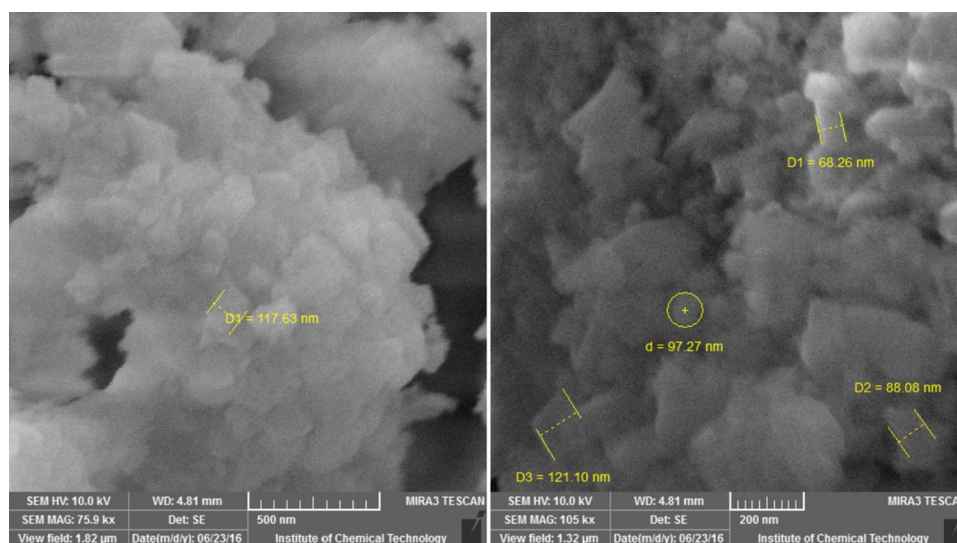
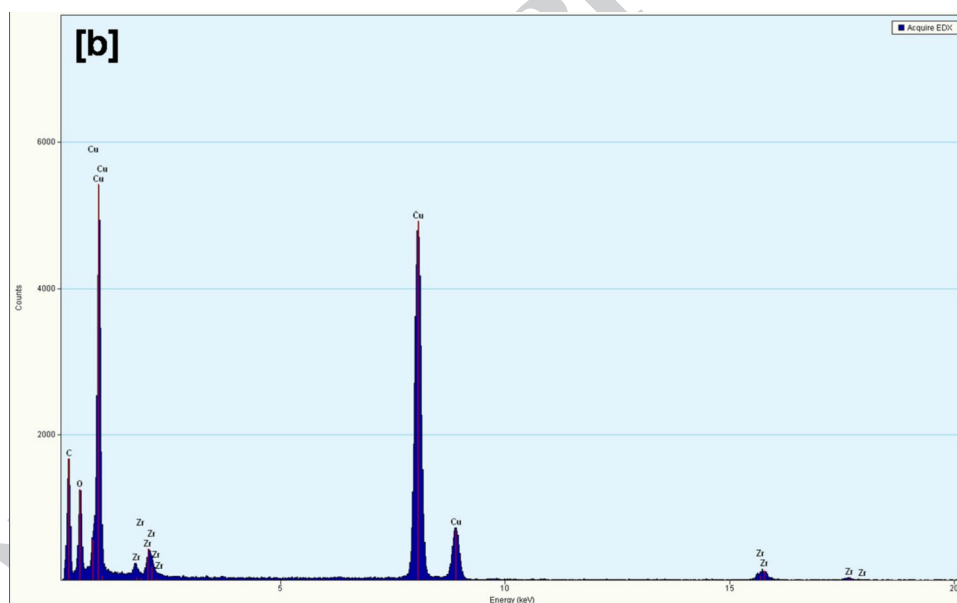


Fig. 3 EDS analysis of CuNPs@ZrO₂ catalyst



141 the values calculated from XRD data for Cu nanoparticles.
 142 HR-TEM of recycled catalyst clearly showed agglomera-
 143 tion of CuNPs which decreases the catalyst activity Fig. 4b.

144 2.6 XRD Analysis

145 The XRD analysis of fresh and recycled CuNPs@ZrO₂
 146 catalyst (Fig. 5) indicated three characteristic peaks at
 147 $2\theta = 33.5^\circ$, 50.89° , 74.45° corresponding to (111), (200),
 148 and (220) planes, respectively, indicate the presence of the
 149 crystalline phases of metallic Cu [50]. All diffraction char-
 150 acteristic peaks and positions match those from the JCPDS
 151 card (Joint Committee on Powder Diffraction Standards no.
 152 04-0836), calculated from Scherrer's equation. The X-ray
 153 diffraction pattern also confirmed the formation of highly

crystalline CuNPs. The XRD analysis of recycled catalyst
 clearly indicated presence of the crystalline phases of metal-
 lic Cu.

157 2.7 XPS Analysis

158 XPS analysis was studied to analyze the surface chemical
 159 compositions and oxidation states of the metals. From the
 160 typical survey spectrum in Fig. 6, as expected, remarkable
 161 signals of Cu, Zr, O, and C are evident. The carbon peak
 162 resulted from the carbon tape, which was used for XPS
 163 analysis. The XPS spectra indicated the Cu 2p XPS binding
 164 energy region of the sample indicated the presence of Cu(0)
 165 species. The binding energy peak at 932.4 eV was assigned
 166 to Cu 2p_{3/2}, and the binding energy peak at 950.1 eV was

Fig. 4 HR-TEM analysis of **a** fresh CuNPs@ZrO₂; **b** recycled CuNPs@ZrO₂ catalyst

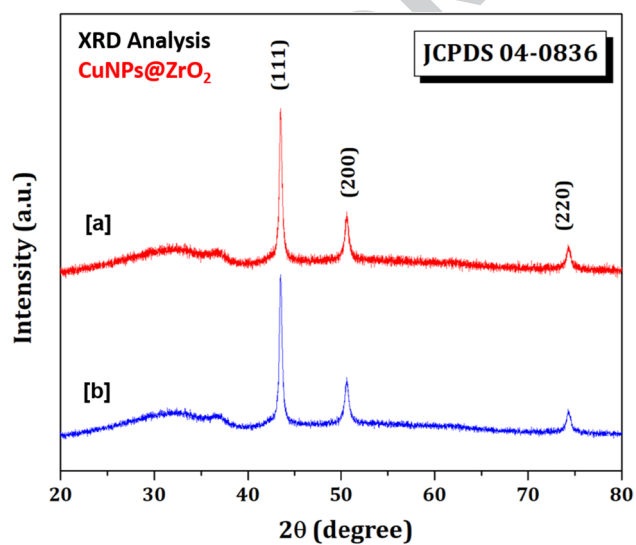
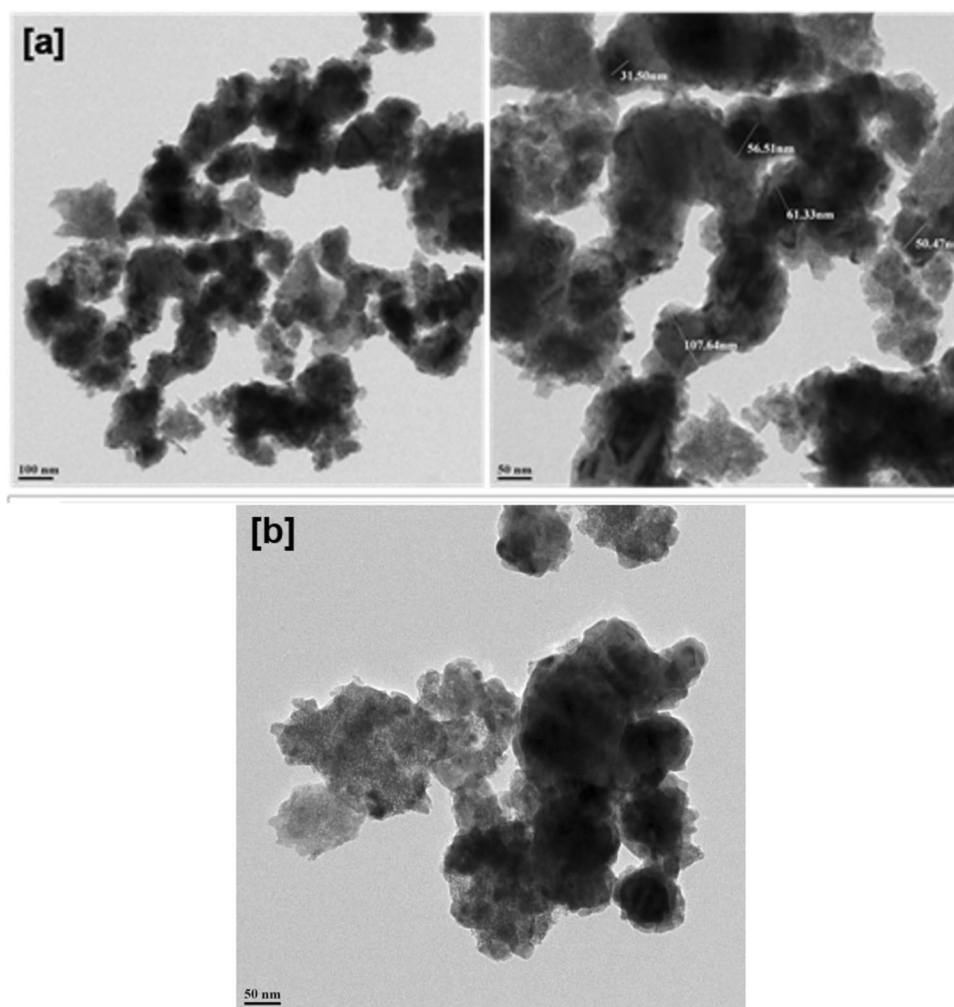


Fig. 5 XRD pattern of **a** fresh CuNPs@ZrO₂ catalyst, **b** recycled CuNPs@ZrO₂ catalyst

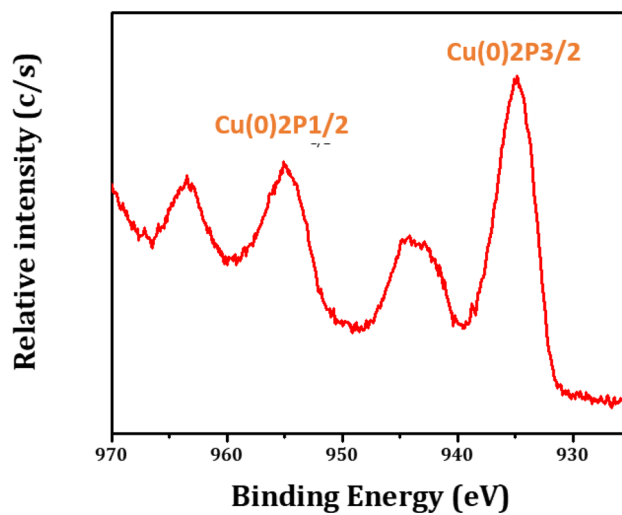


Fig. 6 XPS pattern of CuNPs@ZrO₂ catalyst

167 attributed to Cu 2p_{1/2} was assigned to Cu(0). No satellite
 168 peaks of the sample were observed, as depicted in XPS.
 169 This result indicated the formation of Cu(0) species on the
 170 catalytic surface [51, 52]. The XPS spectra analysis was con-
 171 sensus with the crystal structure detected by the TEM and
 172 XRD analysis which revealed that the Cu was effectively
 173 supported on the ZrO₂ metal oxide.

174 2.8 BET Analysis

175 The specific surface area and pore-size distribution prepared
 176 catalysts were estimated by the Brunauer–Emmett–Teller
 177 (BET) analysis method (Table 1). The specific surface area
 178 of the catalyst was found to be 21.3 m² g⁻¹ with pore vol-
 179 ume 0.07 cc g⁻¹. Furthermore, the CuNPs@ZrO₂ catalyst

Table 1 N₂ Adsorption–desorption isotherms data summary

| Catalysts | A/m ² g ⁻¹ | V _T /cm ³ g ⁻¹ | <d>/nm |
|------------------------|----------------------------------|---|--------|
| CuNPs@ZrO ₂ | 21.3 | 0.07 | 2.5 |

180 displayed a mesoporous property with an average pore size
 181 of 2.5 nm.

182 2.9 TGA–DTA Analysis

183 The study of the thermal behavior of CuNPs@ZrO₂ catalyst
 184 has a great effect on its catalytic activity and recyclability
 185 because the Sonogashira and Ullmann coupling reactions are
 186 carried out under high-temperature conditions. TGA profile
 187 (Fig. 7) of the catalyst indicated that the catalyst is stable
 188 up to 300 °C. Weight loss observed from 25 °C to 150 °C
 189 temperature was assigned to the loss of loosely bound water
 190 on the surface of ZrO₂ (4–5%). The second weight loss of
 191 22–23% observed at 150 °C to 600 °C is due to the decom-
 192 position of grafted organic material. The sharp exothermic
 193 peak was exhibited by DSC at the temperature 378 °C, and
 194 80 wt % of oxide and Cu remained as residue.

195 The catalytic activity of synthesized CuNPs@ZrO₂ cata-
 196 lyst was studied for Suzuki–Miyaura coupling reaction. To
 197 study the optimized reaction, condition the 4-bromo toluene
 198 (1 mmol) and phenylacetylene (1 mmol) were selected as

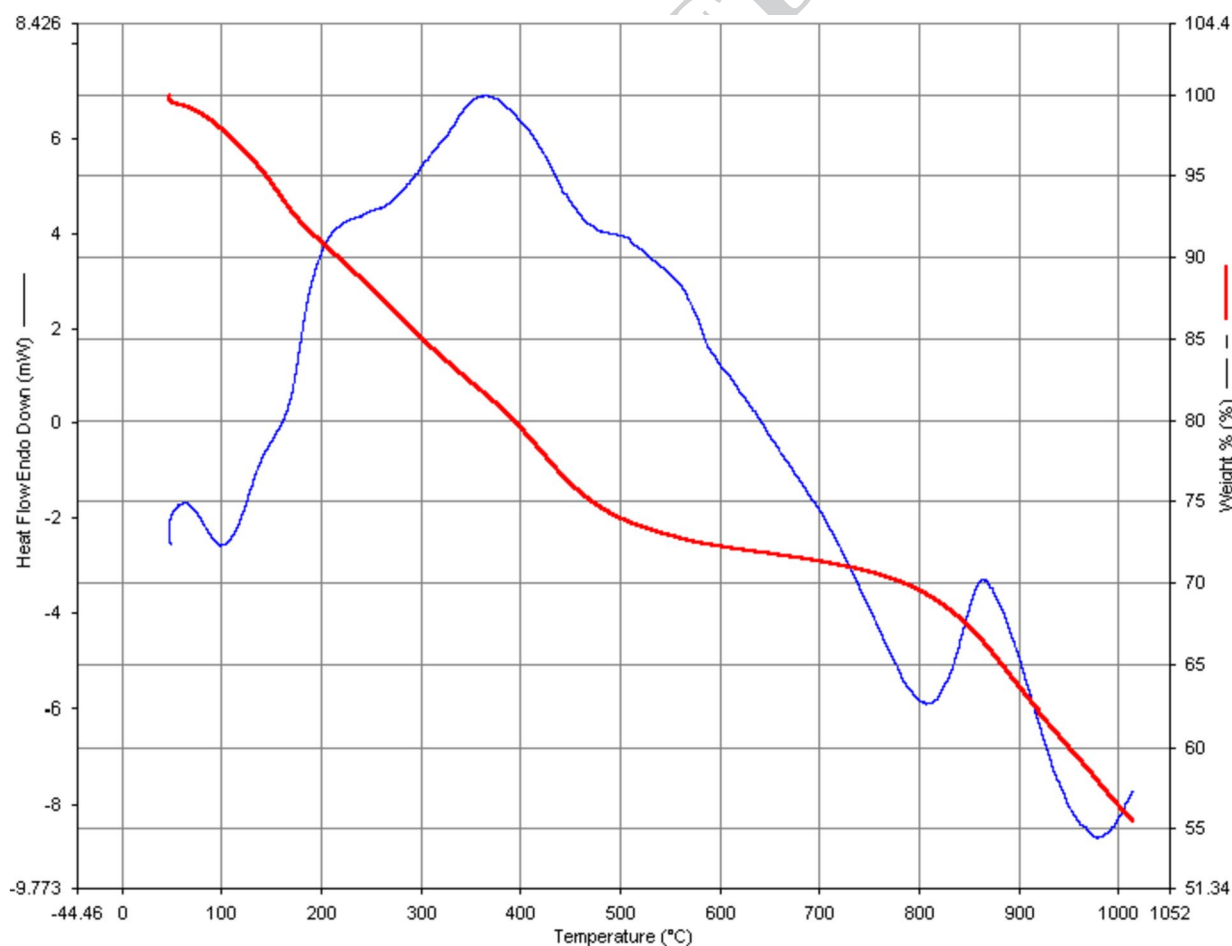


Fig. 7 TGA–DTA analysis of CuNPs@ZrO₂ catalyst

199 model reaction partners under different reaction conditions.
200 Initially, the effect of solvent on the Sonogashira coupling
201 reaction showed that DMF was found to be the best solvent
202 in the presence of 1 mol% catalyst and K₂CO₃ as a base at
203 110 °C. The desired coupling product was obtained with a
204 90% yield in 12 h (Table 2, entry 7). However, others like
205 MeCN, THF, Water, MeOH, THF, IPA, and toluene gave
206 poor to moderate yields under identical reaction conditions
207 (Table 2, entries 1–6).

208 The base plays a vital role in the cross-coupling reactions,
209 especially in the reductive elimination step. Hence the influ-
210 ence of nature as well as the amount of different bases were
211 studied in THF at 110 °C (Table 3). It was observed that
212 2 mmol K₂CO₃ gave a 94% yield of the desired product in
213 8 h (Table 2, entry 1). Other bases like pyrrolidine, dimeth-
214 ylamine, and piperidine are less efficient (Table 2, entry
215 1). It is notable to mention that reducing the quantity of
216 K₂CO₃ from 2.0 mmol to 1.0 mmol considerably decreased
217 the yield of the desired coupling product (Table 3, entries
218 11–14) while increasing the amount has less effect (Table 3,
219 entries 11–14). In addition, the effect of loading of cata-
220 lysts revealed that 1 mol% catalyst was highly efficient as it
221 gave the maximum yield (94%) of the desired product in 8 h
222 (Table 3, entries 15).

223 Moreover increasing the reaction temperature signifi-
224 cantly increased the yield of the product in the presence of
225 1 mol% catalyst, K₂CO₃ as a base in DMF at 110 °C (Fig. 8).

226 As Sonogashira coupling is the superficial route for
227 the construction of acetylene compounds which are core

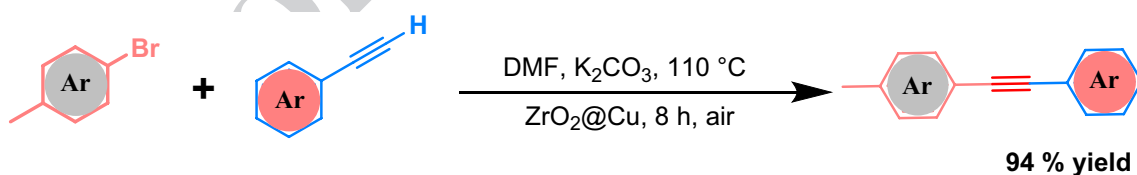
228 components present in many bioactive compounds, we
229 focused our attention to prepare a variety of phenyla-
230 cetylene compounds under optimized reaction condi-
231 tions (Table 4). A good to excellent catalytic performance
232 was observed for all the 4aryl bromides containing both
233 electron-donating and withdrawing groups as the desired
234 products were 85–93% yields in 8 h.

235 Considering the great importance of Ulhaman cou-
236 pling reaction in the synthesis of biaryls [53, 54], we also
237 extended the applicability of catalyst for the involving aryl
238 iodides. The results shown in Table 5 indicated that all
239 the iodides showed maximum conversion in the range of
240 81–90% in DMF at 150 °C in 8 h.

2.10 Heterogeneity Test of Catalyst

241 During heterogeneous catalysis, leaching of the metal dur-
242 ing the reaction is a major problem. To analyze this issue,
243 hot filtration and leaching tests were conducted by cou-
244 pling 4-bromotoluene and phenylacetylene under optimal
245 reaction conditions. After analyzing the GC results and
246 obtaining 71% conversion of the 4-bromotoluene, the cata-
247 lyst was isolated at a temperature of 110 °C. The reaction
248 continued for an additional 2 h at 110 °C, and no further
249 conversion of reactants was observed, indicating that the
250 catalyst was indeed heterogeneous in nature (Fig. 9). To
251 test for leaching, the Cu content in the reaction mixture
252 was measured using ICP–AES. The results showed that
253 there was no leaching of Cu in the reaction mixture.
254

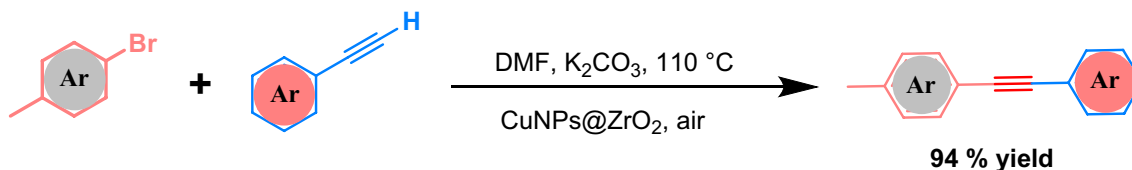
Table 2 The effect of the base on the cross-coupling of 4-bromotoluene with phenyl acetylene



| Entry | Solvent | Time (h) | Yield (%) ^a |
|-------|-----------------------------------|----------|------------------------|
| 1 | DMSO instead of DMF | 12 | 88 |
| 2 | CH ₃ CN instead of DMF | 12 | 15 |
| 3 | <i>i</i> -PrOH instead of DMF | 12 | 20 |
| 4 | THF instead of DMF | 12 | 10 |
| 5 | Toluene instead of DMF | 12 | 53 |
| 6 | Methanol instead of DMF | 12 | 18 |
| 7 | H ₂ O instead of DMF | 12 | 10 |

Reaction conditions: 4-methylbromobenzene (1 mmol), phenylacetylene (1 mmol), CuNPs@ZrO₂ (Sub.: Cat. Mol ratio; 10:1), K₂CO₃ (2 mmol), DMF (5.0 mL), at 110 °C in air.

^aIsolated yields.

Table 3 The effect of base and catalysts loading the on the cross-coupling of 4-bromotoluene with phenyl acetylene

| Entry | Base (mmol) | Catalyst (mol ratio) Sub.: Catal. | Time (h) | Yield (%) ^a |
|----------------------------------|---|--------------------------------------|----------|------------------------|
| Optimization of base | | | | |
| 1 | K ₂ CO ₃ (2 mmol) | 10:1 | 8 | 94 |
| 2 | Et ₃ N (2 mmol) | 10:1 | 12 | 10 |
| 3 | DABCO (2 mmol) | 10:1 | 12 | 26 |
| 4 | Pyrrolidine (2 mmol) | 10:1 | 12 | 60 |
| 5 | Me ₂ NH (2 mmol) | 10:1 | 12 | 25 |
| 6 | Pipridine (2 mmol) | 10:1 | 12 | 30 |
| 7 | K ₃ PO ₄ (2 mmol) | 10:1 | 12 | 66 |
| Optimization of amount of base | | | | |
| 8 | K ₂ CO ₃ (1 mmol) | 10:1 | 8 | 54 |
| 9 | K ₂ CO ₃ (1.5 mmol) | 10:1 | 8 | 80 |
| 10 | K ₂ CO ₃ (2.5 mmol) | 10:1 | 8 | 94 |
| 11 | K ₂ CO ₃ (3 mmol) | 10:1 | 8 | 92 |
| Optimization of catalyst loading | | | | |
| 12 | K ₂ CO ₃ (2 mmol) | 10:0.25 | 8 | 49 |
| 13 | K ₂ CO ₃ (2 mmol) | 10:0.50 | 8 | 75 |
| 14 | K ₂ CO ₃ (2 mmol) | 10:0.75 | 8 | 81 |
| 15 | K ₂ CO ₃ (2 mmol) | 10:1 | 8 | 94 |
| 16 | K ₂ CO ₃ (2 mmol) | 10:2 | 8 | 94 |

Reaction conditions: 4-methylbromobenzene (1 mmol), phenylacetylene (1 mmol), CuNPs@ZrO₂ (mole ratio), base (2 mmol), DMF (5.0 mL), at 110 °C in air.

^aIsolated yields.

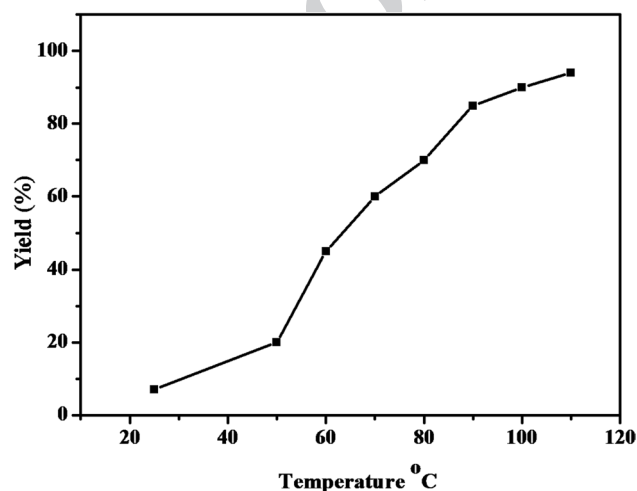
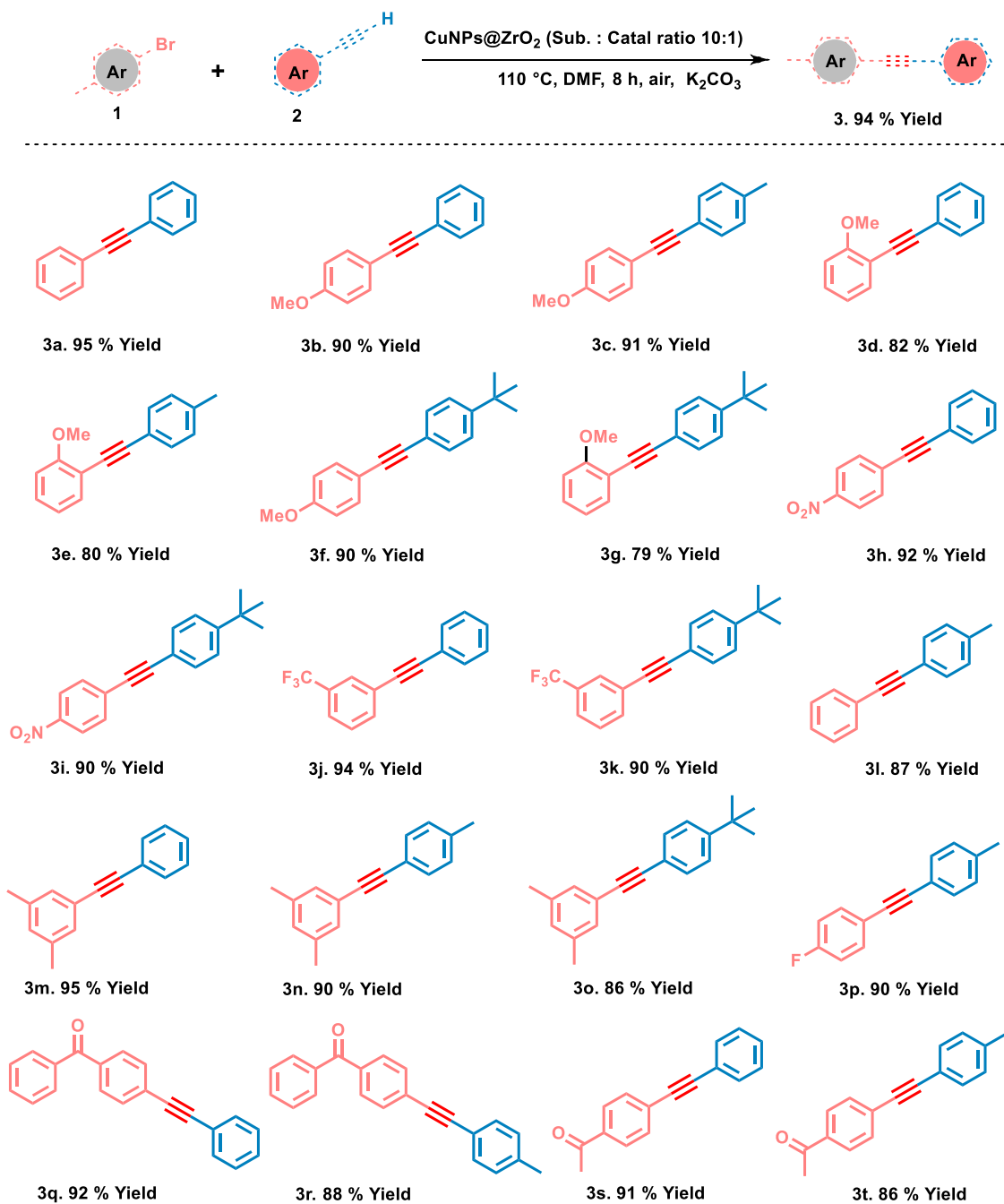


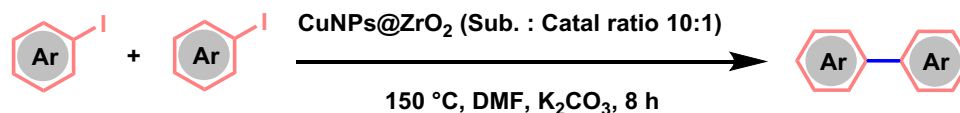
Fig. 8 The effect of temperature on the cross-coupling of 4-bromotoluene with phenyl acetylene

2.11 Recyclability of Catalyst

The recovery and reusability of the catalyst are very important aspects from an economic and environmental point of view. The reusability of the catalysts was investigated for the model reaction under optimized reaction conditions for Sonogashira and Ullmann coupling reactions (Table 6). After the completion of the reaction, the catalyst was separated by centrifugation and reused at least five times with decreased product yield. As per the XRD analysis of the recycled catalyst clearly indicated presence of the crystalline phases of metallic Cu. HR-TEM of recycled catalyst clearly showed agglomeration of CuNPs which decreases the catalyst activity during the mechanistic cycle. ICP-AES analysis of recycled CuNP_s@ZrO₂ catalyst showed 0.024 mmol g⁻¹ CuNPs.

Table 4 The generality of the reaction protocol of coupling aryl bromides with phenyl acetylenes

^aReaction conditions: aryl bromides (1 mmol), acetylenes (1 mmol), CuNPs@ZrO₂ (Sub. : Catal ratio 10:1), K₂CO₃ (2.0 mmol), DMF (5.0 mL), at 110 °C in air, 8 h. ^bIsolated yields.

AQ2 Table 5 The generality of the Ullmann coupling reaction of aryl iodides

| Sr. No | Aryl halide | Product | Yield (%) ^b |
|--------|-------------|---------|------------------------|
| 1 | | | 90 |
| 2 | | | 85 |
| 3 | | | 85 |
| 4 | | | 81 |
| 5 | | | 88 |
| 6 | | | 86 |

^aReaction conditions: aryl iodides (2 mmol), CuNPs@ZrO₂ (Sub.: Catal ratio 10:1), DMF (5.0 mL), at 150 °C, 8 h

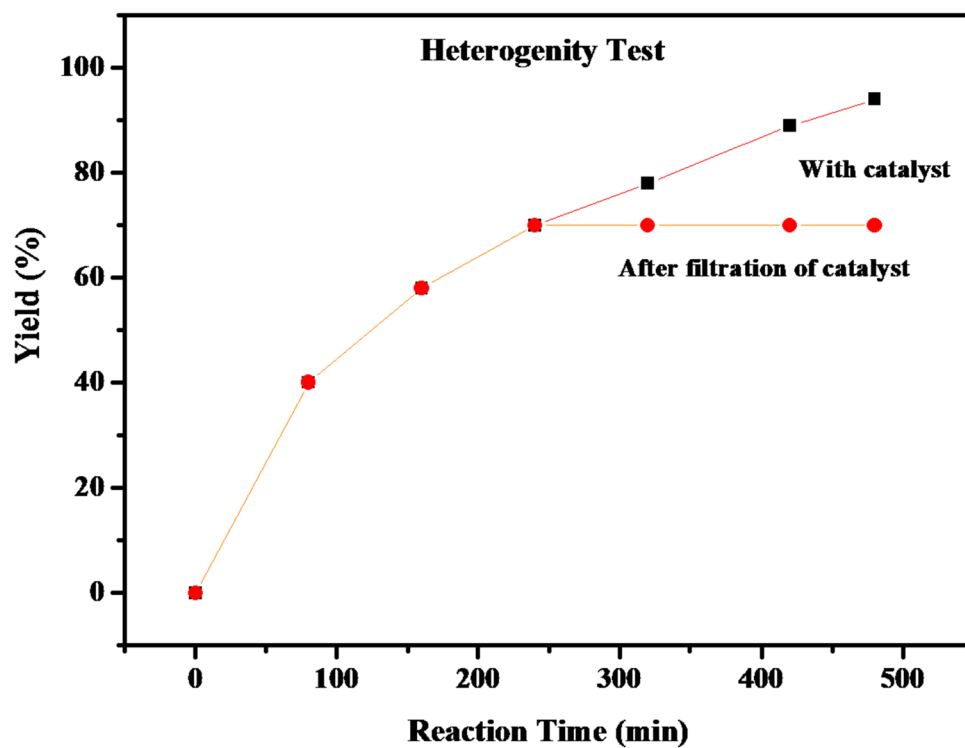
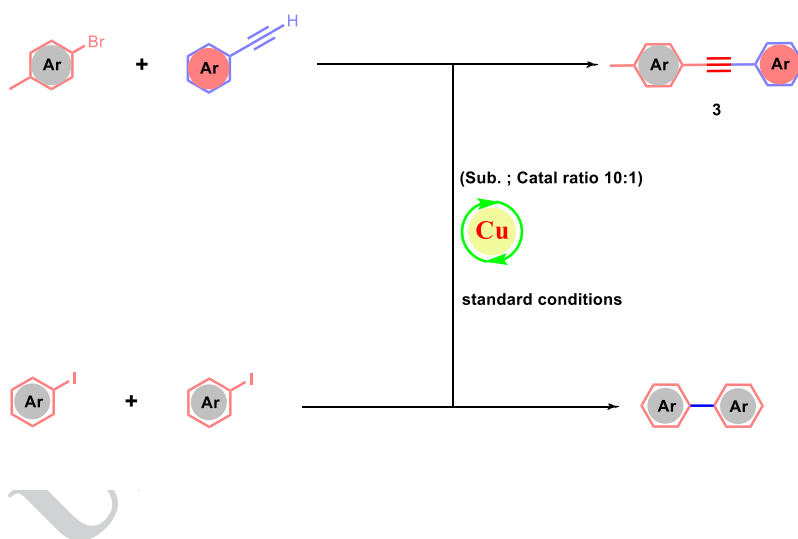
^bIsolated yields

270 The present reaction protocol was compared with those
 271 similar catalysts reported for Sonogashira and Ullmann cou-
 272 pling reactions (Table 7). It was observed that the present
 273 method is more efficient as compared to some heterogeneous
 274 Cu catalysts.

275 3 Conclusion

276 In conclusion, we developed a highly effective and safe
 277 catalytic protocol for Sonogashira and Ullmann coupling
 278 reactions using a CuNPs@ZrO₂ catalyst. The catalyst has

279 successfully converted a series of aryl halides including ones
 280 with challenging sterically hindered aryl-substituted termi-
 281 nal alkynes into their corresponding products. This cata-
 282 lytic protocol broadens the scope of CuNPs@ZrO₂-catalyzed
 283 Sonogashira and Ullmann coupling reactions and provides
 284 an easy and effective method for synthesizing alkynes and
 285 biaryls with various functional groups. This catalytic system
 286 is more affordable than traditional Pd-catalyzed Sonogashira
 287 cross-coupling of terminal alkynes with aryl iodides and is
 288 also tolerant and versatile. Moreover, the catalyst can be
 289 reused for at least five catalytic cycles without a signifi-
 290 cant change in product yield. These characteristics make

Fig. 9 Hot filtration test of catalyst in Sonogashira coupling reaction**Table 6** Recyclability of catalyst in Sonogashira and Ullmann coupling reactions

| Cycle | Time (h) | 3 Yield % |
|-------|----------|-----------|
| Fresh | 8 | 94 |
| 1 | 12 | 90 |
| 2 | 18 | 85 |
| 3 | 24 | 79 |
| 4 | 24 | 65 |

| Cycle | Time (h) | 3 Yield % |
|-------|----------|-----------|
| Fresh | 8 | 90 |
| 1 | 14 | 85 |
| 2 | 20 | 81 |
| 3 | 24 | 77 |
| 4 | 24 | 70 |

Table 7 Comparison of the present method with heterogeneous Cu based catalysts

| Catalyst (mol %) | Solvent | Temp (°C) | Time (h) | Yield (%) | Ref |
|--|------------------|-----------|----------|-----------|--------------|
| Cu(OAc) ₂ (0.1) | DMF | 120 | 24 | 96 | [31] |
| Cu-pincer bis(NHC) (0.05) | DMF | 140 | 24 | 96 | [55] |
| Cu(I)-f-GO (0.049) | H ₂ O | 100 | 12 | 95 | [56] |
| CuNPs/zeolite (5) | DMF | 120 | 8–24 | 99 | [57] |
| Cu ₂ O@Cu | DMF | 110 | 8–10 | 94 | [58] |
| nano-CuO (0.1) | DMSO | 160 | 12 | 88 | [59] |
| CuO/Al (10) | DMF | 110 | 12 | 95 | [60] |
| γ-Fe ₂ O ₃ @PEG@PAMAM G0-Cu (0.8) | H ₂ O | 80 | 4–8 | 90 | [61] |
| CuNPs@ZrO ₂ (10:1) | DMF | 110 | 8 | 94 | Present work |

291 the catalytic system suitable for gram-scale production and
292 commercialization for industrial purposes.

293 **Supplementary Information** The online version contains supplement-
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302 Declarations

303 **Conflict of Interest** The authors declare that they have no known com-
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