Silica-Immobilized CuI: An Efficient Reusable Catalyst for Three-Component Coupling Reaction of Aldehyde, Amine and Alkyne

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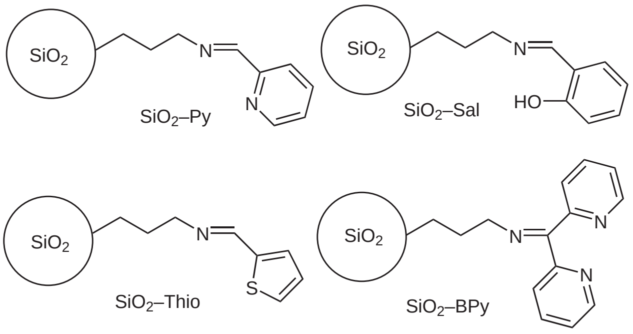
Received 11 April 2007

Abstract: Silica-supported copper catalysts were effectively used in the three-component coupling of aldehydes, amines and alkynes to afford the corresponding propargylamines in moderate to excellent yields. The catalyst was quantitatively recovered from the reaction by a simple filtration and reused for a number of cycles with almost consistent activity.

Key words: silica, copper, three-component coupling, propargylamines, reusable catalyst

The catalytic one-pot multicomponent coupling reaction is an attractive strategy in organic synthesis to introduce several elements of diversity into a molecule in a single step.[1] Three-component coupling of aldehydes, amines and alkynes (A^3 coupling) is one of the best examples of such a process and has received much attention in recent times.[2] The resultant propargylamines obtained by A^3 coupling reactions are important synthetic intermediates for potential therapeutic agents and polyfunctional amino derivatives.[3] There are several transition-metal catalysts able to carry out A^3 coupling reaction via C–H activation. These include Ag(I) salts,[4] Au(I)/Au(III) salts,[5] Au(III)–salen complexes,[6] Cu(I) salts,[7] and a Cu/Ru bimetallic system[8] under homogeneous conditions. But all of these systems suffer from the loss of the precious catalysts at the end of the reaction. To achieve the recyclability of the metal catalyst, Li et al.[9] and Park et al.[10] used room-temperature ionic liquid immobilized catalysts. Our group reported hydroxyapatite-supported copper (Cu-HAP)[11] and layered double hydroxide supported gold (LDH-$AuCl_4$),[12] and Reddy et al. reported heteropolyacid-supported silver (Ag-HPA)-catalyzed[13] A^3 coupling reactions. Recently Kidwai et al. have reported[14] gold nanoparticles reusable for the A^3 coupling reactions.

The development of heterogeneous catalysts for fine chemicals synthesis has become a major area of research recently, as the potential advantages of these materials (simplified recovery and reusability, the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can have a major impact on the environmental performance of a synthesis.[15] The majority of these novel catalysts are based on silica, primarily since silica displays many advantageous properties, namely, excellent stability (chemical and thermal), high surface area, good accessibility, and organic groups can be robustly anchored to the surface, to provide catalytic centers.[16] By exploiting these advantages of silica, we recently reported imine-functionalized silica-immobilized copper complex catalyzed N-arylation of amines (Scheme1).[17] Herein we wish to report the silica-immobilized copper-catalyzed A^3 coupling reaction.

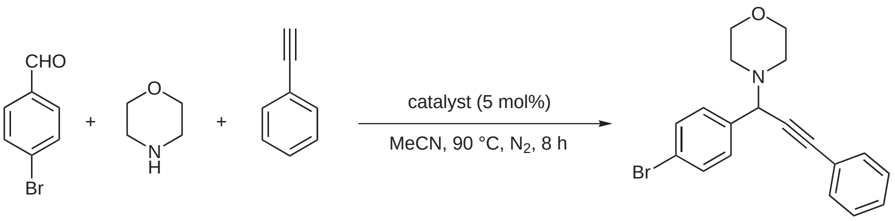


Scheme 1 Different imine-functionalized silica supports

3-Aminopropyl-functionalized silica (AFS, 9% functionalization, purchased from Aldrich) was derivatized with different carbonyl compounds to the corresponding imine.[17] Thus appropriate imine-functionalized silica support was then subsequently complexed with copper salts to afford the final silica-immobilized copper catalysts (Table 1, entries 1–6).[18] To find the best catalyst for the A^3 coupling reaction, we have chosen the three-component reaction of 4-bromobenzaldehyde, morpholine and phenylacetylene in acetonitrile as the model reaction (Scheme 2) and the results are summarized in Table 1. From Table 1, it can be seen that SiO_2–Py–CuI is the best catalyst amongst the catalysts screened.

To check the solvent effect on the outcome of the reaction, different solvents were employed in the A^3 coupling reaction and the results are summarized in Table 2. It was observed that acetonitrile was the most effective solvent, so it was used in all reactions. It is noteworthy that water can also be used as solvent, albeit with moderate yields (Table 2, entry 6). Even at room temperature SiO_2–Py–CuI afforded 45% product in 48 hours (Table 2, entry1).

SYNLETT 2007, No. 14, pp 2301–2303
Advanced online publication: 24.07.2007
DOI: 10.1055/s-2007-984921; Art ID: D10807ST



Scheme 2 Three-component coupling using silica-immobilized copper catalysts

Table 1 Catalyst Screening for the Three-Component Coupling of 4-Bromobenzaldehyde, Morpholine, and Phenylacetylene[a] (see Scheme 1)

Entry	Catalyst (5 mol%)	Isolated yield (%)
1	SiO_2–Py–Cu(OAc)$_2$	68
2	SiO_2–Sal–Cu(OAc)$_2$	39
3	SiO_2–Thio–Cu(OAc)$_2$	42
4	SiO_2–BPy–Cu(OAc)$_2$	56
5	SiO_2–Py–$CuCl_2$	65
6	SiO_2–Py–CuI	95
7	CuI	90

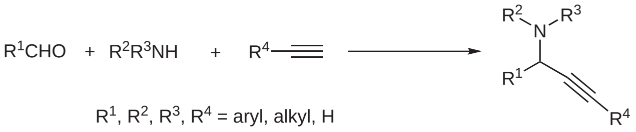
[a] Reaction conditions: aldehyde (1 mmol), amine (1.2 equiv), alkyne (1.5 equiv), MeCN (3 mL), 90 °C for 8 h, N_2 atmosphere.

Table 2 Solvent Effect on the Three-Component Coupling of 4-Bromobenzaldehyde, Morpholine, and Phenylacetylene Using SiO_2–Py–CuI Catalyst[a]

Entry	Solvent (3 mL)	Isolated yield (%)
1	MeCN	92, 45[b]
2[c]	THF	30
3	Dioxane	35
4	MeOH	85
5	Toluene	80
6	Water	42, 40[d]

[a] Reaction conditions: aldehyde (1 mmol), amine (1.2 equiv), alkyne (1.5 equiv), catalyst (5 mol%), 90 °C for 8 h, N_2 atmosphere.
[b] Reaction at r.t. for 48 h.
[c] Reaction temperature: 66 °C.
[d] Yield after 2nd cycle (leaching: 1.01%).

Table 3 Coupling of Aldehyde, Amine and Alkyne Catalyzed by SiO_2–Py–CuI[a]



Entry	R^1	R^2, R^3	R^4	Time (h)	Yield (%)[b]
1	Ph	Morpholine	Ph	8	90
2	4-BrC_6H_4	Morpholine	Ph	8	92, 89[c]
3	4-ClC_6H_4	Morpholine	Ph	8	92
4	4-MeC_6H_4	Morpholine	Ph	12	78
5	4-$MeOC_6H_4$	Morpholine	Ph	14	75
6	4-$NO_2C_6H_4$	Morpholine	Ph	24	n.r.[d]
7	Cyclohexyl	Morpholine	Ph	8	90
8	Ph$(CH_2)_2$	Morpholine	Ph	8	88
9	Ph	Piperidine	Ph	6	90
10	Ph$(CH_2)_2$	Piperidine	Ph	6	89
11	Ph	Pyrrolidine	Ph	6	93
12	4-BrC_6H_4	$R^2 = R^3$ = allyl	Ph	8	90
13	Ph	$R^2 = R^3$ = allyl	Ph	8	91
14	Ph	$R^2 = R^3$ = benzyl	Ph	10	92
15	Ph	Morpholine	4-MeC_6H_4	8	88
16	4-BrC_6H_4	Morpholine	4-MeC_6H_4	8	90
17	Ph	Morpholine	Bu	12	72
18	Ph	R^2 = 4-BrC_6H_4, R^3 = H	Ph	18	54

[a] Reaction conditions: aldehyde (1 mmol), amine (1.2 equiv), alkyne (1.5 equiv), catalyst (5 mol%), MeCN (3 mL), 90 °C, N_2 atmosphere.
[b] Isolated yields.
[c] Yields after the 5th cycle.
[d] n. r. = no reaction.

To widen the scope of the SiO_2–Py–CuI catalyst in A^3 coupling, several other aldehydes, amines and alkynes were allowed to react under the optimized conditions[19] and the results are summarized in Table 3. Aromatic aldehydes with both electron-donating and electron-withdrawing functionalities afforded good to excellent yields of the corresponding propargylamines (Table 3, entries 2–5). 4-Nitrobenzaldehyde did not yield the desired product, which is in accordance with the earlier studies.[11,13] Both the cyclic and acyclic aldehydes reacted with equal ease to give excellent yields (Table 3, entries 7, 8, and 10). Both the cyclic and acyclic secondary amines gave good yields. Aromatic amine also reacted to give the corresponding product but yields were low (Table 3, entry 18). Aromatic alkynes afforded better yields than the aliphatic alkyne (Table 3, entry 17).

For any heterogeneous catalyst, it is important to know its ease of separation and possible reusability. The catalyst was separated by simple filtration and washed with ethyl acetate followed by water and finally with acetone and air-dried. The recovered catalyst was used in the next run and almost consistent activity was noticed for five consecutive cycles (Table 3, entry 2). To check whether the reaction occurs mainly due to the leached metal or supported catalyst, a reaction was terminated after a small conversion (1 h, 13% conversion) and the catalyst was filtered off by hot filtration and the reaction was continued with the filtrate for the required period of time. Almost no change in conversion was observed. This confirmed that no active species was leached during the reaction. Moreover, the copper content of the fresh catalyst, and the catalyst after the 5th cycle were found almost unchanged (only 2% difference).

In conclusion, we have developed an efficient heterogeneous protocol for the three-component coupling of aldehydes, amines and alkynes to afford the corresponding propargylamines using silica-immobilized CuI catalyst, which is easily separable from the reaction mixture and reusable with consistent activity.

Acknowledgment

We wish to thank the CSIR for financial support under the Task Force Project COR-0003. S.R. and M.S.S. thank CSIR and M.R. thanks UGC for providing research fellowships.

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(18) **Preparation of Imine-Modified Silica-Supported Copper Catalysts**:[17]
SiO_2–Py–Cu(OAc)$_2$: SiO_2–Py (1 g) was stirred with a solution of Cu(OAc)$_2$ (1 mmol) in acetone (25 mL) for 24 h to get SiO_2–Py–(CuOAc)$_2$. The copper content was measured by ICP–AES and it was found to be 0.43 mmol/g. Similarly SiO_2–Sal–Cu(OAc)$_2$ (Cu: 0.41 mmol/g), SiO_2–BPy–Cu(OAc)$_2$ (Cu: 0.39 mmol/g), and SiO_2–Thio–Cu(OAc)$_2$ (Cu: 0.41 mmol/g) were prepared from Cu(OAc)$_2$ in acetone. SiO_2–Py–CuCl$_2$ (Cu: 0.47 mmol/g) was prepared from an acetone solution of CuCl$_2$. SiO_2–Py–CuI was prepared from a MeCN solution of CuI and the copper content was 0.45 mmol/g.

(19) **Typical Procedure for A^3 Coupling Reaction:** A mixture of aldehyde (1 mmol), amine (1.2 mmol), alkyne (1.5 mmol) and SiO_2–Py–CuI (110 mg, 5 mol%) in MeCN (3 mL) was stirred in a round-bottomed flask at 90 °C under nitrogen. After completion of the reaction (monitored by TLC) the catalyst was filtered. After removing the solvent at reduced pressure, the crude material was purified by chromatography on silica gel using hexane–EtOAc mixture as eluent to afford the corresponding propargylamines. Spectroscopic data of the new compounds are given below:
Diallyl-[1-(4-bromophenyl)-3-phenylprop-2-ynyl]amine (Table 3, entry 12): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.40–7.62 (m, 6 H), 7.28–7.38 (m, 3 H), 5.70–5.91 (m, 2 H), 5.24 (d, J = 17.0 Hz, 2 H), 5.12 (d, J = 9.3 Hz, 2 H), 4.99 (s, 1 H), 3.16–3.29 (m, 2 H), 2.90–3.06 (m, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.5, 136.3, 131.8, 131.1, 129.8, 128.4, 122.8, 121.4, 117.4, 88.1, 84.7, 55.9, 53.5. ESI–MS: m/z = 368 [M + 1], 366 [M + 1], 271, 269, 146, 104. Anal. Calcd for C$_{19}$H$_{20}$BrN: C, 66.67; H, 5.89; N, 4.09. Found: C, 66.71; H, 5.92; N, 4.01.
4-[1-(4-Bromophenyl)-3-*p*-tolylprop-2-ynyl]morpholine (Table 3, entry 16): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.45–7.61 (m, 4 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 4.69 (s, 1 H), 3.61–3.79 (m, 4 H), 2.52–2.68 (m, 4 H), 2.38 (s, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.5, 137.1, 131.8, 131.3, 130.3, 129.0, 121.7, 119.8, 89.1, 83.5, 67.2, 61.4, 49.8, 21.4. EI–MS: m/z = 371 [M$^+$], 369 [M$^+$], 285, 283, 214, 205, 189, 128, 86, 56. Anal. Calcd for C$_{20}$H$_{20}$BrNO: C, 64.87; H, 5.44; N, 3.78. Found: C, 64.89; H, 5.47; N, 3.75.