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Silica-Functionalized Cul: An Efficient and Selective Catalyst for N-Benzylation, Allylation, and Alkylation of Primary and Secondary Amines in Water

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SILICA-FUNCTIONALIZED Cul: AN EFFICIENT AND SELECTIVE CATALYST FOR *N*-BENZYLATION, ALLYLATION, AND ALKYLATION OF PRIMARY AND SECONDARY AMINES IN WATER

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GRAPHICAL ABSTRACT



Abstract Silica-functionalized CuI has been reported as an efficient and selective catalyst for the selective mono-N- and N,N-dibenzylation, allylation, and alkylation of primary amines with benzylic, allylic, and alkyl halides using NaOH as base in aqueous medium. By changing the reaction temperature, mono- or di-benzylation, allylation, or alkylation could be achieved in good yield and selectivity. Secondary amines have also been benzylated, allylated, and alkylated under similar conditions. SiO₂-CuI has been characterized by Fourier transform–infrared, atomic absorption spectrometry, thermalgravimetric analysis, X-ray diffraction, scanning electron microscopy, and transmission electron microscopy, and found to be highly selective and recyclable under the reaction conditions.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Aqueous conditions; heterogeneous catalysis; *N*-alkylations; selectivity; silica-functionalized CuI

INTRODUCTION

Replacement of homogeneous with heterogeneous catalysis and replacement of volatile organic solvents by environmentally friendly ones such as water have been key areas of research in recent years. Among various heterogeneous catalysts developed over the past decades,^[1] silica-supported nanometals have taken the lead because of their greater activity and selectivity.^[2] Recently, use of water has been explored in heterogenized homogeneous catalysis, because it is non-toxic, non-inflammable,

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abundantly available, inexpensive, and cheap. During the past two decades, a large number of reactions have been performed successfully in aqueous media.^[3] It is generally found that organic compounds have limited solubility in water, and efficient water-mediated reactions with high selectivities and reactivities are still relatively limited. Hence, there is a need for close examination of such research areas. Our main motive for using water as a reaction medium is aimed at reducing the use of organic solvents and acheiving more selectivity.

Amines and their derivatives are some of the most common structural features of various naturally occuring biologically active compounds and are widely used as basic intermediates for the preparation of dyes, solvents, fine chemicals, fluorescence probes, pharamaceuticals, agrochemicals, and catalysts for polymerization.^[4] Owing to the immense importance of amines and their derivatives, the development of versatile and efficient methods for their synthesis have become an active area of research.^[5] Traditionally, amines are benzylated, allylated, and alkylated by treatment with suitable halide in the presence of a base^[6] such as KOH or *t*-BuOK, sodium amide, CsOH, thallium(I)ethoxide, CsF/celite, and Hunig's base. In some cases, methanol, dimethyl carbonate, and dimethylsulfate have also been used as alkylating agents.^[7] Various other methods^[8] include Mannich-type reaction, reductive and catalytic amination, metal-initiated amination of alkenes, alkynes, and aryl halides, deamination of quaternary hydrazinium halides, and reduction of N-tosylamidines. Although these methods are quite reliable, most of them (especially those involving direct nucleophilic attack of amines to halides) suffer from overalkylation, thus leading to a mixture of secondary and tertiary amines and even quaternary ammonium salts. The prevention of overalkylation becomes more difficult when highly reactive alkylating agents such as methyl, ethyl, benzyl, and allyl halides are used as alkylating agents.^[9] Recently, various groups have carried out selective N-alkylation of amines with excellent yields. For example, Chiappe et al.^[10] have carried out the selective mono-N-alkylation of anilines in ionic liquids; Marzaro et al.^[11] have reported the selective N-alkylation of amines using alkyl halides in an aqueous basic (NaOH) medium under microwave irradiation, which has been found to be quite satisfactory^[12] but requires the use of specialized microwave equipment; and Zhao et al.^[13] have used iron(III) bromide in combination with dl-pyroglutamic acid and 1,2,3,4,5-pentamethylcyclopenta-1,3-diene at 160 °C under an Ar atmosphere for carrying out selective N-alkylation. Though this method involves the use of quite expensive additives, high selectivity makes this method quite attractive. Zhang et al.^[14] have used iron oxide-immobilized palladium catalyst for the selective N-alkylation of amines with alcohols under base- and organic

RNH₂ + R'X
$$\xrightarrow{\text{TBAB, NaOH, SiO}_2\text{-Cul}}$$
 RNHR' or RN(R')₂
1 2 RNHR' or RN(R')₂
X = Cl, Br

Scheme 1. N- and N,N-Dibenzylation, allylation, and alkylation of primary amines using SiO₂-CuI in water.



Scheme 2. N-Benzylation, allylation, and alkylation of secondary amines using SiO₂-CuI in water.

ligand-free conditions with excellent yields. Again this method requires high temperature and argon atmosphere to obtain good yield and selectivity.

To make this synthesis selective as well as economical, we herein describe the selective mono-N- and N,N-dibenzylation, allylation, and alkylation of primary (Scheme 1) and secondary amines (Scheme 2) in an aqueous medium under mild conditions. Advantages of this protocol include no need for organic solvents, low reaction temperature, no need for inert atmosphere, good yield of products with greater selectivity, and both mono-N- and N,N-dialkylation could be achieved by just changing the reaction temperature.

RESULTS AND DISCUSSION

The silica-functionalized Cu(I) iodide [SiO₂-CuI] was prepared according to our earlier reported work^[15] with slight modification (Scheme 3). The SiO₂-CuI was characterized in a way similar to that reported earlier.^[15] For X-ray diffractometry (S1),



Scheme 3. Preparation of silica-functionalized Cu(I) iodide.

scanning electron microscopy (SEM) image (S2), and transmission electron microscopy (TEM) micrograph (S3), see the electronic supporting information.

Catalytic activity of SiO₂-CuI was studied for the selective N-benzylation, allylation, and alkylation of primary amines. Benzyl amine was selected as the test substrate and benzylation, allylation, and alkylation were carried out with benzyl chloride, allyl bromide, and *n*-butyl chloride using NaOH as base in various solvents such as toluene, acetonitrile, ethanol, and water (Table 1) at different temperatures so as to achieve maximum selectivity for mono-N-alkylation. The results in Table 1 indicated that water is an excellent reaction medium in terms of selectivity. Further, addition of phase-transfer catalyst (TBAB) has increased reaction rate by facilitating the migration of a reactant from one phase into another where reaction occurs. Such rate enhancements have already been reported elsewhere.^[16] The reaction conditions were screened for various temperatures between 0 and 80 °C, and 15 °C was the optimum reaction temperature for mono-N-alkylation, because at higher temperature, dialkylation also occurs and hence selectivity for monoalkylation decreases. It was also found that the reaction remained selective for a certain period of time (i.e., 4h) with 80% conversion of benzyl amine to dibenzyl amine. If the reaction was carried out beyond this time, dialkylation starts and selectivity decreases. So to keep the reaction selective, we stopped the reaction after this time, and mono-N-alkylated product was separated by column chromatography. Thus, the optimum conditions selected are benzyl amine (0.5 mmol), benzyl chloride or allyl bromide or nbutyl chloride (0.5 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu), and $15 \,^{\circ}\text{C}$ as the reaction temperature using water as the reaction medium. To demonstrate the generality of the developed protocol, various primary amines were subjected to N-benzylation, allylation, and alkylation using SiO₂-CuI in water at 15 °C and excellent results were obtained (Table 2).

Once we were able to carry out the *N*-benzylation, allylation, and alkylation selectively, then reaction conditions were screened for the selective *N*,*N*-dibenzylation,

Table 1. Effect of solvent on SiO₂-CuI-catalyzed *N*-benzylation, allylation, and alkylation of amines at $15 \,^{\circ}$ C in water



Entry ^a	Solvent ^b	N-Benzylation		N-Allylation		N-Alkylation	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1	Toulene	4	20	4	15	8	10
2	Ethanol	4	25	4	20	8	10
3	Acetonitrile	4	40	4	40	8	20
4	Water	4	75	4	75	8	75

RX= Benzyl bromide, allyl bromide, n-butyl chloride

"Reaction was carried out by stirring a mixture of amine (0.5 mmol), halide (0.5 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu) at 15 °C in different solvents.

^bYield refers to column chromatography yield.

Table 2. SiO₂-CuI-catalyzed *N*-benzylation, allylation, and alkylation of primary amine with benzyl chloride, allyl bromide, or *n*-butyl chloride at 15° C in water

TBAB, NaOH, SiO₂-CuI

	$RNH_2 + \Sigma$	R'X — $K=Cl, Br$	water, 15 °C		RNHR'	
Entry ^a	R	R ′	Time (h)	Yield ^b (%)	Mp or Bp/lit. mp or bp	
1	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	4	75	103-104/104 ^[18]	
2	$4-BrC_6H_4$	C ₆ H ₅ CH ₂	4	74	52-53/51-52 ^[19]	
3	$4-ClC_6H_4$	C ₆ H ₅ CH ₂	4	74	46-47/46-47 ^[19]	
4	$4-CH_3C_6H_4$	C ₆ H ₅ CH ₂	4	72	245-246/244-245 ^[20]	
5	4-OCH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂	4	74	51-52/52-53 ^[19]	
6	C ₆ H ₅ CH ₂	CH ₂ =CHCH ₂	3	74	liq/bp 115–117 ^[21]	
7	$4-BrC_6H_4$	CH ₂ =CHCH ₂	3	73	liq/bp 145.5–147 ^[22]	
8	$4-ClC_6H_4$	CH ₂ =CHCH ₂	3	73	liq/bp 267–270 ^[23]	
9	4-CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂	3	72	liq/bp 105–109 ^[24]	
10	4-OCH ₃ C ₆ H ₄	CH ₂ =CHCH ₂	3	72	liq/bp 126–127 ^[25]	
11	C ₆ H ₅ CH ₂	$n-C_4H_9$	8	74	liq/bp 124–126 ^[26]	
12	$4-BrC_6H_4$	$n-C_4H_9$	9	72	liq/bp 95–96 ^[27]	
13	$2-ClC_6H_4$	$n-C_4H_9$	9	72	liq/bp 89–90 ^[27]	
14	4-CH ₃ C ₆ H ₄	$n-C_4H_9$	9	71	liq/bp 70–71 ^[27]	
15	$4\text{-OCH}_3\text{C}_6\text{H}_4$	$n-C_4H_9$	9	72	liq/bp 80-81 ^[27]	

^aReaction was carried out by stirring a mixture of amine (0.5 mmol), halide (0.5 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu) at 15 °C in water (4 mL).

^bYield refers to column chromatography yield.

allylation, and alkylation using SiO₂-CuI. Benzyl amine was again selected as the test substrate and dibenzylation, allylation, and alkylation were carried out with benzyl chloride, allyl bromide, and *n*-butyl chloride respectively using NaOH as base under similar conditions but for extended period of time. It was found that up to 15 h, the conversion to disubstitution increased but reaction did not go to completion. To drive the reaction to completion, the reaction temperature was increased up to 100 °C, and surprisingly the reaction was completed in 2 h. No monosubstituted product was observed on thin-layer chromatography (TLC). Thus, the optimum conditions for disubstitution selected are benzyl amine (0.5 mmol), benzyl chloride, allyl bromide or *n*-butyl chloride (1 mmol), NaOH (2 mmol), TBAB (0.25 mmol) and SiO₂-CuI (0.1 g, 5 mol% Cu), water (4 mL), and 70–100 °C as the reaction temperature. To demonstrate the generality of the developed protocol, various primary amines were subjected to *N*,*N*-dibenzylation, allylation, and alkylation using SiO₂-CuI in water at 70–100 °C, and excellent results were obtained (Table 3).

The SiO₂-CuI-catalyzed *N*-benzylation, allylation, and alkylation of secondary amines has also been attempted. To select the optimum reaction conditions, morpholine was selected as the test substrate, and benzylation, allylation, and alkylation was carried out with benzyl chloride, allyl bromide, and *n*-butyl chloride respectively under similar conditions as for *N*,*N*-disubstitution. Different solvents have been screened (Table 1) and again we found that water was the most suitable solvent. TBAB also increased the reaction rate. The optimum conditions selected are morpholine (0.5 mmol), benzyl chloride, allyl bromide, or *n*-butyl chloride (0.5 mmol),

Table 3. SiO₂-CuI catalyzed *N*,*N*-dibenzylation, allylation, and alkylation of primary amine with benzyl chloride, allyl bromide, or *n*-butyl chloride at 70–100 °C^{*a*} in water

RNH ₂	+ R'X —	$\frac{\text{SiO}_2\text{-}\text{CuI}}{100\ ^0\text{C}}$	$\blacktriangleright RN(R')_2$	
	X=Cl, Br			
R	R′	Time (h)	Yield ^c (%)	Mp or Bp/lit. mp

Entry ^b	R	R ′	Time (h)	Yield ^c (%)	Mp or Bp/lit. mp or bp (°C)
1	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	2	94	90-91/91 ^[28]
2	$4-BrC_6H_4$	C ₆ H ₅ CH ₂	6	93	125-126/124-126 ^[29]
3	$4-ClC_6H_4$	$C_6H_5CH_2$	6	93	103-104/104-105[30]
4	$4-CH_3C_6H_4$	C ₆ H ₅ CH ₂	5.5	92	63-64/63-64 ^[31]
5	4-OCH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂	5.5	92	85-86/85-87 ^[31]
6	C ₆ H ₅ CH ₂	CH ₂ =CHCH ₂	9	93	lig/bp 89 ^[32]
7	$4-BrC_6H_4$	CH ₂ =CHCH ₂	10	93	liq. (oil) ^[33]
8	$4-ClC_6H_4$	CH ₂ =CHCH ₂	10	92	liq/bp 95–97 ^[34]
9	C ₆ H ₅ CH ₂	n-C ₄ H ₉	21	93	$lig/bp 134-136^{[35]}$
10	$4-BrC_6H_4$	$n-C_4H_9$	22	90	lig/bp 156–158 ^[36]
11	$4-ClC_6H_4$	$n-C_4H_9$	23	90	$lig/bp 107-112^{[37]}$
12	$4-CH_3C_6H_4$	n-C ₄ H ₉	23	90	$liq/bp > 260^{[37]}$

^aAllylation was carried out at 70 °C.

^bReaction was carried out by stirring a mixture of amine (0.5 mmol), halide (1 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu) at 70–100 °C in water (4 mL).

^cIsolated yield (entries 1–5), column chromatography yield (entries 6–12).

NaOH (2 mmol), TBAB (0.25 mmol), SiO₂-CuI (5 mol%, 0.1 g), water (4 mL), and 100 °C as the reaction temperature. To demonstrate the generality of the developed protocol, various secondary amines were chosen, and excellent results were obtained (Table 4).

To find out the role of SiO₂-CuI for *N*-benzylation, allylation, and alkylation, we carried out the reaction in the case of entries 1, 6, 11 (Table 2) with activated silica, 3-aminopropyl silica (AMPS), ligand-grafted silica (imine), and in the absence of SiO₂-CuI under the similar conditions as applied for SiO₂-CuI. The results are summarized in Table 5. Thus, it was found that SiO₂-CuI catalyses the reaction and the corresponding amine was obtained in good yield and selectivity. It is pertinent to mention that reaction does take place without any catalyst, but regioselectivity is poor. The possible explaination for the catalytic activity of SiO₂-CuI might be illustrated on the basis of cyclic mechanism reported earlier.^[17] Catalytic oxidative addition of Cu(I) into the aryl–halogen bond take place to form the copper(III) intermediate, which undergoes an exchange of the halide with the nucleophile (i.e., amine) to form another intermediate, which finally undergo subsequent reductive elimination to form the product, and Cu(I) catalyst is regenerated back. Several literature reports evoke the involvement of copper(III) intermediate in the Ullmann reaction mechanism.^[17]

In the case of heterogeneous catalysis, deactivation and hence recyclability are the important issues. To test this, a series of seven consecutive runs for the *N*-benzylation of benzyl amine (entry 1, Table 2) and *N*,*N*-dibenzylation of benzyl amine (entry 1, Table 3) were carried out, and the results are represented in Fig. 1, **Table 4.** SiO₂-CuI-catalyzed *N*-benzylation, allylation, and alkylation of secondary amines with benzyl chloride, allyl bromide, or *n*-butyl chloride at 100 °C in water^{*a*}

DNU	+ P'V TB	AB, NaOH,	SiO ₂ -CuI		D ND'
K ₂ INII	т ка	water, 10	0 °C		K ₂ INK
	X=Cl, Br				
Amine	R′	Time (h)	Vield ^b (%)	Mn (or Bn / lit mn or bn

 $\sim \sim$

Entry	Amine	R'	Time (h)	Y ield [*] (%)	Mp or Bp / lit. mp or bp (°C)
1	Morpholine	C ₆ H ₅ CH ₂	2	96	194–195/194 ^[38]
2	Imidazole	$C_6H_5CH_2$	4	85	72-73/71-72 ^[39]
3	Piperidine	$C_6H_5CH_2$	1	97	$177 - 178 / 178 - 179^{[40]}$
4	Diphenyl amine	$C_6H_5CH_2$	5	50	87-88/86-87 ^[41]
5	Morpholine	CH ₂ =CHCH ₂	3	94	liq/bp 156–158 ^[32]
6	Piperidine	CH ₂ =CHCH ₂	2	94	$50-51/51-52^{[42]}$
7	Diphenyl amine	CH ₂ =CHCH ₂	5	51	liq/bp 185–195 ^[43]
8	Morpholine	$n-C_4H_9$	2	93	$lig/bp 67-68^{[44]}$
9	Imidazole	$n-C_4H_9$	15	78	237-238/238-239[45]
10	Piperidine	$n-C_4H_9$	2	92	lig/bp 176 ^[46]
11	Diphenyl amine	n-C ₄ H ₉	20	68	liq/bp 145–147 ^[47]

^{*a*}Reaction was carried out by stirring a mixture of amine (0.5 mmol), halide (0.5 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu) at 100 °C in water (4 mL). ^{*b*}Isolated yield (entries 1–4) and column chromatography yield (entries 5–11).

which demonstrated that SiO_2 -CuI is highly active, selective, stable, and recyclable. Up to run 5, there was no loss of activity; however, after run 5, there was a significant decrease in the activity of the catalyst. This decrease in the activity may be due to the microscopic changes on the surface of the catalyst. Further, negligible leaching of Cu was observed by AAS analysis.

Table 5. Effect of catalyst on the N-benzylation, allylation, and alkylation of amines at 15 °C in water



Entry	Catalyst	N-Benzylation		N-Allylation		N-Alkylation	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1	No catalyst	4	30	4	25	8	Traces
2	Silica	4	40	4	30	8	10
3	AMPS	4	40	4	30	8	10
4	Imine	4	45	4	40	8	10
5	SiO ₂ -CuI	4	75	4	74	8	74

RX= Benzyl bromide, allyl bromide, n-butyl chloride

"Reaction was carried out by stirring a mixture of amine (0.5 mmol), halide (0.5 mmol), NaOH (2 mmol), TBAB (0.25 mmol), and SiO₂-CuI (0.1 g, 5 mol% Cu) at 15 °C in water (4 mL).

^bYield refers to column chromatography yield.

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Figure 1. Recyclability of SiO₂-CuI.

CONCLUSION

In conclusion, we have developed a mild, simple, and cost-effective procedure for selective *N*-benzylation, allylation, and alkylation; *N*,*N*-dibenzylation, allylation, and alkylation of primary amines; and *N*-benzylation, allylation, and alkylation of secondary amines in the presence of recyclable SiO₂-CuI using water as the reaction medium. Moreover, the mild reaction conditions, high selectivity, good yield of products, ease of workup, and cost-effective procedure will make the present method a useful and important addition to the present methodologies for the synthesis of *N*-substituted secondary and tertiary amines.

EXPERIMENTAL

All chemicals used were purchased from Aldrich Chemical Company. A Bruker DPX-200 NMR spectrometer (200 MHz) in CDCl₃ using tetramethylsilane as an internal standard was used for recording ¹H NMR spectra; a Perkin-Elmer FTIR spectrophotometer using KBr disc was used for IR; and mass spectral data were recorded on an Esquire 3000 (ESI). Thermal analysis was done on a DTG-60 Shimadzu thermal analyzer with heating rate of $10 \,^{\circ}C/min$, x-ray diffraction patterns were measured on a Bruker AXSD8 X-ray diffraction spectrometer, SEM was studied on a Jeol T-300 scanning electron microscope, and transmission electron microscopy (TEM) was done on a H7500 Hitachi. The amount of copper in SiO₂-CuI was determined on a GBC 932 AB atomic absorption spectrophotometer manufactured in Australia. The catalyst was stirred in diluted HCl for 5 h and then subjected to AAS analysis. All yields refer to the isolated or column chromatography yields.

General Procedure for the Selective *N*-Benzylation, Allylation, and Alkylation or *N*,*N*-Dibenzylation, Allylation, and Alkylation of Primary and Secondary Amines

SiO₂-CuI (0.1 g, 5 mol% Cu) was added to a mixture of amine (0.5 mmol), benzyl chloride, allyl bromide, or *n*-butyl chloride (0.5 mmol for *N*-substitution

and 1 mmol for *N*,*N*-disubstitution), NaOH (2 mmol), and TBAB (0.25 mmol) in a round-bottom flask (25 mL) in water (4 mL). The reaction mixture was stirred at 15 °C (in the case of *N*-benzylation, allylation, or alkylation of primary amines, Table 2) or 70–100 °C (in the case of *N*,*N*-dibenzylation, allylation, or alkylation of primary amines, Table 3), and 100 °C (*N*-benzylation, allylation, and alkylation of secondary amines, Table 4) for an appropriate time. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was triturated with EtOAc (20 mL) and the SiO₂-CuI was filtered off. The product was obtained after removal of the solvent under reduced pressure followed by column chromatography or crystallization from EtOAc–petroleum. ether. The SiO₂-CuI was washed with distilled water (200 mL) followed by methylene chloride ($3 \times 15 \text{ mL}$) and dried at 110 °C for 2 h. It was used further for carrying out the reaction. The structures of products were confirmed by IR, ¹H NMR, mass spectral data (see supporting information, S4) and comparison with authentic samples obtained commercially or prepared according to the literature methods.

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