



Chitosan-supported copper as an efficient and recyclable heterogeneous catalyst for A^3 /decarboxylative A^3 -coupling reaction

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ABSTRACT

Chitosan-supported copper (chit@copper) based heterogeneous catalysts have been explored for A^3 -coupling and decarboxylative A^3 -coupling. The developed protocol employs low catalyst loading, solventless condition and easy work-up for the synthesis of diversely substituted propargylamines. More importantly, the catalyst could be recovered and reused without any significant loss in the activity. This offer huge advantages as recyclability issues are rarely addressed in decarboxylative A^3 -coupling. Leaching studies were carried out using AAS and ICPMS analysis. It is envisaged that chit@copper catalysts can have potential applications in terms of efficiency and recyclability in the emerging area of decarboxylative C–H bond activation/functionalization strategies.

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Environmental degradation is one of the major concerns¹ of environmentalists and political discourse at the international level. The toxic waste generated by the chemical industries is one of the major threats to human, animals and plant lives on the earth. Novel reagents, solvent free synthesis² and recyclable catalytic systems³ are being developed to minimize the waste in chemical synthesis. From the last few years, heterogeneous catalysis^{4,5} has been proved to be an effective strategy to improve the efficiency and recyclability of the catalysts. In recent years, abundantly available and renewable biopolymers such as starch, cellulose, chitin, chitosan etc., have received a phenomenal attention for their use as a support for metals and their application in heterogeneous catalysis.^{6–10}

Chitosan,⁸ an amino-polysaccharide, is the second most abundant biopolymer after cellulose. This biodegradable polymer is insoluble in most of the organic solvents as well as in water and can act as a suitable material for the heterogeneous catalysis.^{11,12} The presence of free amino and hydroxyl groups on chitosan enables it to coordinate with different metal atoms/ions and make it an attractive polymeric support for the immobilization of metal catalysts such as Pd,¹³ Rh,¹⁴ Cu,¹⁵ Ti,¹⁶ Ru,¹⁷ etc. Furthermore, chitosan based catalysts exhibit high thermal stability and can be used in various organic transformations. Recently, Zhang and

co-workers have reported chit@Cu(OAc)₂ as a highly active and recoverable heterogeneous catalyst for the C–S cross-coupling reaction which has led to the green synthesis of antiulcer drug zolimidine.¹⁸ Similarly, chit@CuSO₄ as a heterogeneous catalyst has been employed for the azide-alkyne cycloaddition and for the synthesis of 1,2,3-triazoles using aryl boronic acids.¹⁵

The transition metal-catalyzed three-component coupling of an aldehyde, amine and alkyne (A^3 -coupling) represents an important strategy for the synthesis of diversely substituted propargylamines in an atom economic way.^{19–22} Similarly, decarboxylative A^3 -coupling (coupling of aldehydes, amines and alkynyl carboxylic acids) is a useful and challenging transformation wherein alkynyl carboxylic acids act as economical and stable surrogate for polymerization prone alkynes *via* in situ decarboxylation.^{23–26} There are only few protocols for decarboxylative A^3 -coupling which mainly focus on substrate scope without addressing the recyclability aspect of the catalyst. Thus, development of efficient and recyclable heterogeneous catalytic system in such coupling is an important objective as generation of huge amount of metal waste is incongruous to the principles of Green Chemistry. This in particular is highly desired during synthesis of drug like molecules where even trapping of traces of metal impurity in the final product could be potentially harmful.

Following our research interest on the development of environmentally friendly methodologies,^{27–29} we herein report chitosan-supported copper(I) as an efficient recyclable heterogeneous catalyst for A^3 -coupling reaction. The versatility of developed

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chit@Cu(I) catalytic system was successfully extended towards decarboxylative A^3 -coupling. To the best of our knowledge this is the first report wherein recyclable chitosan-supported copper catalyst has been reported for the decarboxylative A^3 -coupling.

Results and discussion

In A^3 -coupling, mechanistically, aldehyde and amine react to generate imine/iminium ion, followed by nucleophilic addition of alkyne (in situ generated metal-alkyne complex).¹⁹ Recently, the research group of Dekamin¹² has demonstrated that OH and NH_2 group on biopolymer chitosan facilitate the imine formation from corresponding aldehyde and amine *via* hydrogen bonding network. These findings and mechanistic rationale of A^3 -coupling incited us to explore the chitosan-supported metal catalysts for this reaction. Various chitosan-supported copper catalysts (chit@CuI, chit@CuBr, chit@Cu(OAc)₂ and chit@CuSO₄) were prepared.¹⁸ These catalysts were analysed by FT-IR, FE-SEM-EDS, TGA, ICP-MS and AAS spectroscopy. For instance, the amount of Cu content of freshly prepared chit@CuI catalyst, as measured by ICPMS and AAS was found to be 2 wt%. FT-IR spectra of chitosan showed characteristic overlapping absorption bands of O–H and N–H stretching vibrations around 3429 cm^{-1} which became a bit sharper and stronger in case of chit@CuI catalyst with a little shift in the position of other characteristics bands (See; SI). FE-SEM analysis of chit@CuI catalyst clearly showed the morphological changes on the surface of chit@CuI catalyst when compared with pure chitosan polymer (Fig. 1a and b). The FE-SEM-EDS analysis clearly illustrate the presence of copper and iodine in the chitosan supported catalyst (Fig. 1c).

FE-SEM-EDS elemental maps were recorded at a selected region of chit@CuI catalyst which clearly represent the dispersity of copper on the surface of chitosan (Fig. 2).

TGA was used to determine the thermal stability of chitosan and chit@CuI catalyst (See; SI). Two well defined signals were obtained at heating rate of 10 °C/min. The first signal at $T < 100$ °C is connected to loss of water which is loosely bound on chitosan surface whereas second signal (254–580 °C) represents 60.7% weight loss due to the release of volatile components by the thermal degradation of chitosan.

To evaluate the efficacy of the synthesized catalysts (Table 1), a model reaction employing 3-chlorobenzaldehyde (**1a**), morpholine (**2a**) and phenylacetylene (**3a**) as coupling partners was conducted. Initially, it was planned to check the ability of chitosan@copper catalysts for this reaction using benign solvents such as water or ionic liquids. The screening of various chitosan@copper catalysts (100 mg per 0.77 mmol of **1a**) was carried out in water (2 mL) at 100 °C (Table 1, entries 1–4), wherein chit@CuI provided **4a** in 17% yield (entry 3). Use of chit@CuI catalyst along with ionic liquid [bmim]Br increased the yield of **4a** up to 42% (entry 5). However,

ionic liquid [bmim]OH could provide **4a** only in 29% yield (entry 6). Interestingly, reaction under solventless conditions dramatically enhanced the product yield (**4a**, 72%, entry 7). Further, the catalyst amount in the reaction was optimized (entries 8–11) and it was observed that the reaction proceeded efficiently when the catalyst amount was reduced from 100 mg to 10 mg (**4a**, 92%, entry 10). Further, when the reaction temperature was increased from 100 °C to 140 °C the reaction completes within 45 min using 10 mg of the catalyst (entry 13, **4a**, 93%). As expected, no product could be detected when A^3 reaction was performed with chitosan alone (entry 15). The reaction was also conducted under microwave irradiations and a significant reduction in the reaction time was observed (15 min) while the product **4a** was obtained in comparative yield (90%, entry 14). So, the final optimized conditions for the reaction were **1a** (0.77 mmol), **2a** (0.85 mmol) and **3a** (1.00 mmol), chit@CuI (10 mg, 0.04 mmol%) at 140 °C under nitrogen atmosphere. Use of 1:1:1 of **1a**:**2a**:**3a** under similar reaction condition, provided comparatively lower yield of the product. Here it is important to mention that while conducting the reaction under N_2 atmosphere (entries 1–15), we haven't observed the formation of any homocoupling product of alkyne (i.e., diphenylbutadiyne). However, when A^3 -coupling was performed under air, a small amount of homocoupling product was detected (<4% yield, GC–MS) along with desired **4a** in 87% yield (entry 16).

The scopes and limitations of the developed reaction conditions (Table 1, entry 13) were ascertained using a variety of optionally substituted aldehydes, amines and alkynes as coupling partners (Table 2). The chit@CuI catalyst was found compatible with aliphatic as well as aromatic benzaldehydes (irrespective of *o,m,p*-position of substituents) bearing electron-donating (EDG's) or electron-withdrawing groups (EWG's). However, reaction of benzaldehyde containing strong EWG, NO_2 was found slow and corresponding product could be isolated in comparatively lower yield³⁰ (**4e**, 58%) along with unreacted starting material and unidentified side products. On the other hand, hydroxy substituent on benzaldehyde **4f** and sterically hindered aromatic aldehydes **4g** were well tolerated. In comparison to aromatic aldehydes, the reaction of an aliphatic aldehyde along with morpholine and phenylacetylene (**4h**, 76%) provided A^3 product in comparatively lower yield. The catalytic system was found compatible with different types of cyclic secondary amines such as morpholine, piperidine, *N*-methyl/phenyl piperazine and acyclic secondary amine such as *N*-methylbenzyl amine. However, reaction with primary amines (**4q**, **4r** and **4s**) as one of the A^3 component could not proceed under present reaction condition. Notably, aryl alkyne provided comparatively better yield than aliphatic alkynes (**4u**). No product could be isolated using trimethyl silylacetylene as a coupling partner (**4v**). The reaction was also conducted using acetophenone (replacing aldehyde with ketone), amine and phenylacetylene but no product (**4w**) formation was observed.

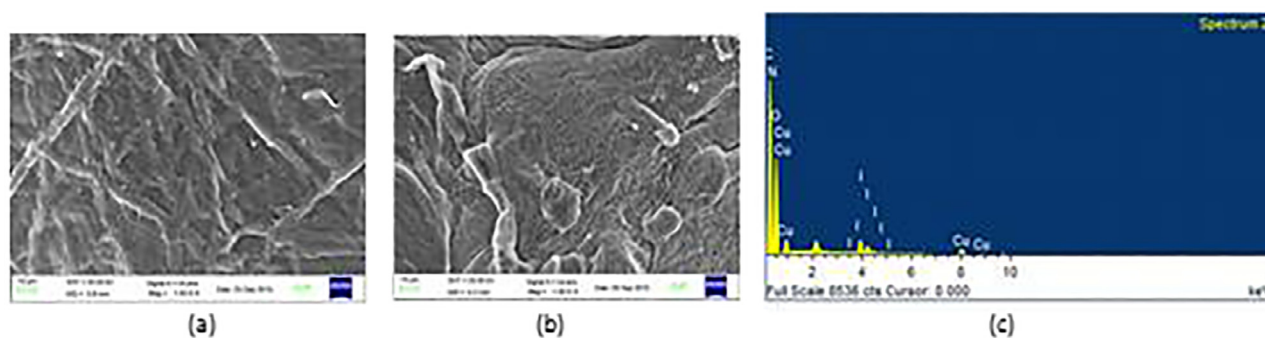


Fig. 1. (a) FE-SEM image of chitosan, (b) FE-SEM image of chit@CuI catalyst, (c) FE-SEM-EDS spectrum of chit@CuI catalyst.

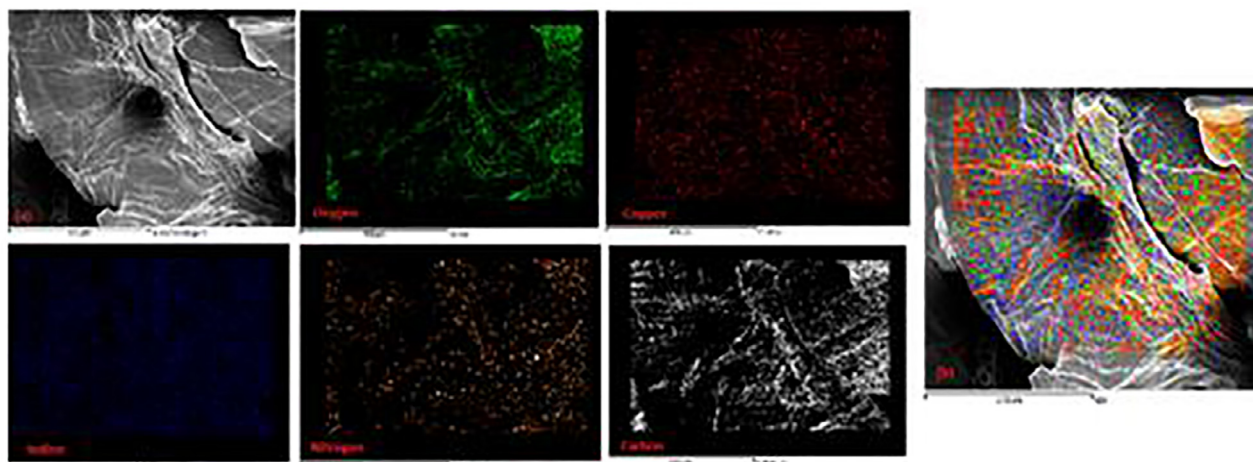


Fig. 2. (a) FE-SEM image of chit@CuI catalyst, selected area elemental maps showing the presence of O, Cu, I, N and C, (b) FE-SEM image of the selected area depicting the overall elemental maps.

Table 1
Screening of chitosan@copper catalysts for A³-coupling.^a

Entry	Catalyst	Catalyst	Time (h)/Temp (°C)	Solvent	Yield ^b 4a (%)
1	Chit@CuBr	100 mg	3/100	H ₂ O	13
2	Chit@CuSO ₄	100 mg	3/100	H ₂ O	8
3	Chit@CuI	100 mg	3/100	H ₂ O	17
4	Chit@Cu(OAc) ₂	100 mg	3/100	H ₂ O	<5
5	Chit@CuI	100 mg	3/100	[bmim]Br ^c	42
6	Chit@CuI	100 mg	3/100	[bmim]OH ^d	29
7	Chit@CuI	100 mg	3/100	- ^e	72
8	Chit@CuI	50 mg	3/100	-	83
9	Chit@CuI	30 mg	3/100	-	91
10	Chit@CuI	10 mg	3/100	-	92
11	Chit@CuI	5 mg	3/100	-	84
12	Chit@CuI	10 mg	2/120	-	93
13	Chit@CuI	10 mg	0.75/140	-	93
14 ^f	Chit@CuI	10 mg	0.25/140	-	90
15 ^g	Chitosan	10 mg	24/140	-	nd
16 ^h	Chit@CuI	10 mg	0.75/140	-	87

^aGeneral condition: **1a** (0.77 mmol), **2a** (0.85 mmol), **3a** (1.00 mmol), chitosan@copper catalyst (5–100 mg) at 100–140 °C under N₂ atmosphere.

^bYield of isolated product after column chromatography.

^cIonic liquid, 1-butyl-3-methylimidazolium bromide.

^dIonic liquid, 1-butyl-3-methylimidazolium hydroxide.

^eWithout any solvent.

^fMicrowave irradiation at 250 W, 140 °C.

^gUsing chitosan support only i.e., without copper loading, nd: not detected.

^hIn air (without N₂ atm.).

Recyclability of chit@CuI in A³-coupling

Reusability and recyclability of the transition metal catalyst is highly desired, from both economical and environmental point of view. To assess the reusability of the catalyst, we performed the A³-coupling reaction under the optimized conditions (Table 1, entry 13). After the completion of reaction, the product was extracted with diethyl ether and the catalyst was recovered, dried on rotary evaporator and reused for next cycle.³¹ Using the above

procedure after each cycle, the catalyst was reused efficiently for six consecutive cycles to afford **4a** in 93%, 92%, 88%, 85%, 83% and 78% yields (Fig. 3).

Chit@CuI catalyst in decarboxylative A³-coupling and its recyclability

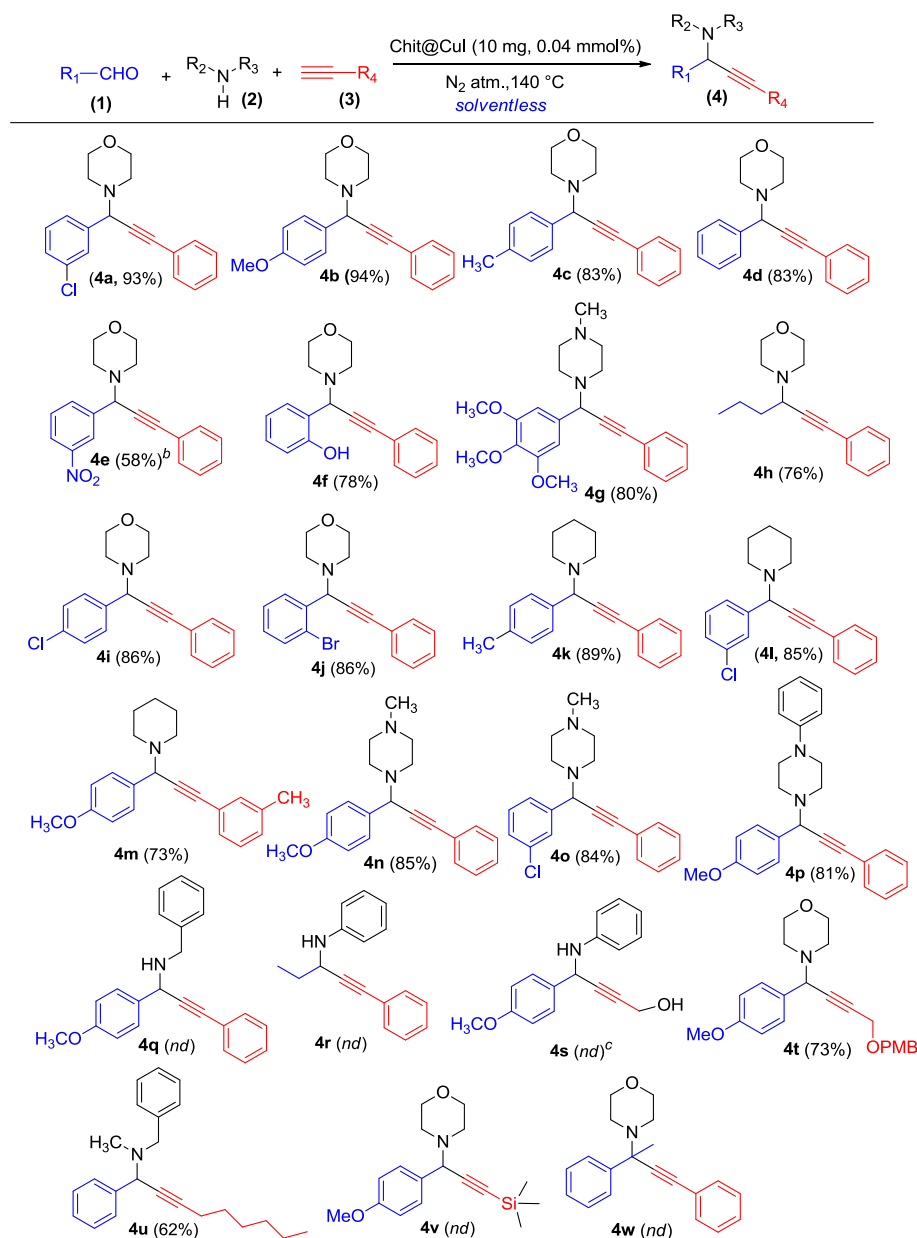
To check the efficacy and recyclability of our chit@CuI catalyst in decarboxylative A³-coupling, a mixture of **1a**, **2a** and phenylpropionic acid (**5a**) was heated at 140 °C (using 10 mg catalyst) and corresponding propargylamine **4a** was obtained in 86% yield (Scheme 1). Reuse of this catalyst for the next cycle³¹ produced the desired product nearly in same yield (85%). The catalyst could be recycled and reused successfully up to four cycles (yield ranging from 86% to 78%). In the 5th cycle **4a** was obtained in 65% yield (Scheme 1). Here it is worth to mention that a majority of the protocols reported for decarboxylative A³-coupling mainly focus on substrate scope without addressing the recyclability aspect of the catalyst.

Also, there is no need for N₂ atmosphere and the reaction proceeded well in air without formation of any homocoupling product, diphenylbutadiyne. Mechanistically, it is presumed that incipient chit@Cu-alkyne complex **B** (formed in situ via chit@CuI assisted decarboxylation of phenylpropionic acid) undergoes addition to the iminium ion **A** (formation assisted by OH and NH₂ group of chitosan¹²) resulting in the formation of propargylamines (Scheme 2).^{23–26}

The reaction was successfully extended to other substituted benzaldehydes containing EWG's and EDG's including a heteroaldehyde and an aliphatic aldehyde (Table 3).

Encouraged by above results, we tried to explore the potential of this catalyst for a novel domino oxidative-decarboxylative A³ coupling using benzylalcohol in place of aldehyde (Scheme 3). However, the desired product could be isolated only in 23% yield.

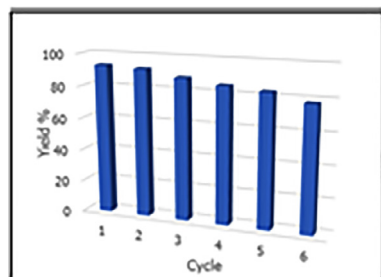
Finally, we carried out the leaching studies of Cu metal from the catalyst in case of A³-coupling as well as in decarboxylative A³-coupling. In A³-coupling, after the completion of 1st, 2nd and 3rd cycle, the quantitative analysis of the recovered catalyst by ICPMS revealed no change in wt% of Cu content. We further analysed the extracted product of the 3rd cycle and no leaching of Cu metal was detected. After 6th cycle, the amount of Cu content as measured by ICPMS in the recovered catalyst was 1.93 wt% as compared to 2 wt% in the freshly prepared chit@CuI catalyst. This confirms that chitosan provides enough binding sites on its surface to minimize deterioration and metal leaching and facilitates its efficient recycling.

Table 2Scope of chit@CuI catalyzed coupling of aldehyde, amine and alkyne under solventless conditions.^a

^aGeneral condition: aldehyde (**1**, 0.77 mmol), amine (**2**, 0.85 mmol), alkyne (**3**, 1.00 mmol), chit@CuI (10 mg) at 140 °C for 45 min under N₂ atmosphere, yield in parenthesis represents the yield of isolated product after column chromatography.

^bHeating at 140 °C for 2 h.

^cInseparable side products obtained, nd: not detected.

**Fig. 3.** Recyclability of chit@CuI catalyst in A³-coupling.

Similarly, in case of decarboxylative A³-coupling, after 1st and 2nd cycle no leaching of the Cu content was observed in the recovered catalyst as well as in the extracted product as determined by ICPMS analysis. However, after the 5th cycle, the amount of Cu content was reduced to 1.8% as compared to 2 wt% in the freshly prepared chit@CuI catalyst. The above results were further confirmed using AAS analysis. Despite negligible metal leaching, the loss in the activity of catalyst (during recycling experiments) may be attributed to the poisoning of the surface site of the catalyst by contact with H₂O and CO₂ (released during A³/decarboxylative A³-coupling).

Although various A³/decarboxylative A³-methodologies using copper based catalytic systems besides expensive metal catalysts

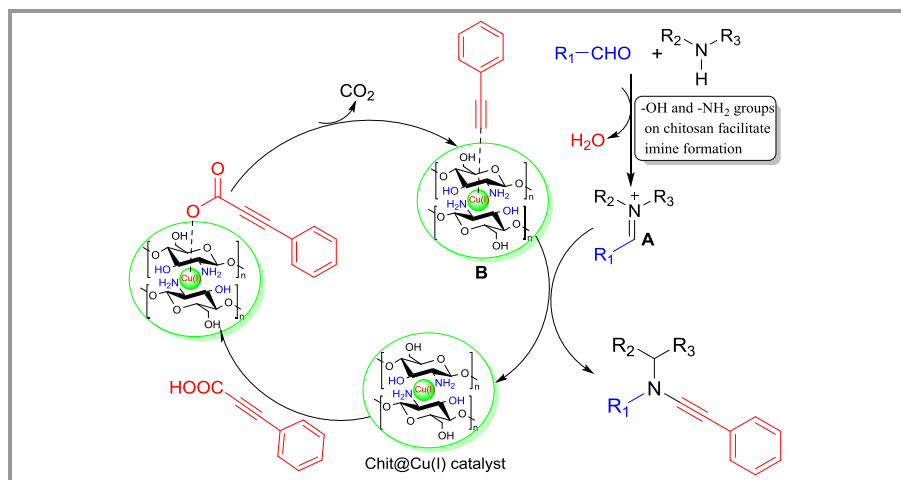
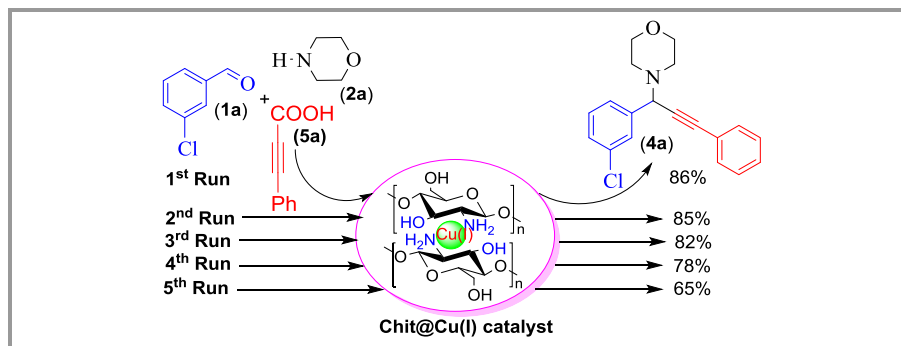
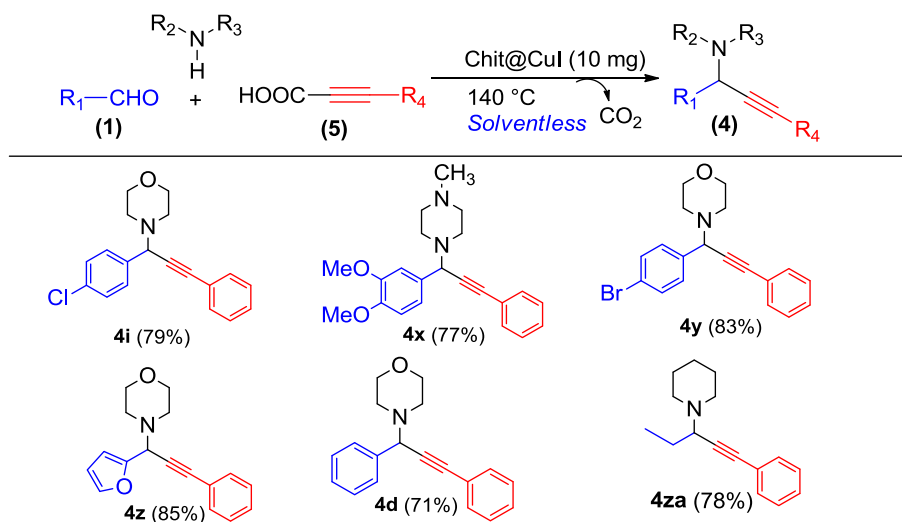


Table 3
Chit@Cu catalyzed decarboxylative A³-coupling.^a

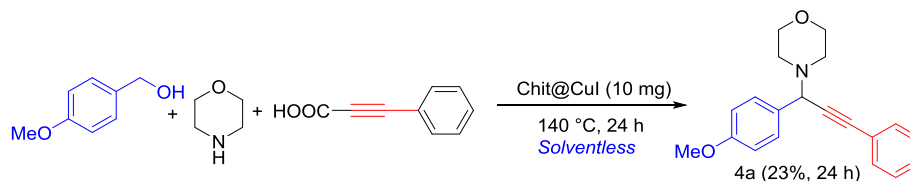


^aGeneral condition: aldehyde (**1**, 0.77 mmol), amine (**2**, 0.85 mmol), phenylpropionic acid (**5**, 1.00 mmol), chit@Cu (10 mg), 140 °C for 45 min.

^bYield in parenthesis represents the yield of isolated product.

of gold and silver have been explored, however, recyclability of these catalysts, particularly in case of decarboxylative A³-coupling has rarely been addressed. Furthermore, easy synthesis of the

catalyst from abundantly available biopolymer besides waste-free synthesis of propargylamines under solventless conditions are some other advantages of our developed protocol.



Scheme 3. Tandem oxidative-decarboxylative A³-coupling.

In conclusion, we have successfully explored the role of chitosan@copper based heterogeneous catalysts for A³-coupling and decarboxylative A³-coupling reaction. The developed methodology provided a green route for the synthesis of diversely substituted propargylamines which are important precursors^{32–35} for various biologically active heterocyclic scaffolds and natural products. Significant features of the developed protocol include (i) low catalyst loading (ii) easy synthesis and recyclability of the catalyst (iii) use of abundantly available and renewable polymeric support (iv) solvent-free synthesis. The developed protocol is the first report on the use of chitosan-supported copper based recyclable catalysts in decarboxylative A³-coupling. The present catalytic system could be a versatile strategy for the development of various other green decarboxylative C–H bond activation/functionalization reactions. Further, evaluation of the synthesized propargylamines for their MAO inhibitor activity is currently under progress.

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A. Supplementary data

Supplementary data (experimental details, ¹H and ¹³C NMR data, NMR spectra of some representative compounds) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tetlet.2018.03.052>.

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- Catalyst recycling: after completion of the reaction between **1a**, **2a** and **3a** (Table 1, entry 13), the crude mixture was extracted with diethyl ether and the chit@CuI catalyst was separated by simple filtration. The catalyst was dried on rotary evaporator at 60 °C for 4 h and then used for the next cycle. Using the same procedure after each cycle, the catalyst could be successfully reused. Similarly, the above method was applied for the recyclability of the catalyst in case of decarboxylative A³-coupling between **1a**, **2a** and **5a** (Scheme 1).
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