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Diastereoselective Synthesis of Propargylamines Catalyzed by Cu-MCM-41

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ABSTRACT

In this work, a rapid, efficient and protecting group free diastereoselective synthesis of propargylamines through a multicomponent coupling reaction between (*S*)-prolinol, phenylacetylene and commercially available aldehydes catalyzed by Cu-MCM-41 in heterogeneous phase is reported. The reactions were carried out under solvent free conditions with good yields and moderate reaction times. In all the cases, catalyst was recovered and reused up to five cycles. Recyclability of the catalyst, low catalyst loading, solvent and protecting group free conditions, and the use of inexpensive catalyst are the key features that provide green aspects to this synthetic protocol.

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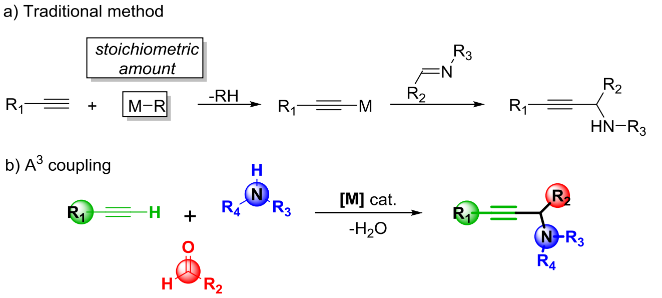
Introduction

Propargylamines are present in several biomolecules[1] and are also important synthetic intermediates for the preparation of many nitrogen-containing compounds.[2] The traditional strategy for the synthesis of propargylamines is the addition of a metal acetylide to an imine group. However, the use of stoichiometric amounts of strong bases for the generation of the organometallic reagent as well as the moisture sensitivity of these reagents, makes sometimes this strategy unattractive. The A^3-coupling approach is a convenient and atom economic method since the direct nucleophilic addition occurs previous C-H activation of the terminal alkynes to the C=N double bond of imine or iminium ion *in situ* from aldehyde and an amine. (Scheme 1).[3]



Scheme 1 Typical strategies for the synthesis of propargylamines.

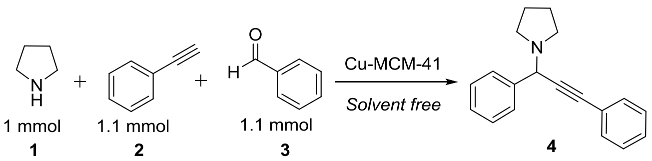
Due to the extensive chemistry associated with these synthons, significant efforts have been devoted to the development of methodologies for their stereoselective preparation.[4] The need for the development of environmentally benign, efficient, economical and green processes in which for example, the catalyst could be recovered and recycled is mandatory.[5] Thus, heterogeneous catalysis has been employed to recover and reuse the catalyst during several reaction cycles. Porous mesostructured silicates type MCM-41 have attracted a great attention in heterogeneous catalysis research since their first synthesis in 1992,[6] because of their ordered porous and easily modifiable large specific surface. However, in order to enhance their weak catalytic ability, they have been modified by doping them with transition metals such as Cu.[7]

Cu-MCM-41[8] has been successfully used as a catalyst in reactions such as: Baeyer-Villiger oxidation of cyclohexanones,[9] synthesis of 5-substituted 1*H*-tetrazoles,[10] likewise for efficient synthesis of propargylamines in three-component coupling of aldehydes, amines and alkynes.[11]

Based on the importance of the propargylamine moiety herein we report a simple and efficient protocol for the addition of reactive acetylides to iminium ions to afford diastereoselective propargylamines using Cu-MCM-41 as catalyst and under solvent-free conditions. The relationship between the catalytic activity and the recyclability of the catalyst was also studied.

Results and Discussion

The Cu-MCM-41 was synthesized according to typical procedure[12] and the percentage of Cu content was estimated (2.87% wt). To evaluate the catalytic activity of Cu-MCM-41, benzaldehyde **3**, pyrrolidine **1**, and phenylacetylene **2** was tested as a model reaction (Scheme 2).



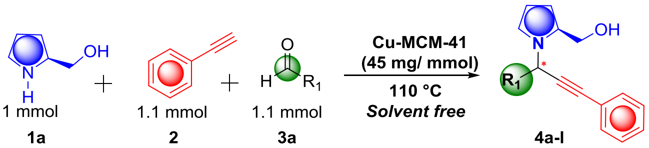
Scheme 2 Cu-MCM-41 catalyzed A^3 coupling.

To optimize, screening of a variety of reaction conditions were studied (Table 1). To our delight, the reaction proceeded successfully in the presence of 45 mg/mmol (2.87% wt of copper) of Cu-MCM-41 solvent-free condition at 110 °C to afford propargylamine **4** in good yield (Table 1, entry 10).

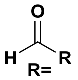
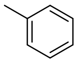
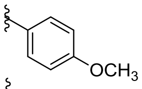
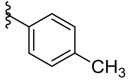
Entry	Catalyst (mg/1 mmol of 1)	Temperature (°C)	Time (h)	Yield (%) of 4
1	10	rt	1-48	0
2	20	rt	1-48	0
3	45	rt	1-48	0
4	20	50	1-48	0
5	45	50	1-48	0
6	20	70	1-48	traces
7	45	85	1-48	10
8	45	90	1-48	20
9	45	100	1-48	60
10	**45**	**110**	**20**	**90**

Table 1 Screening of Cu-MCM-41 catalyst for the synthesis of **4**.

With the optimized reaction conditions, the scope and limitations of the reaction were studied (Scheme 3). A variety of commercial aldehydes (Table 2, entries 1-12) was investigated and pyrrolidine **1** was replaced by (*S*)-prolinol **1a** as a substrate under the heterogenous catalysis. Pleasingly we found this protocol to be very general for different aldehydes in a highly stereoselectively fashion.



Scheme 3 Cu-MCM-41 catalyzed A^3 coupling with (*S*)-prolinol and different aldehydes.

Entry		**Yield** [a]	**Product (d.r.)** [b]
1		90%	**4a** (93:7)
2		85%	**4b** (9:1)
3		88%	**4c** (9:1)

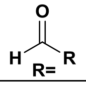
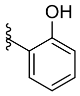
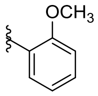
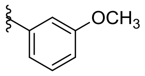
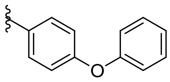
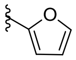
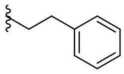
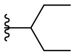
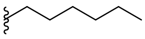
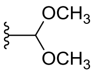
Entry		Yield [a]	Product (d.r.) [b]
4		78%	**4d** (9:1)
5		82%	**4e** (9:1)
6		84%	**4f** (9:1)
7		87%	**4g** (92:8)
8		78%	**4h** (8:1)
9		85%	**4i** (9:1)
10		80%	**4j** (98:2)
11		82%	**4k** (86:14)
12[c]		65%	**4l** (4:1)

Table 2 Screening of Cu-MCM-41 catalyst with several aldehydes for the synthesis of propargylamines **4a-l**.

[a] Isolated yields after flash chromatography. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] glyoxal dimethyl acetal solution 60% wt in H_2O.

As seen in table 2, various aromatic and aliphatic aldehydes were employed. Substituted benzaldehydes bearing at *o*-, *m*-, *p*-positions hydroxy, methyl, methoxy and phenoxy groups, generated the desired products **4a-4g** in satisfactory yields and diastereoselectivities (Table 2, entries 1-7).

The only heterocyclic aldehyde that was evaluated exhibited high reactivity and diastereoselectivity to afford expected product **4h** (entry 8). On the other hand, aliphatic aldehydes such as hydroxycinnamaldehyde, 2-ethylbutyraldehyde and heptanal (entries 9–11) also reacted under the optimized reaction conditions, generating propargylamines **4i**–**4k** in satisfactory yields and diastereoselectivities.

Notably glyoxal dimethyl acetal (60% wt in H_2O) tolerated the reaction conditions (entry 12) furnishing the desired product **4l** in 65% yield, albeit in a modest diastereoselectivity (entry 12). The latter example showcases that, in contrast to classical acetylide generation under strong basic conditions, water does not considerably affect the chemical efficiency of the reaction in our protocol, allowing the preparation of complex propargylamines under mild and under non-inert conditions.

Next, the recyclability of the catalyst was studied (see Supporting Information for details). The recovered catalyst worked well up to four catalytic runs with marginal loss and a decrease in chemical yield of 50% for the synthesis of **4a** after 5 cycles (Figure 1). It should be mentioned that in all cases the diastereoselectivity was conserved.

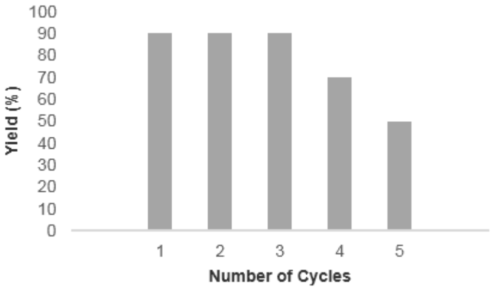
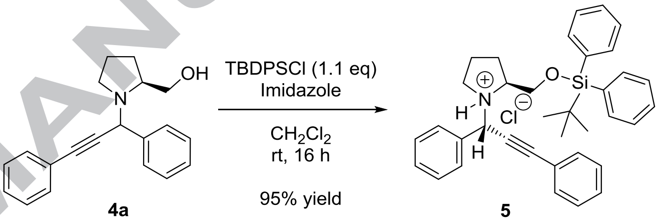


Figure 1 Reuse of Cu-MCM-41 in the synthesis of **4a**.

The recovered catalyst was characterized and shown to retain its morphology intact even though the amount of copper decreased notably from 2.87% wt to 0.71% wt (see Supporting Information). Finally, with the aim of stablish the stereochemistry of the new stereogenic center, we perform different tests for the protection of OH group of **4a**. Fortunately we were pleased when we used the reaction conditions reported by Deslogchamps[13] using TBDPSCl and imidazole (Scheme 4).



Scheme 4

The structure and absolute configuration of **5** was confirmed by a single-crystal X-ray diffraction analysis[14] (Figure 2) which indicates that the newly formed stereocenter possesses the (*S*) absolute configuration. The stereocenter of the other products (**4b-4l**) was tentatively assigned as (*S*) by analogy.

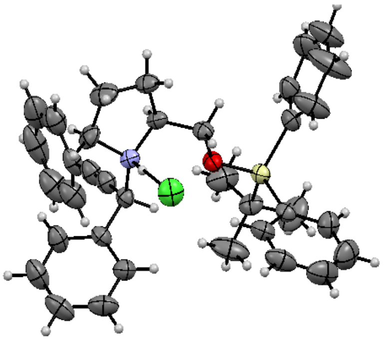
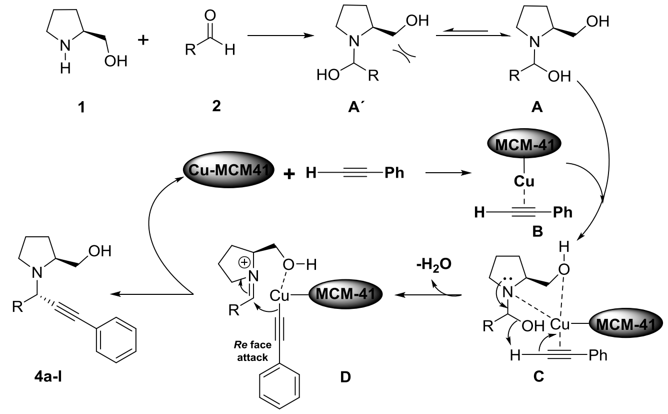


Figure 2 ORTEP drawing of compound **5**.

A plausible mechanism for heterogeneous copper catalyzed three-component coupling reaction is illustrated in Scheme 5.[2d, 2l] First, (*S*)-prolinol **1** reacts with aldehyde **2**, providing the iminium intermediate **A**, an π-metal–alkyne complex **B** might be formed first making the alkyne proton more acidic for further abstraction in **C**. Subsequent attack of an in situ formed copper acetylide **D** resulting in the formation of propargylamines **4a-l** with concomitant regeneration of the metal catalyst. Presumably, the origin of diastereoselectivity may due to coordination of the amino and hydroxyl moieties[4j, 15] in the transition states **C** and **D**.



Scheme 5 Plausible mechanism for diastereoselective synthesis of propargylamines catalyzed by Cu-MCM-41.

Conclusions

We demonstrated that Cu-MCM-41 is an efficient catalyst for the diastereoselective synthesis of propargylamines through a three component coupling between different commercial aldehydes, (*S*)-prolinol, and phenylacetylene via C–H activation. This method offers several advantages including solvent free conditions, good yields, simple work-up, ease for separation, and recycling of the catalyst, as well as a wide tolerance to different functional groups in the aldehyde. Additionally, the catalyst could be readily recovered and reusable up to five times thus making this procedure more environmentally friendly. Further experimental studies are in progress and will be reported soon.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http:xxxx.

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12. The synthesis of Cu-MCM-41 was carried out by an ultrasonic assisted template-ion exchange (TIE) method to insert metal ions without collapsing the mesoporous structure. For experimental details, please see supporting information.
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14. Crystallographic data for the crystal structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 1549206. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).
15. Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P. O. *Org. Lett.* **2012**, *14*, 2932-2935.

Graphical Abstract

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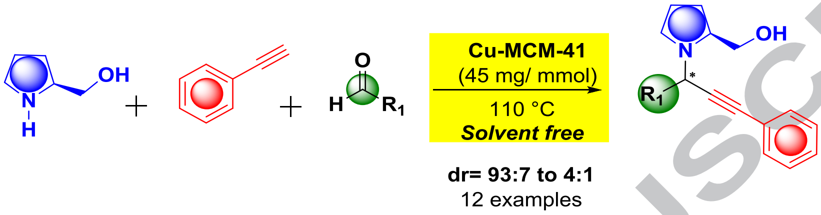

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Highligths

- Diastereoselective synthesis of propargylamines.
- Multicomponent coupling reaction by a simple catalyst in heterogeneous phase.
- The reactions were carried out under solvent free conditions.
- The catalyst was recovered and reused up to five cycles.