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A highly efficient heterogeneous copper-catalyzed three-component coupling of tetrahydroisoquinolines, aldehydes and 1-alkynes

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A highly efficient heterogeneous three-component coupling of tetrahydroisoquinolines, aldehydes and 1-alkynes was achieved in toluene at 70 °C in the presence of an 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper(I) complex [MCM-41-2N-CuI], yielding a variety of C1-alkynylated tetrahydroisoquinolines (*endo*-yne-THIQs) in good to excellent yields with high regioselectivity. This heterogeneous copper catalyst can be easily prepared by a simple two-step procedure from commercially available and inexpensive reagents, and recovered by a simple filtration and reused for at least 10 times without any decreases in activity.

Introduction

Tetrahydroisoquinolines (THIQs) form a large class of natural and unnatural alkaloids with a great diversity of important biological activities.[1] Considerable effort has been devoted to the development of new tetrahydroisoquinoline structures and new methods for their constructions.[2] Traditional methods for the preparation of this class of compounds include the Bischer-Napieralski cyclization/reduction[2b,3] and the Pictet-

Spengler reaction.[2b,4] Recently, the synthesis of C1-substituted THIQ derivatives from readily available unsubstituted THIQs by using the cross-dehydrogenative coupling (CDC) strategy has received much attention.[5-7] For example, Li *et al.* have developed copper-catalyzed CDC reaction of THIQs with terminal alkynes for the synthesis of C1-alkynylated THIQs.[8] A similar transformation was also achieved by visible-light photoredox catalysis.[9] However, THIQs with *N*-aromatic or *N*-acyl substitutions and stoichiometric exogenous oxidants have to be employed in these CDC alkynylation reactions.

In recent years, one-pot multicomponent coupling reactions have emerged as an attractive and powerful strategy for the formation of carbon-carbon and carbon-heteroatom bonds in a step- and atom-economical fashion.[10] Among these reactions, the transition metal-catalyzed three-component coupling reactions using aldehydes, alkynes, and amines as starting materials have provided novel, efficient and practical methods for the synthesis of a number of heterocyclic compounds.[11] In 2007, Yan and Liu described a gold-catalyzed three-component coupling/cycloisomerization reaction of heteroaryl aldehydes, alkynes, and amines leading to aminoindolizines.[12] In 2010, Gevorgyan's group developed a copper-catalyzed three-component coupling reaction of aldehydes, 2-aminopyridines, and 1-alkynes to form imidazoheterocycles.[13] Ji and co-workers reported a gold-catalyzed synthesis of the complex butenolides from amines, 1-alkynes, and glyoxylic acid.[14] Very recently, Yu and Ma groups developed a copper-catalyzed A^3 reaction of THIQs, aldehydes and alkynes toward C1-alkynylated THIQs.[15] Liu and co-workers reported $AuBr_3$-catalyzed three-component coupling of

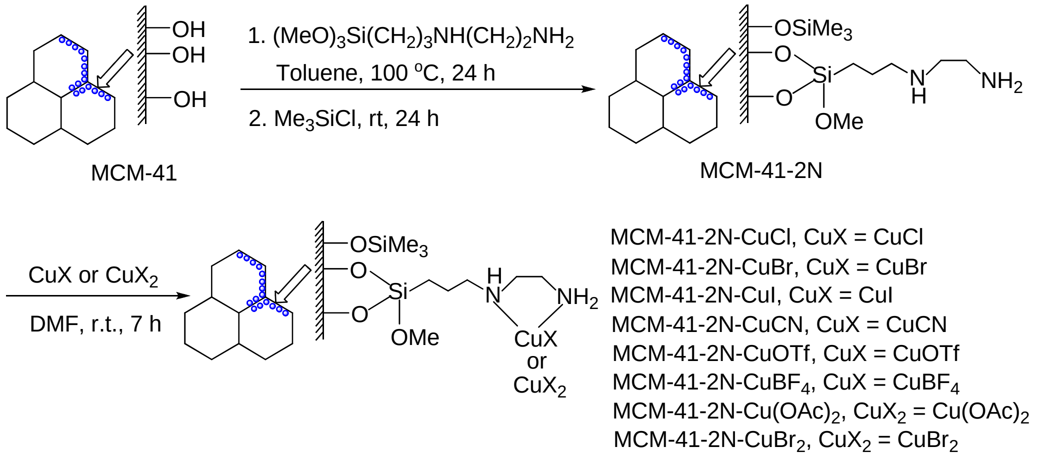
1-alkynes, amines, and phenylglyoxal derivatives to form furan derivatives and the three-component coupling of 1-alkynes, THIQ, and indole-2-carboxaldehyde to give C1-alkynylated THIQs.[16]

Although these transition metal-catalyzed three-component coupling reactions are highly efficient for the construction of a number of heterocyclic compounds, the problem with homogeneous catalysis is the difficulty to separate the catalyst from the reaction mixture and the impossibility to reuse it in consecutive reactions. In addition, homogeneous catalysis might result in heavy metal contamination of the desired isolated product, which is a particularly significant drawback for its application in the pharmaceutical industry. These problems are of particular environmental and economic concerns in large-scale syntheses and in industry. In contrast, heterogeneous catalysts can be easily separated from the reaction mixture by a simple filtration of the reaction solution and reused in successive reactions provided that the active sites have not become deactivated. To overcome these problems, the development of highly efficient and recyclable heterogeneous catalysts, for example by immobilization of catalytically active species onto a solid support to produce a molecular heterogeneous catalyst is challenging and important.[17] In spite of tremendous effort dedicated to the immobilization of homogeneous palladium complexes over the last two decades,[18] organic transformations catalyzed by supported copper complexes have received less attention,[19] and to the best of our knowledge, no three-component coupling reaction of aldehydes, tetrahydroisoquinolines (THIQs), and alkynes catalyzed by a supported copper complex has been reported until now.

The discovery of mesoporous MCM-41 materials has given an enormous stimulus to research in heterogeneous catalysis and provided a new possible candidate for a solid support for immobilizing homogeneous catalysts because of their outstanding advantages such as extremely high surface areas, large and uniform pore size, big pore volume and rich silanol groups in the inner walls.[20] Its large pore size allows passage of large molecules such as organic reactants and metal complexes through the pores to reach to the surface of the channel.[21] To date, some functionalized MCM-41-immobilized palladium, rhodium, and molybdenum complexes have been prepared and successfully used in organic reactions.[22] Recently, we reported the first synthesis of 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper(I) complex [MCM-41-2N-CuI] and found that it is highly efficient and recyclable heterogeneous catalysts for the homo- and heterocoupling of terminal alkynes.[23] In continuing our efforts to develop greener synthetic pathways for organic transformations,[24] herein we wish to report a highly efficient heterogeneous three-component coupling reaction of tetrahydroisoquinolines (THIQs), aldehydes and terminal alkynes catalyzed by an 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper(I) complex [MCM-41-2N-CuI] under mild reaction conditions. The reactions generated a variety of C1-alkynylated tetrahydroisoquinoline derivatives in good to excellent yields with high regioselectivity, and the heterogeneous copper complex can be easily recovered by a simple filtration of the reaction solution and its catalytic efficiency remains unaltered even after recycling ten times.

Results and discussion

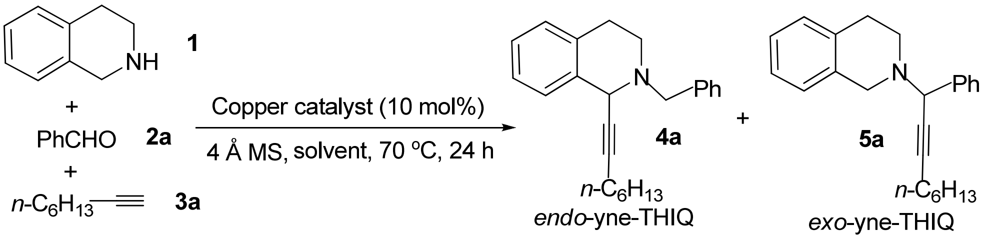
A series of 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper complexes [MCM-41-2N-CuX(CuX_2)] were conveniently prepared starting from commercially available and inexpensive 3-(2-aminoethylamino)propyltrimethoxysilane and simple copper salts such as CuX or CuX_2 (X = Cl, Br, I, CN, OTf, BF_4, OAc) according to our previous procedure (Scheme 1).[23] Firstly, the mesoporous material MCM-41 was reacted with 3-(2-aminoethylamino)propyltrimethoxysilane in toluene at 100 °C for 24 h, followed by the silylation with Me_3SiCl in dry toluene at room temperature for 24 h to give 3-(2-aminoethylamino)propyl-functionalized MCM-41 (MCM-41-2N). The latter was subsequently treated with various copper salts in DMF at room temperature for 7 h to generate the corresponding 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper complexes [MCM-41-2N-CuX(CuX_2)] as pale blue powders.



Scheme 1. Preparation of 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper complexes

In our initial screening experiments, the three-component coupling of tetrahydroisoquinoline (THIQ), benzaldehyde and 1-octyne was investigated as a model reaction to optimize the reaction conditions, and the results are summarized in Table 1. We first screened various MCM-41-supported copper catalysts with toluene as solvent in the presence of 4 Å molecular sieves at 70 °C under an atmosphere of argon and a significant catalyst effect was observed. We found that the regioselectivity of this reaction can be, to some extent, well tuned by using different supported copper catalysts. Both MCM-41-2N-CuCl and MCM-41-2N-CuBr can promote the reaction effectively to afford *exo*-yne-THIQ **5a** as the major product (Table 1, entries 1 and 2), while the reactions catalyzed by MCM-41-2N-CuI and MCM-41-2N-CuCN gave the *endo*-yne-THIQ **4a** with excellent regioselectivity in 90 and 45% yields, respectively (Table 1, entries 3 and 4). We proposed that the reaction catalyzed by MCM-41-2N-CuI or MCM-41-2N-CuCN starts from generation of an *exo*-iminium ion from a secondary amine and aldehyde. The *exo*-iminium ion then isomerizes into an *endo*-iminium ion, which reacts with MCM-41-supported copper acetylide to afford *endo*-yne-THIQ **4a**. Although both MCM-41-2N-CuBr and MCM-41-2N-CuI are highly efficient for this three-component coupling, completely opposite regioselectivity was observed. When other heterogeneous copper(I) complexes such as MCM-41-2N-CuOTf and MCM-41-2N-$CuBF_4$ were used as catalysts, both yield and regioselectivity were poor (Table 1, entries 5 and 6). MCM-41-2N-$Cu(OAc)_2$ and MCM-41-2N-$CuBr_2$ were also tested, it was found that they were substantially less effective compared to MCM-41-2N-CuI (Table 1, entries 7 and 8). So, MCM-41-2N-CuI was finally selected as the catalyst for the reaction. Our next studies focused on the effect of solvent on the model reaction. Low yields and poor regioselectivity were observed when other solvents such as THF, 1,4-dioxane, 1,2-dimethoxyethane, dichloromethane and 1,2-dichloroethane were used (Table 1, entries 9-13). Lowering the reaction temperature to 50 or 30 ºC resulted in decreased yields (Table 1, entries 14 and 15). Finally, the amount of supported copper catalyst was also screened, and 10 mol% loading of copper was found to be optimal, a lower yield was observed and a longer reaction time was required when the amount of the catalyst was decreased (Table 1, entry 16). Increasing the amount of copper catalyst could shorten the reaction time, but both yield and regioselectivity were decreased slightly (Table 1, entry 17). Thus, the optimized reaction conditions for this transformation are the MCM-41-2N-CuI (10 mol%) in toluene using 4 Å molecular sieves as dehydrating agent at 70 °C under Ar for 24 h (Table 1, entry 3).

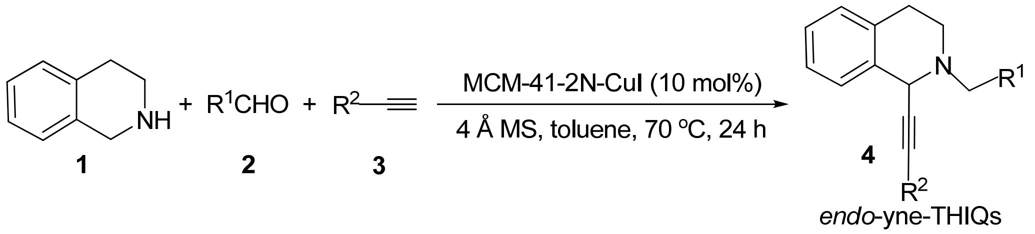
Table 1 Optimization of conditions for the coupling reaction of THIQ, benzaldehyde and 1-octyne.[a]



Entry	Copper catalyst	Solvent	Yield (%)[b] **4a** + **5a**	Ratio[c] **4a**/**5a**
1	MCM-41-2N-CuCl	toluene	86	1:8
2	MCM-41-2N-CuBr	toluene	91	1:18
3	MCM-41-2N-CuI	toluene	90	1:0
4	MCM-41-2N-CuCN	toluene	45	1:0
5	MCM-41-2N-CuOTf	toluene	24	4:1
6	MCM-41-2N-$CuBF_4$	toluene	28	9:1

7	MCM-41-2N-Cu(OAc)$_2$	toluene	55	7:1
8	MCM-41-2N-CuBr$_2$	toluene	62	8:1
9	MCM-41-2N-CuI	THF	16	5:1
10	MCM-41-2N-CuI	dioxane	12	7:1
11	MCM-41-2N-CuI	DME	8	6:1
12	MCM-41-2N-CuI	DCM	24	2:1
13	MCM-41-2N-CuI	DCE	35	8:1
14[d]	MCM-41-2N-CuI	toluene	64	1:0
15[e]	MCM-41-2N-CuI	toluene	38	1:0
16[f]	MCM-41-2N-CuI	toluene	75	1:0
17[g]	MCM-41-2N-CuI	toluene	81	40:1

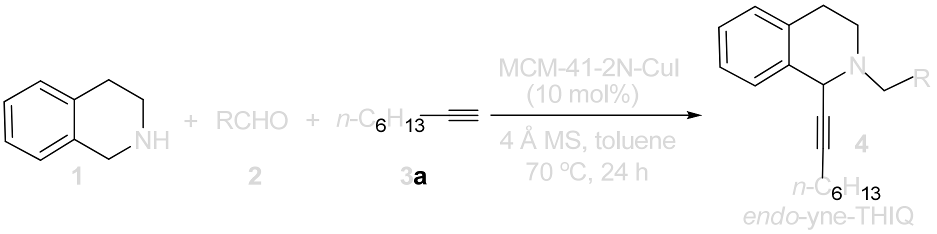
[a] Reaction was performed with **1** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), 4 Å MS (150 mg), copper catalyst (0.05 mmol) in solvent (2 mL) at 70 °C under Ar for 24 h. [b] Isolated combined yield of **4a** and **5a**. [c] Ratio was determined by NMR prior to purification. [d] At 50 ºC for 36 h. [e] At 30 ºC for 48 h. [f] 5 mol% MCM-41-2N-CuI was used for 48 h. [g] 20 mol% MCM-41-2N-CuI was used for 15 h.

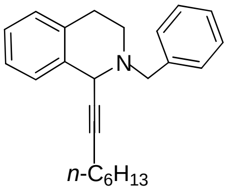


Scheme 2. Synthesis of C1-alkynylated tetrahydroisoquinolines (*endo*-yne-THIQs) via heterogeneous copper-catalyzed three-component coupling reaction.

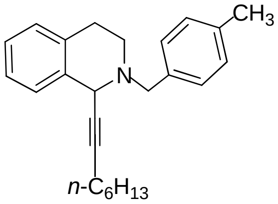
With the optimal reaction conditions established, we tried to investigate the scope and limitations of this heterogeneous copper-catalyzed three-component coupling reaction using a wide range of aldehydes and various 1-alkynes as substrates (Scheme 2). Firstly, the reactions of THIQ with various aldehydes and 1-octyne were examined and the results are summarized in Table 2. The reactions of a variety of substituted benzaldehydes bearing both electron-donating and electron-withdrawing groups with THIQ and 1-octyne proceeded smoothly, leading to the desired C1-alkynylated THIQs **4b-4f** in good to excellent yields. The results indicated that the electronic effect of substituents on the benzene ring has limited influence on this heterogeneous copper-catalyzed three-component coupling reaction. It is noteworthy that, for 4-methoxy-benzaldehyde with a strong electron-donating group, the reaction had to be performed at 90 °C to obtain high yield, while when 4-trifluoromethylbenzaldehyde was used as the substrate, poor regioselectivity was observed and the corresponding *exo*-yne-THIQ was also isolated in 11% yield, probably due to the slow isomerization of the *in situ* generated iminium. The reactions of sterically hindered aromatic aldehydes such as 2-methylbenzaldehyde and 2-bromobenzaldehyde also proceeded smoothly to give the desired products **4g** and **4h** in high yields. In addition to aromatic aldehydes, bulky 1-naphthaldehyde and a heterocyclic aldehyde were also applicable under the optimized reaction conditions to afford the corresponding products **4i** and **4j** in 87% and 75% yields, respectively. An aliphatic aldehyde such as cyclopropanecarbox-aldehyde can be used in this three-component coupling reaction, but the target product **4k** was obtained in only 58% yield due to poor regioselectivity.

Table 2 Scope of aldehydes in heterogeneous copper-catalyzed C1-alkynylation of THIQ.[a,b]

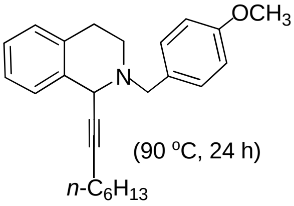




4a, 90% yield

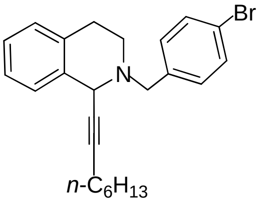


4b, 93% yield

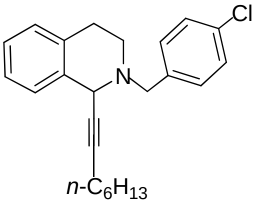


(90 °C, 24 h)

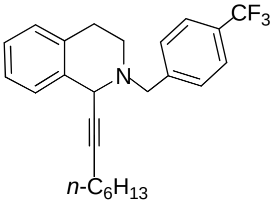
4c, 88% yield



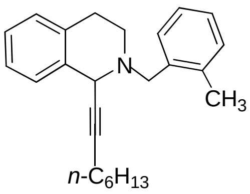
4d, 91% yield



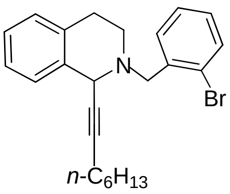
4e, 90% yield



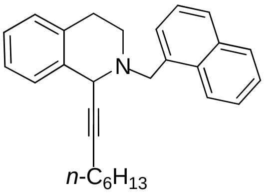
4f, 78% yield



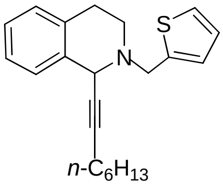
4g, 85% yield



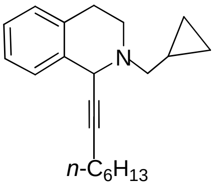
4h, 88% yield



4i, 87% yield



4j, 75% yield



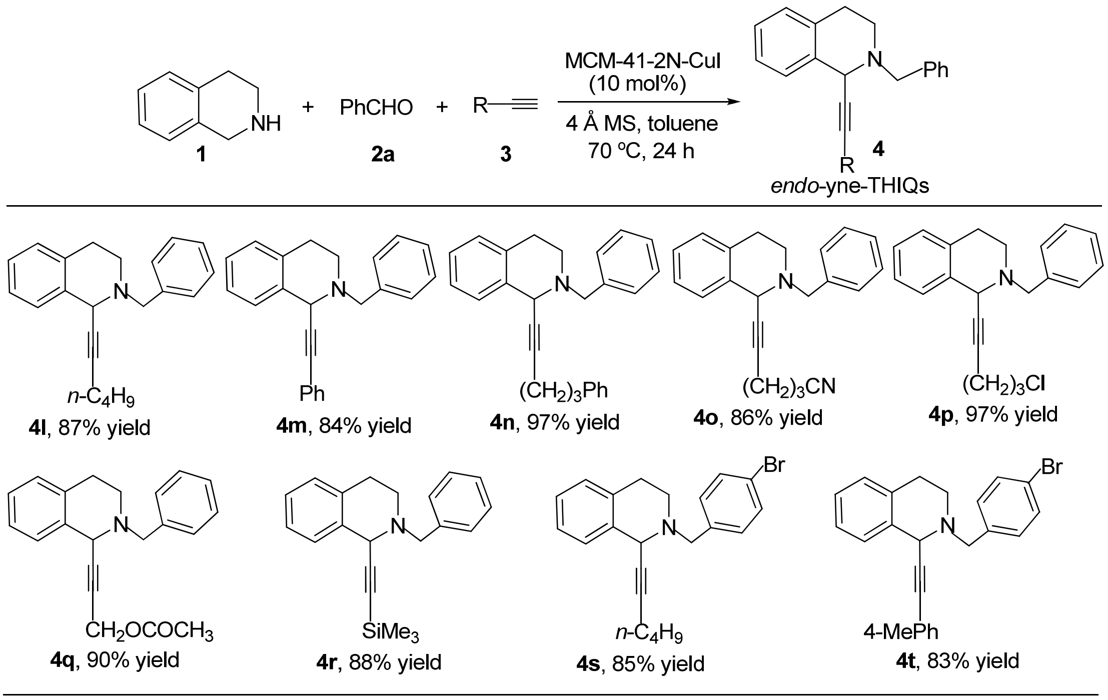
4k, 58% yield

[a] Reaction was performed with **1** (0.5 mmol), **2** (0.5 mmol), **3a** (0.5 mmol), 4 Å MS (150 mg), copper catalyst (0.05 mmol) in toluene (2 mL) at 70 °C under Ar for 24 h. [b] Isolated yield.

Encouraged by the above results, we next studied the scope of terminal alkynes by using THIQ and benzaldehyde as the fixed partners and the results are listed in Table 3. When the standard substrate 1-octyne was changed to 1-hexyne, the reaction still worked well to afford the desired product **4l** in high yield. The reaction of aromatic alkynes such as phenylacetylene also gave the corresponding product **4m** in 84% yield. Aliphatic alkynes with different functional groups such as phenyl, cyano, chloro, and ester at the terminal position can participate in the C1-alkynylation reaction effectively, generating the corresponding *endo*-yne-THIQs **4n-4q** in excellent yields with high regioselectivity. In order to prepare a useful terminal alkyne-type product, trimethylsilylacetylene was used as alkyne partner and the desired *endo*-yne-THIQ **4r** was obtained exclusively in 88% yield. In addition, the reactions of THIQ with

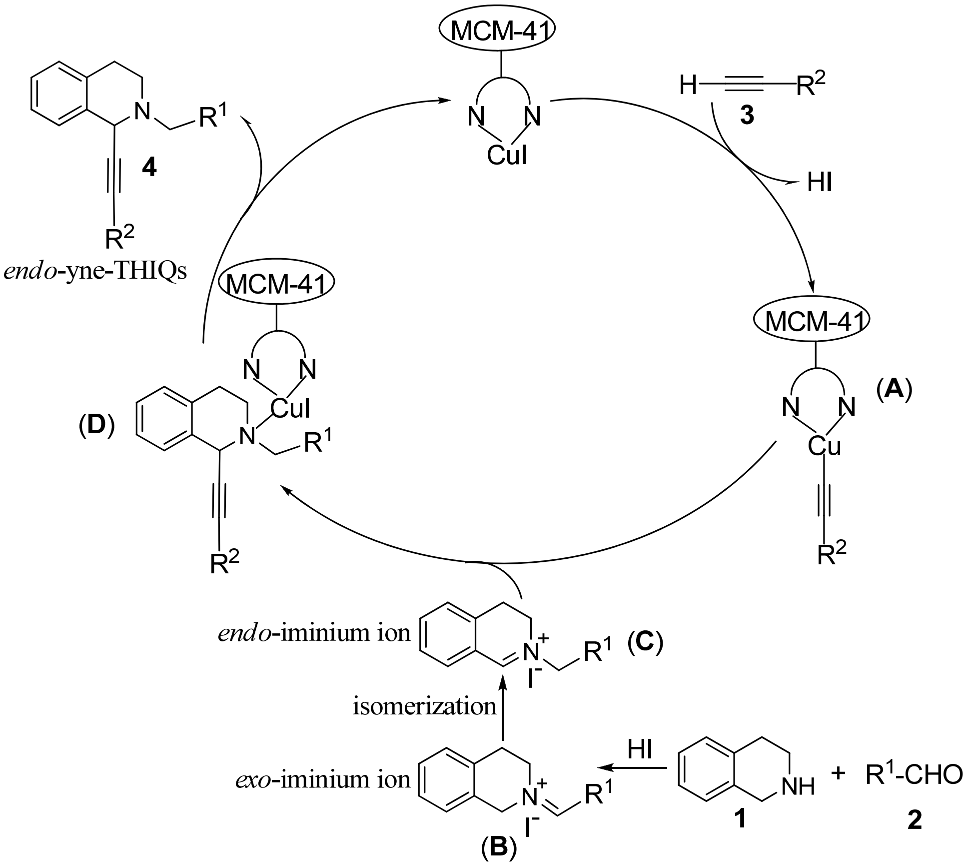
4-bromobenzaldehyde and various alkynes also performed smoothly to give the corresponding products **4s** and **4t** in high yields.

Table 3 Scope of 1-alkynes in heterogeneous copper-catalyzed C1-alkynylation of THIQ.[a,b]



[a] Reaction was performed with **1** (0.5 mmol), **2a** (0.5 mmol), **3** (0.5 mmol), 4 Å MS (150 mg), copper catalyst (0.05 mmol) in toluene (2 mL) at 70 °C under Ar for 24 h. [b] Isolated yield.

To verify whether the observed catalysis was due to the heterogeneous MCM-41-2N-CuI or to a leached copper species in solution, we performed the hot filtration test.[25] We focused on the three-component coupling reaction of tetrahydroisoquinoline (THIQ), benzaldehyde and 1-octyne. After completion of 30% of the reaction the liquid phase was collected by filtration of the reaction solution at the reaction temperature (70 °C). If copper was leaching from the solid surface during the reaction, the liquid phase should contain copper. ICP analysis of the liquid phase indicated that any detectable copper was absent in the reaction mixture. Simultaneously the coupling reaction did not proceed further after the filtration of MCM-41-2N-CuI from the batch reactor at 70 ºC. It was further noted that copper was also not detected in the liquid phase after the completion of reaction. These results suggest that the Cu is not being leached out from the solid surface of the catalyst during the reaction.

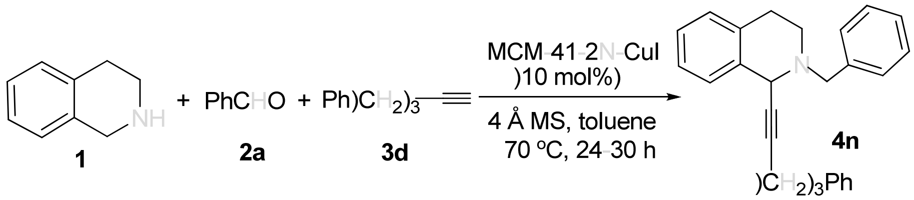


Scheme 3. Possible mechanism for heterogeneous copper-catalyzed three-component coupling reaction.

A plausible mechanism for heterogeneous copper-catalyzed three-component coupling reaction of tetrahydroisoquinolines (**1**), aldehydes (**2**) and terminal alkynes (**3**) is illustrated in Scheme 3. First, the reaction of MCM-41-2N-CuI with terminal alkyne (**3**) with liberation of HI generates an MCM-41-immobilized copper acetylide intermediate (**A**). In the presence of HI and 4 Å molecular sieves, tetrahydroisoquinoline (**1**) undergoes a condensation reaction with aldehyde (**2**) to afford an *exo*-iminium ion (**B**), which then isomerizes into an *endo*-iminium ion (**C**). The latter reacts with the MCM-41-immobilized copper acetylide intermediate (**A**) to form a coordinatively saturated intermediate (**D**). Finally, the newly generated intermediate (**D**) dissociates a nitrogen ligand to give the desired *endo*-yne-THIQ (**4**) and regenerate the MCM-41-2N-CuI complex.

For a heterogeneous transition-metal catalyst, it is important to know its ease of separation, recoverability and reusability. We next investigated the recyclability of the MCM-41-2N-CuI by using the three-component coupling reaction of THIQ (0.5 mmol) with benzaldehyde (0.5 mmol) and 5-phenyl-1-pentyne (0.5 mmol) in toluene (2 mL) in the presence of MCM-41-2N-CuI (0.05 mmol) and 4 Å MS (150 mg) at 70 ºC under argon. Each time, after completion of the reaction, the catalyst and 4 Å MS were recovered by simple filtration and then washed thoroughly with EtOAc and EtOH. After being separated from 4 Å MS (strip form), the recovered catalyst was dried under vacuum at 100 ºC for 3 h. This used catalyst was re-employed in ten successive cycles under identical conditions and the results are summarized in Table 4. It was seen that for the fresh catalyst and 2-6 cycles the reaction was completed within 24 h, but for the other 7-10 cycles the desired conversion was achieved within 26-30 h. The kinetic curves for the 1st to the 10th cycles are presented in Figure 1. It was obvious that the initial rates of 2-6 cycles were almost as the same as that of the 1st cycle, but the initial rates of 7-10 cycles were slightly lower than that of the 1st cycle and decreased gradually with the increase in reused times due to the loss of the catalyst by filtration.

Table 4 Three-component coupling reaction of THIQ with benzaldehyde and 5-phenyl-1-pentyne catalyzed by the recycled catalyst.[a]



Cycle	Time (h)	Yield (%)[b]	Cycle	Time (h)	Yield (%)[b]
1	24	97	2	24	96
3	24	96	4	24	97
5	24	96	6	24	95
7	26	95	8	28	96
9	28	95	10	30	95

[a] Reaction was carried out with THIQ (0.5 mmol), benzaldehyde (0.5 mmol), 5-phenyl-1-pentyne (0.5 mmol), MCM-41-2N-CuI (0.05 mmol), 4 Å MS (150 mg), toluene (2.0 mL) at 70 °C under Ar.

[b] Isolated yield.

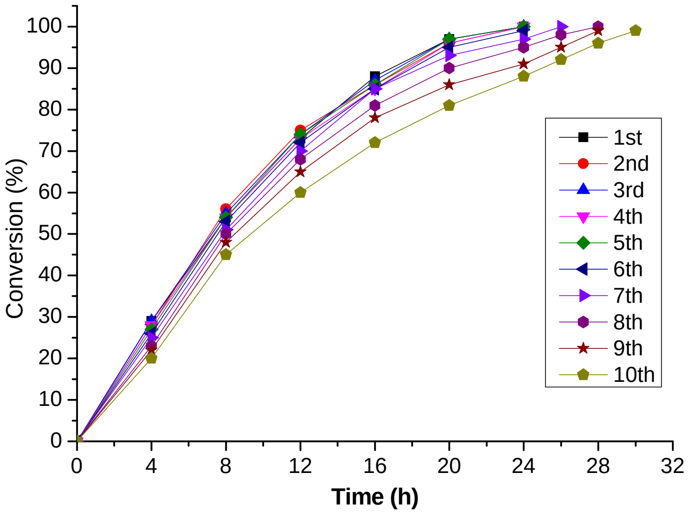


Figure 1 Kinetic curves of the A^3 coupling reaction for the 1st to the 10th cycles

Reaction conditions: THIQ (0.5 mmol), benzaldehyde (0.5 mmol), 5-phenyl-1-pentyne (0.5 mmol), MCM-41-2N-CuI (0.05 mmol), 4 Å MS (150 mg), toluene (2.0 mL) at 70 °C under Ar. Conversion of THIQ was based on GC analysis.

To ascertain the structural integrity of the recycled catalyst, we performed pore size measurements of the fresh MCM-41-2N-CuI and the recovered MCM-41-2N-CuI catalyst after ten cycles and the results are listed in Table 5. As shown in Table 5, the surface area and pore volume of the recycled catalyst decreased slightly compared to those of the fresh one, indicating that the ordered mesoporous structure of the catalyst was maintained upon ten runs of reaction. The high stability and excellent reusability of the catalyst should result from the chelating action of bidentate 2-aminoethylamino ligand on copper and the mesoporous structure of the MCM-41 support. The result is important from industrial and environmental points of view.

Table 5 Textural parameters of the catalytic materials

Materials	Surface area [a] (m^2/g)	Pore volume [b] (cm^3/g)	Diameter [c] (nm)
MCM-41	901.6	0.81	2.7
MCM-41-2N	637.4	0.48	2.1
MCM-41-2N-CuI	576.9	0.44	2.0
MCM-41-2N-CuI (used)	567.7	0.42	2.0

[a] BET surface area; [b] Single point total pore volume; [c] Pore diameter according to the maximum of the BJH pore size distribution.

Conclusions

In summary, we have successfully developed a novel, practical and environmentally friendly method for the synthesis of C1-alkynylated THIQ derivatives through the three-component coupling reaction of THIQ, aldehydes and 1-alkynes by using an 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper(I) complex [MCM-41-2N-CuI] as catalyst. This heterogeneous catalyst can be easily prepared by a simple two-step procedure from commercially available and inexpensive reagents and exhibits high catalytic activity and regioselectivity. The reactions generated a variety of C1-alkynylated THIQ derivatives in good to excellent yields and were applicable to a wide range of 1-alkynes and various aldehydes. In addition, this novel methodology offers the competitiveness of recyclability of the catalyst without any loss of activity, and the catalyst can be readily recovered by a simple filtration of the reaction solution and recycled for at least 10 times, thus making this procedure environmentally more acceptable.

Experimental

All chemicals were reagent grade and used as purchased. All solvents were dried and distilled before use. The products were purified by flash chromatography on silica gel. Mixture of EtOAc and hexane was generally used as eluent. ^{1}H NMR spectra were recoded on a Bruker Avance 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$ as solvent. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 MHz spectrometer in $CDCl_3$ as solvent. Copper content was determined with inductively coupled plasma atom emission Atomscan16 (ICP-AES, TJA Corporation). Microanalyses were measured by using a Yanaco MT-3 CHN microelemental analyzer. GC analysis was performed on an Agilent HP-5890 instrument with an FID detector and an HP-5 capillary column with argon as the carrier gas. The BET surface area and pore analysis were performed on ASAP2010 (micromeritics) by N_2 physical adsorption-desorption at 77.4 K.

Preparation of 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper complexes [MCM-41-2N-CuX(CuX_2)][23]

A solution of 1.54 g of 3-(2-aminoethylamino)propyltrimethoxysilane in 18 mL of dry chloroform was added to a suspension of 2.2 g of the MCM-41 in 180 mL of dry toluene. The mixture was stirred for 24 h at 100 °C. Then the solid was filtered and washed by $CHCl_3$ (2 × 20 mL), and dried in vacuum at 160 °C for 5 h. The dried white solid was then soaked in a solution of 3.1 g of Me_3SiCl in 100 mL of dry toluene at room temperature under stirring for 24 h. Then the solid was filtered, washed with acetone (3 × 20 mL) and diethyl ether (3 × 20 mL), and dried in vacuum at 120 °C for 5 h to obtain 3.49 g of hybrid material MCM-41-2N. The nitrogen content was found to be 1.84 mmol g^{-1} by elemental analysis.

In a small Schlenk tube, 1.0 g of the above-functionalized MCM-41 (MCM-41-2N) was mixed with CuI (96 mg, 0.50 mmol) in 10 mL of dry DMF. The mixture was stirred at room temperature for 7 h under an argon atmosphere. The solid product was filtered by suction, washed with DMF and acetone and dried at 40 °C/26.7 Pa under Ar for 5 h to give 1.053 g of a pale blue copper complex (MCM-41-2N-CuI). The copper content was found to be 0.45 mmol g^{-1}. The other supported copper complexes such as MCM-41-2N-CuCl, MCM-41-2N-CuBr, MCM-41-2N-CuCN, MCM-41-2N-CuOTf, MCM-41-2N-$CuBF_4$, MCM-41-2N-$Cu(OAc)_2$ and MCM-41-2N-$CuBr_2$ were also obtained by reactions of 1.0 g of MCM-41-2N with various copper salts (0.50 mmol) in a similar manner, and the copper contents were determined to be 0.46 mmol g^{-1}, 0.43 mmol g^{-1}, 0.47 mmol g^{-1}, 0.42 mmol g^{-1}, 0.44 mmol g^{-1}, 0.49 mmol g^{-1} and

0.45 mmol g^{-1}, respectively.

General procedure for the synthesis of C1-alkynylated THIQs 4a-4t by heterogeneous copper-catalyzed three-component coupling reaction of THIQ with aldehydes and 1-alkynes:

A reaction mixture of THIQ (0.5 mmol), aldehyde (0.5 mmol), alkyne (0.5 mmol), newly activated 4 Å molecular sieves (150 mg), and MCM-41-2N-CuI (111 mg, 0.05 mmol) in toluene (2 mL) was stirred at 70-90 °C under Ar for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and filtered. The MCM-41-2N-CuI complex was washed with ethyl acetate (2 × 5 mL), ethanol (2 × 5 mL), and dried under reduced pressure at 100 °C for 3 h and reused in the next run. The combined filtrate was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel to provide the corresponding *endo*-yne-THIQ product.

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Graphical Abstract

A highly efficient heterogeneous copper-catalyzed three-component coupling of tetrahydroisoquinolines, aldehydes and 1-alkynes

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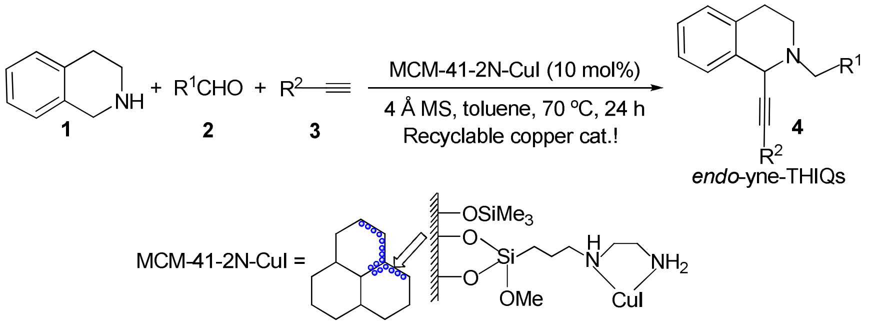

A highly efficient heterogeneous copper-catalyzed three-component coupling of tetrahydroisoquinolines, aldehydes and 1-alkynes has been described.