Reusable Cu₂O-Nanoparticle-Catalyzed Amidation of Aryl Iodides

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Abstract: The amidation of aryl iodides using Cu₂O nanoparticles is described. It is a heterogeneous process, no leaching of the Cu₂O species occurs, and the catalyst can be recovered and recycled without loss of activity.

Key words: Cu₂O nanoparticles, heterogeneous catalysis, crosscoupling reaction, amide, aryl iodide

Transition-metal-catalyzed aryl-heteroatom bond formation by cross-coupling reaction constitutes a powerful strategy for the synthesis of numerous compounds in biological, material, and pharmaceutical sciences.¹ Among them, the N-arylation of amides is of particular interest, as their products contain structural motifs of many natural products and biologically active molecules (Figure 1).² The most common synthetic method used for their preparation is the well-known classical Goldberg cross-coupling reaction.³ However, these reactions usually require harsh conditions such as high temperature (>150 °C) and stoichiometric amounts of copper that, on scale up, leads to the problem of waste disposal. To overcome these drawbacks, palladium-based⁴ catalysts in the presence of sterically hindered phosphines and copper-based^{5,6} catalysts with electron-rich bidentate ligands have been subject to detailed study for amidation of aryl halides. These are homogeneous processes and the ligands chelated with the metals play a crucial role in the catalysis.

The use of copper-based oxide nanoparticles for crosscoupling reactions has attracted considerable interest in recent years.7 CuO nanoparticles have been used for the cross-coupling of N-, O-, and S-nucleophiles with aryl halides;^{7a-7d} while Stille^{7e} and Sonogashira^{7f} reactions have been studied using pre-prepared Cu₂O nanoparticles in tetrabutylammonium bromide. These reactions provide the advantages of atom efficiency, simplified product isolation, and easy recovery and recyclability of the catalysts. Herein, we wish to report the synthesis and application of Cu₂O nanoparticles in poly(ethylene glycol) (PEG) for amidation of aryl iodides. The reaction involves a heterogeneous process without an external chelating ligand, and the Cu₂O nanoparticles can be recovered and recycled without loss of activity. Aryl iodides having electrondonating and -withdrawing groups are compatible to afford the cross-coupled products in high yield.

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Figure 1 Examples for biologically important molecules

The reaction conditions were optimized with benzamide and 1-iodo-4-methylbenzene as the model substrates (Table 1). A series of reactions was performed in PEG having molecular weights of 200, 400, 1500, 4000, and 6000 with different bases and copper sources at varied temperature. The best results were observed when the reaction was carried out at 120 °C in the presence of 10 mol% CuI in PEG₄₀₀₀. Other systems such as PEG₂₀₀, PEG_{400} , PEG_{1500} , and PEG_{6000} were inferior to PEG_{4000} by either providing 4-methylphenol as byproduct or exhibiting decreased reactivity. Among the bases, KOH was superior to NaOH, K₂CO₃, Cs₂CO₃, and K₃PO₄. The reaction with CuI provided the best results in comparison to commercial Cu₂O (<5 micron), CuO nanoparticles (ca. 33 nm),^{7a-c} CuSO₄·5H₂O, and CuCl₂·2H₂O. Control experiments without the copper source showed no reaction. Similarly, bromobenzene and chlorobenzene exhibited no reaction.

To study the scope of the protocol, the reactions of other substrates were next investigated (Table 2). Benzamide proceeded reaction with a series of aryl iodides to produce the corresponding *N*-arylamides in 70–80% yield (entries 1–7). Aryl iodides having electron-donating and -with-drawing substituents were compatible affording the cross-coupled products (entries 2–6). In addition, aliphatic amides such as acetamide, hexanoamide, and 2-oxazoli-dinone underwent reaction with iodobenzene to provide the corresponding *N*-arylamides in 70–75% yield. Aliphatic amines exhibited greater reactivity compared to aryl amides.

In these reactions, first CuI undergoes reaction with KOH to give the Cu₂O nanoparticles that catalyze the reaction (Equation 1).^{8a} The role of the PEG is to facilitate the formation and stabilization of the nanoparticles.⁹ The size of Cu₂O nanoparticles ranges from 7–10 nm and was deter-

 Table 1
 N-Arylation of Benzamide with 1-Iodo-4-methylbenzene^a



Entry	PEG	Base	Cu source	Time (n)	Produc	t (%)**
					2a	3a
1	PEG ₂₀₀	КОН	CuI	12	56	24
2	PEG ₄₀₀	КОН	CuI	12	62	10
3	PEG ₁₅₀₀	КОН	CuI	12	68	7
4	PEG ₄₀₀₀	КОН	CuI	12	79	n.d.
5	PEG ₆₀₀₀	КОН	CuI	20	72	n.d.
6	PEG ₄₀₀₀	NaOH	CuI	12	60	n.d.
7	PEG ₄₀₀₀	Cs ₂ CO ₃	CuI	12	30	n.d.
8	PEG ₄₀₀₀	K ₂ CO ₃	CuI	12	36	n.d.
9	PEG ₄₀₀₀	K_3PO_4	CuI	12	46	n.d.
10	PEG ₄₀₀₀	КОН	CuI	12	67 ^c	n.d.
11	PEG ₄₀₀₀	КОН	Cu ₂ O	12	69 ^d	n.d.
12	PEG ₄₀₀₀	КОН	CuO nano	12	53	n.d.
13	PEG ₄₀₀₀	КОН	CuCl ₂	12	32	n.d.
14	PEG ₄₀₀₀	КОН	$CuSO_4$	12	37	n.d.
15	PEG ₄₀₀₀	КОН	Cu ₂ O	12	35	n.d.

^a Benzamide (1.2 mmol), 1-iodo-4-methylbenzene (1 mmol), copper source (10 mol%), and base (1.5 mmol) were stirred at 120 °C in PEG (1 g) under nitrogen atmosphere.

- ^b Determined from 400 MHz ¹H NMR.
- ^c 5 mol% CuI used.
- $^{\rm d}$ 5 mol% Cu₂O used.

 $e^{n.d.} = not detected.$

mined by transmission electron microscopy (TEM, Figure 2) and their identities were established using the powder X-ray diffraction analysis (Figure 3).^{8b}

2Cul
$$\xrightarrow{+ 2KOH}$$
 2Cu(OH) $\xrightarrow{- H_2O}$ Cu₂O nanoparticles



Finally, the recyclability of the Cu₂O nanoparticles was studied. After completion of the reaction of benzamide with 1-iodo-4-methylbenzene, the reaction material was treated with ethyl acetate (10 mL) and water (5 mL). The aqueous layer having the Cu₂O nanoparticles were centrifuged, and the precipitate was washed with deionized water (3×2 mL) and acetone (3×2 mL). After drying under



Figure 2 TEM images of Cu_2O nanoparticles of PEG_{4000} . Reaction after (a) first cycle and (b) third cycle.



Figure 3 Powder XRD pattern of Cu_2O nanoparticles of PEG_{4000} . Reaction after (a) first cycle and (b) third cycle.

vacuum, the Cu₂O nanoparticles were reused for reaction of benzamide with 1-iodo-4-methylbenzene. This process was repeated for three runs, and the results are presented in Table 3. The reactions proceeded well to afford the C-N cross-coupled product in >78% yield. The TEM micrograph and powder X-ray diffraction analysis of the Cu₂O nanoparticles recovered from the third run were identical to those of the first run which clearly suggests that the shape and size of the nanoparticles remain intact during the recyclability (Figures 2 and 3). In addition, to study the leaching of the Cu₂O nanoparticles in PEG, CuI and KOH were stirred in PEG₄₀₀₀ at 120 °C for 10 hours, and the residue was dissolved in ethyl acetate and centrifuged. The supernatant layer was collected and ethyl acetate was evaporated. The resulting PEG4000 residue was investigated for the cross-coupling reaction of benzamide with 1iodo-4-methylbenzene at 120 °C for 10 hours. However,



Scheme 1 Proposed catalytic cycle

no reaction was observed, and the starting material was recovered intact. These results clearly reveal that no leaching of the catalyst is involved.

The proposed catalytic cycle for these reactions is shown in Scheme 1. The PEG-stabilized Cu₂O nanoparticles a may undergo reaction on the surface with the aryl iodide

Table 2 N-Arylation of Amides with Aryl Iodides^a

to give intermediate b. The latter with the nitrogen nucleophiles can give intermediate c that could complete the catalytic cycle by reductive elimination of the cross-coupled product.

In conclusion, the synthesis and catalysis of Cu₂O nanoparticles for amidation of aryl iodides is described in

R ¹ R ² NH +	Cu ₂ O nano (5 PEG ₄₀₀₀ , KO 120 °C	$\frac{\text{mol}\%)}{\text{DH}} \Rightarrow \text{R}^{1}\text{R}^{2}\text{NH} \longrightarrow \text{R}^{3}$ $\text{R}^{3} = \text{OMe, Br, Me}$	3		
Entry	R ¹ R ² NH	Aryl iodide	Time (h)	Product	Yield (%) ^b
1	NH ₂		10	O NH	73
2	NH ₂	OMe	17	N H OMe	70
3	O NH ₂	Br	12	O Br H	76
4	NH ₂		12	N N N N N N N N N N N N N N N N N N N	75
5	NH ₂	MeO	15	OMe H	75
6	NH ₂		16	N H	72
7	NH ₂		12		80
8	O NH ₂		3	Ů, IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	75
9	O M NH ₂		3	NA NA	70
10	O NH		5		75

a Amide (1.2 mmol), aryl iodide (1 mmol), CuI (10 mol%), and KOH (1.5 mmol) were stirred at 120 °C in PEG₄₀₀₀ (1 g) under nitrogen atmosphere. b Isolated yield.



a Benzamide (6 mmol), 1-iodo-4-methylbenzene (5 mmol), CuI (10 mol%), and KOH (7.5 mmol) were stirred at 120 °C in PEG_{4000} (5 g) under nitrogen atmosphere.

b Recovered Cu₂O nanoparticles used.

 PEG_{4000} .¹⁰ It is free from the addition of the external chelating ligands, and the catalyst can be recycled without loss of activity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (10) General Procedure for Amidation of Aryl Iodides Aryl iodide (1 mmol), amide (1.2 mmol), and CuI (10 mol%) were stirred at 120 °C in the presence of KOH (1 mmol) in PEG_{4000} (1 g) under N₂ atmosphere. Progress of the reaction was monitored by TLC. After completion, the reaction flask was cooled to r.t., and the reaction mixture was treated with EtOAc (10 mL). The resulting solution was washed with H₂O (3 × 2 mL). Drying (Na₂SO₄) and evaporation of the

solvent gave a residue that was purified on a short pad of silica gel using hexane and EtOAc as eluent. All the isolated products were characterized by IR, ¹H NMR, and ¹³C NMR spectroscopy, and elemental analysis.

Recyclability Experiment

1-Iodo-4-methylbenzene (5 mmol), benzamide (6 mmol), and CuI (10 mol%) were stirred at 120 °C in the presence of KOH (7.5 mmol) in PEG_{4000} (5 g) under N_2 atmosphere.

After the reaction, the reaction material was treated with EtOAc (10 mL) and H_2O (5 mL). The aqueous layer having the Cu₂O nanoparticles were centrifuged, and the precipitate was washed with deionized H_2O (3 × 2 mL) and acetone (3 × 2 mL). After drying in vacuum, the Cu₂O nanoparticles were reused for the fresh reaction of benzamide with 1-iodo-4-methylbenzene.

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