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One-Pot Synthesis of Propargylamines Using Ag(I)-Exchanged K10 Montmorillonite Clay as Reusable Catalyst in Water

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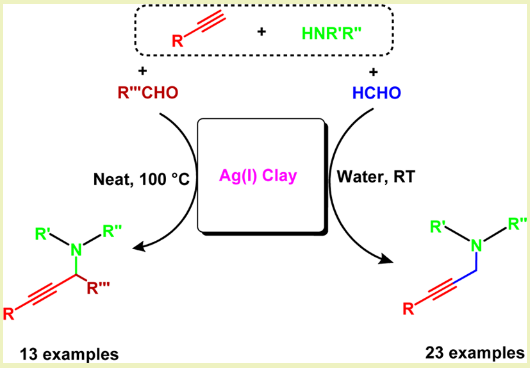
Supporting Information

ABSTRACT: Ag(I)-exchanged K10 montmorillonite clay is found to be an efficient heterogeneous catalyst for the one-pot three-component coupling of terminal alkynes, amines, and aqueous formaldehyde (A^3 coupling) to yield corresponding propargylamines in water. In all the cases, quantitative yields of the desired products are obtained. The catalyst is recovered by filtration and reused several times with only a slight decrease in its catalytic activity. This atom economical methodology does not require an additional co-catalyst or activator, and water is the only byproduct. Interestingly, the reaction can also be performed under solvent-free conditions in the case of aromatic and aliphatic aldehydes, along with formaldehyde, affording propargylamine derivatives in higher yields. A tentative mechanism is also proposed for this transformation.



KEYWORDS: *Propargylamines, Three-component coupling, A^3 coupling, Ag(I)−K10 montmorillonite, Water, Aminomethylation*

INTRODUCTION

Multicomponent reactions are becoming increasingly important as they allow several starting materials to be combined readily in one-pot to form a single compound.[1−3] They deliver less byproducts compared to classical stepwise synthetic routes. Furthermore, in many cases, multicomponent reactions are easy to perform due to the simpler experimental procedures, lower costs, and less time and energy required. The A^3 coupling (aldehyde, alkyne, and amine) is one of the most widely used tools for the synthesis of various propargylamines via C−H bond activation.[4,5] Propargylamines are frequently used as synthetically adaptable key intermediates[6−10] for the production of many nitrogen-containing biologically active compounds such as conformationally restricted peptides, oxotremorine analogues, β-lactams, isosteres, therapeutic drug molecules and natural products,[11] and substituted 1-aryl-3-aminopropynes having antiulceration, sedative, hypnotic, antispasmodic, analgesic, and anti-inflammatory effects.[12] This reaction has been catalyzed by CuI/DMSO,[13] Cu(acac)$_2$,[14] nano In$_2$O$_3$/DABCO,[15] CuCl$_2$/4Å,[16] and CuI/water.[17] Recently, enormous progress has been made in expanding the scope of A^3 coupling by employing various transition metal catalysts such as Ag,[18−22] Au,[23,24] Cu,[25−33] Ir,[34−36] Hg$_2$Cl$_2$,[37] Zr,[38,39] Re,[40] bimetallic systems,[41] In,[42] Fe,[43,44] and Co.[45] However, these catalytic systems suffer from disadvantages such as the need for a stoichiometric amount of catalyst or the catalyst not being able to be recovered and reused. Moreover, the separation of catalyst from the reaction mixture is a tedious task. In order to overcome this problem, catalytically active species have been immobilized to recover and reuse the catalyst and to reduce the overall cost of the process onto various supports such as 12-tungstophosphoric acid,[20] hydroxyapatite,[29] layered double hydroxides,[46] alumina,[47] silica,[48] and zeolites[49,50] as heterogeneous catalysts. Montmorillonites clays are composed of negatively charged layers and an interlayer containing cationic species. The cationic species can be easily replaced by other metal polycations, and these ion-exchanged montmorillonites have great potential as solid acid catalysts.[51−59] Because of their tunable Bronsted and Lewis acidities, both natural and ion-exchanged clays function as efficient catalysts for various organic transformations.[60] Hence, in the present work, we report an environmentally benign and highly efficient three-component A^3 coupling catalyzed by Ag$^{\text{I}}$ exchanged over K10 clay for the preparation of propargylamines via activation of alkyne in water.

RESULTS AND DISCUSSION

Initially, the reaction conditions were optimized using phenylacetylene, aqueous formaldehyde, and diisopropylamine as model substrates, and the observed results are given in Table 1. Blank control experiments showed the absence of product, and 8% yield was observed with K10 clay as the catalyst in water at 12 h (Table 1, entries 1 and 2). On the other hand, silver nitrate as the homogeneous catalyst resulted in 63% yield in water at 8 h (Table 1, entry 3). Moderate yields of propargylamine were observed using Ag$^{\text{I}}$−K10 clay as the

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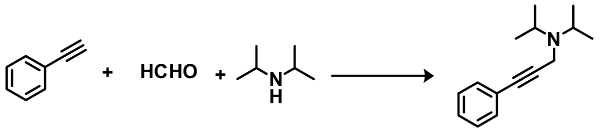
Table 1. Optimization of Reaction Conditions in A^{3} Coupling from Phenylacetylene, Aqueous Formaldehyde, and Diisopropylamine[a]



entry	catalyst	solvent	time (h)	yield (%)[b]
1	none	water	24	–
2	K10	water	12	8
3[c]	$AgNO_3$	water	8	63
4	Ag^{I}–K10	THF	8	41
5	Ag^{I}–K10	ACN	8	48
6	Ag^{I}–K10	toluene	8	54
7	Ag^{I}–K10	1,4-dioxane	8	35
8	Ag^{I}–K10	methanol	8	58
9	Ag^{I}–K10	neat	8	55
10	Ag^{I}–K10	water	2	21
11	Ag^{I}–K10	water	5	55
12[d]	Ag^{I}–K10	water	8	70, 86, 85
13[e]	Ag^{I}–K10	water	12	71, 84, 82
14	Cu^{2+}–K10	water	8	60
15	Al^{3+}–K10	water	8	51
16	Ti^{4+}–K10	water	8	42
17	NaY	water	8	5
18	AgY	water	8	69

[a] Reaction conditions: phenylacetylene (1 mmol), formaldehyde (37% aqueous solution) (0.2 mL), diisopropylamine (1.1 mmol), water (5 mL), and Ag^{I}–K10 (50 mg) at room temperature. [b] Isolated yield and >98% selectivity determined by HPLC. [c] 2.3 mg of $AgNO_3$ used. [d] 20, 50, and 100 mg of catalyst used, respectively. [e] 20, 50, and 100 mg of catalyst used, respectively.

catalyst with various organic solvents (Table 1, entries 4–8). In the absence of solvent, the Ag^{I}–K10 clay catalyst gave 55% yield in 8 h (Table 1, entry 9). In contrast, the propargylamine yield increased gradually in water using Ag^{I}–K10 clay as the catalyst. To our surprise, 86% yield was observed with 50 mg of Ag^{I}–K10 clay in water at 8 h in room temperature (Table 1, entries 10–12). Increasing the catalyst amount to 100 mg, and the reaction time to 12 h showed no further increase in the yield, suggesting that the optimal loading of the catalyst is 50 mg (Table 1, entries 12 and 13). On the other hand, it is interesting to note that the present experimental condition resulted exclusively in the formation of propargylamine using Ag^{I}–K10 clay as the catalyst, and no other byproducts were observed. The catalytic activity of Ag^{I}–K10 clay was compared with other cation-exchanged K10 clays and zeolites, and the observed results are presented in Table 1. For example, Cu^{2+}, Al^{3+}, and Ti^{4+} K10 clays exhibited 60%, 51%, and 42% yields, respectively, after 8 h in water (Table 1, entries 14–16). On the other hand, NaY gave a negligible yield, whereas under the identical conditions AgY showed a 69% yield.

The reusability of Ag^{I}–K10 catalyst was also ascertained in A^{3} coupling under the optimized conditions. After completion of the reaction, the catalyst was recovered by filtration, washed with acetone, and dried at 80 °C for 3 h. The recovered catalyst was used for consecutive runs under identical conditions. It was observed that the catalyst maintained its activity with no significant drop in the yield up to six runs (Table 2).

These interesting results achieved with the Ag^{I}–K10 catalyst for A^{3} coupling in water encouraged us to check the generality of this reaction between aqueous formaldehyde and substituted alkynes/amines, and the observed results are given in Table 3.

Table 2. Reusability of Ag^{I}–K10 in A^{3} Coupling of Phenylacetylene, Aqueous Formaldehyde, and Diisopropylamine[a]

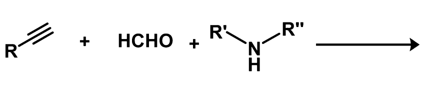
run	1st	2nd	3rd	4th	5th	6th
yield[b] (%)	86	84	83	81	81	80

[a] Reaction conditions: phenylacetylene (1 mmol), formaldehyde (37% aqueous solution) (0.2 mL), diisopropylamine (1.1 mmol), water (5 mL), and Ag^{I}–K10 (50 mg) for 8 h at room temperature. [b] Isolated yield and >99% selectivity determined by ^{1}H NMR.

In general, the present protocol resulted in high yields of propargylamine for a wide range of substrates. A variety of aromatic, cyclic, and heterocyclic alkynes were studied, and in all the cases, the reactions proceeded smoothly to give the corresponding propargylamines. Substituted symmetric as well as nonsymmetric amines were coupled with formaldehyde and various alkynes to give smoothly the corresponding product in high yields under the present reaction conditions. In some cases, the reactions were performed in a 1:1 water:DMSO mixture due to the poor solubility of substrates. It is very clear from these data that the A^{3} coupling catalyzed by Ag^{I}–K10 had resulted in high yield of products without affecting many functional groups on amines/alkynes showing the high tolerance limit of other functional groups.

These encouraging results prompted us to extend this protocol to investigate the catalytic activity of Ag^{I}–K10 with phenylacetylene, benzaldehyde, and pyrrolidine as substrates, and the observed results are given in Table 4. In the absence of catalyst, no product formation was observed, whereas K10 clay resulted in 5% yield at 100 °C in 20 h under neat conditions (Table 4, entries 1and 2). On the other hand, silver nitrate afforded a 60% yield at 100 °C in 20 h under neat conditions

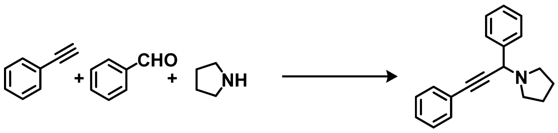
Table 3. A^3 Coupling between Various Alkynes, Amines, and Aqueous Formaldehyde Catalyzed by Ag^{I}–K10 in Water[a]



entry	alkyne (R)	amine (R′, R″)	time (h)	yield (%)[b]
1	C_6H_5	CH_3, C_2H_5	8	80
2	C_6H_5	C_3H_7, C_3H_7	8	86
3	C_6H_5	CH_3, C_3H_7	8	83
4	C_6H_5	C_2H_5, C_2H_5	12	81
5	2-pyridyl	C_4H_9, C_4H_9	12	85
6	3-$NO_2C_6H_4$	C_3H_7, C_3H_7	10	80
7	3-$H_3COC_6H_4$	C_4H_9, C_4H_9	12	76
8	3-$H_3COC_6H_4$	CH_3, C_5H_{11}	12	78
9	3-$H_3COC_6H_4$	C_3H_7, C_4H_9	12	80
10	3,4-di-$CH_3C_6H_3$	CH_3, C_5H_{11}	12	81
11	3,4-di-$CH_3C_6H_3$	C_2H_5, C_2H_5	12	76
12	2-$CH_3C_6H_4$	C_3H_7, C_4H_9	12	78
13	3-$C_6H_5CH_2COONHC_6H_4$	CH_3, C_3H_7	12	81
14	cyclopropyl	CH_3, C_3H_7	12	75
15	cyclopropyl	C_2H_5, C_2H_5	12	78
16	cyclopropyl	CH_3, C_2H_5	12	80
17	cyclopropyl	C_4H_9, C_4H_9	12	75
18	cyclopropyl	C_3H_7, C_3H_7	12	79
19[c]	3-$COOCH_3$–C_6H_4	C_4H_9, C_4H_9	12	85
20[c]	3-$COOCH_3$–C_6H_4	CH_3, C_3H_7	12	81
21	3- $CH_3C_6H_4$	C_4H_9, C_4H_9	12	80
22	2-FC_6H_4	C_3H_7, C_3H_7	12	79
23	2-FC_6H_4	CH_3, C_3H_7	12	82

[a] Reaction conditions: alkyne (1 mmol), formaldehyde (37% aqueous solution) (0.2 mL), amine (1.1 mmol), and Ag^{I}–K10 (50 mg) at room temperature in 5 mL of water. [b] Isolated yield and >98% selectivity determined by ^{1}H NMR. [c] Reaction was carried out in a mixture of water:DMSO (1:1).

Table 4. Optimization of Reaction Conditions for A^3 Coupling between Phenylacetylene, Benzaldehyde, and Pyrrolidine[a]



entry	catalyst	solvent	*T* (°C)	yield (%)[b]
1	none	neat	100	–
2	K10	neat	100	5
3[c]	$AgNO_3$	neat	100	60
4	Ag^{I}–K10	1,4-dioxane	100	38
5	Ag^{I}–K10	toluene	100	52
6	Ag^{I}–K10	DMF	100	41
7	Ag^{I}–K10	water	100	65
8	Ag^{I}–K10	neat	RT	13
9	Ag^{I}–K10	neat	50	43
10	Ag^{I}–K10	neat	80	62
11[d]	Ag^{I}–K10	neat	100	55, 85, 83
12[e]	Ag^{I}–K10	neat	100	54, 84, 80
13	Cu^{2+}–K10	neat	100	65
14	Al^{3+}–K10	neat	100	50
15	Ti^{4+}–K10	neat	100	39
16	NaY	neat	100	8
17	AgY	neat	100	75

[a] Reaction conditions: phenylacetylene (1 mmol), benzaldehyde (1 mmol), pyrrolidine (1 mmol), and Ag^{I}–K10 (50 mg) for 20 h. [b] Isolated yield. [c] 2.3 mg of $AgNO_3$ used. [d] 20, 50, and 100 mg catalyst used, respectively. [e] 20, 50, and 100 mg catalyst used, respectively, at 24 h.

(Table 4, entry 3). Attempts were made to perform the reaction in the presence of organic solvents and water using Ag^{I}–K10 as the catalyst. Moderate yields were observed with organic solvents; however, high yield (65%) was achieved with water as the solvent (Table 4, entries 4−7). In contrast, Ag^{I}−K10 exhibited high activity in the absence of any solvent. For example, 85% yield was achieved under neat conditions at 100 °C in 20 h (Table 4, entry 11). Increasing the catalyst amount to 100 mg and reaction time to 24 h, no further increase in yield was observed, suggesting that the optimal loading of catalyst is 50 mg (Table 4, entries 11 and 12).

Comparison of the catalytic activity of Ag^{I}−K10 with other cation-exchanged K10 clays and zeolites clearly established that Ag^{I}−K10 shows superior activity over other catalysts tested under the present experimental conditions (Table 4, entries 13−17). Further, the initial reaction rate of Ag^{I}−K10 clay was compared with silver nitrate to delineate the advantage of heterogeneous from homogeneous catalysts, and the observed results are given in Figure 1. As expected, silver nitrate showed high activity until 12 h and then it started to deactivate by showing a decrease in its activity. Although Ag^{I}−K10 exhibited a lower reaction rate until 12 h, the activity increased as a function of time and reached the maximum yield. These experiments clearly explain the superior nature of Ag^{I}−K10 over homogeneous silver nitrate; however, the former catalyst can be recycled.

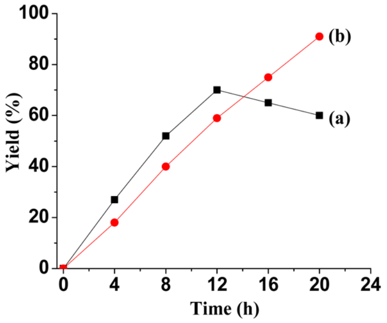


Figure 1. Comparison of catalytic activity of silver nitrate (a) with Ag^{I}−K10 clay (b) as catalysts in A^{3} coupling. Reaction conditions: phenylacetylene (1 mmol), benzaldehyde (1 mmol), pyrrolidine (1 mmol) and Ag^{I}−K10 (50 mg) or AgNO$_3$ (2.3 mg) at 100 °C. Yield corresponds to HPLC yield.

One of the main concerns associated with heterogeneous catalysts is the leaching of active species during the catalytic reaction. To check whether the present reaction proceeds truly by heterogeneity or by dissolved active species, a hot filtration test was performed (Table 4, entry 5). The catalyst was filtered in hot at 18% phenylacetylene conversion, and the filtrate was allowed to continue to react for another 16 h. Although a marginal increase (24%) in phenylacetylene conversion was observed, no significant change in the product yield was noticed. This experiment clearly confirms that catalysis by Ag^{I}−K10 clay is heterogeneous in nature, and no silver ions were leached out from the catalyst. A similar trend was observed when the reaction was performed in water (Table 4, entry 7).

The reusability experiment was performed for Ag^{I}−K10 clay to demonstrate the catalyst long-term stability for A^{3} coupling of phenylacetylene, benzaldehyde, and pyrrolidine as substrates under neat reaction conditions. It was observed that the initial reaction rate decreased marginally from 1 to 6 runs, with no appreciable change in its yield. These experiments clearly confirm that the catalyst stability is retained up to six runs, with no significant loss in its activity observed (Figure 2).

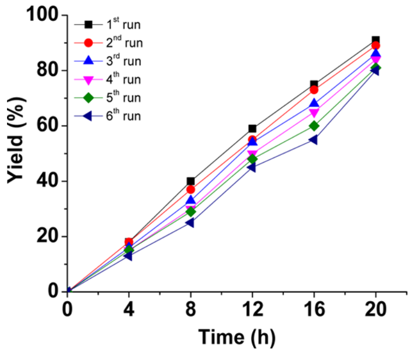


Figure 2. Reusability experiment of Ag^{I}−K10 clay under neat reaction conditions as given in Table 4.

The optimized reaction conditions from Table 4 were used to expand the scope of the Ag^{I}−K10 catalyst with other substrates, and the observed results are given in Table 5. Phenylacetylene and its derivatives reacted smoothly with substituted aromatic aldehydes along with pyrrolidine to give the corresponding propargylamines using Ag^{I}−K10 as the catalyst at 100 °C for 20 h. On the other hand, the reaction between phenylacetylene, benzaldehyde, and aniline/N-methylaniline failed to give the corresponding products. It is also interesting to note that the various substituted alkynes were found to be highly reactive with cyclopropanecarboxaldehyde/isobutyraldehyde and pyrrolidine in the presence of Ag^{I}−K10 as the catalyst, giving high yields of the corresponding propargylamines at room temperature for 15 h.

The interaction of Ag^{I} with the terminal alkyne and the diffusion of organic substrate inside the clay layer was also studied by two control experiments. The reaction of phenylacetylene, benzaldehyde, and pyrrolidine in the presence of pyridine using Ag^{I}−K10 clay as the catalyst showed a 69% yield in 20 h, whereas in the absence of pyridine, it resulted in 85% yield in 20 h. This experiment shows that the addition of pyridine increases the steric hindrance as well as poisons the Lewis acid sites by interacting with Ag^{I} cations. In another experiment under identical experimental conditions, 4-trifluorophenylacetylene reacted with benzaldehyde and pyrrolidine in the presence of Ag^{I}−K10 clay giving a 71% yield in 20 h. The moderate activity of 4-trifluorophenylacetylene, where a substrate containing a substitution at the para position encounters the diffusion limitation to reach the active sites, shows moderate yield.

■ TENTATIVE MECHANISM FOR A^{3} COUPLING

Considering the above experimental results and by analogy with earlier literature reports,[61−65] a tentative mechanism is proposed as shown in Scheme 1. Ag^{I}−K10 interacts with phenylacetylene by generating an initial silver(I)−acetylide intermediate, and it undergoes a subsequent cleavage of one of the oxobridges in clay. An intermediate π-silver−alkyne complex is formed first making the alkyne proton more acidic for further abstraction as well as the formation of iminium ion in situ from aldehydes and secondary amines. Then the silver(I)−acetylide intermediate adds to the iminium ion to give the corresponding propargylamine and regenerate the Ag^{I}−K10 catalyst for a further sequence of reactions.

■ CONCLUSIONS

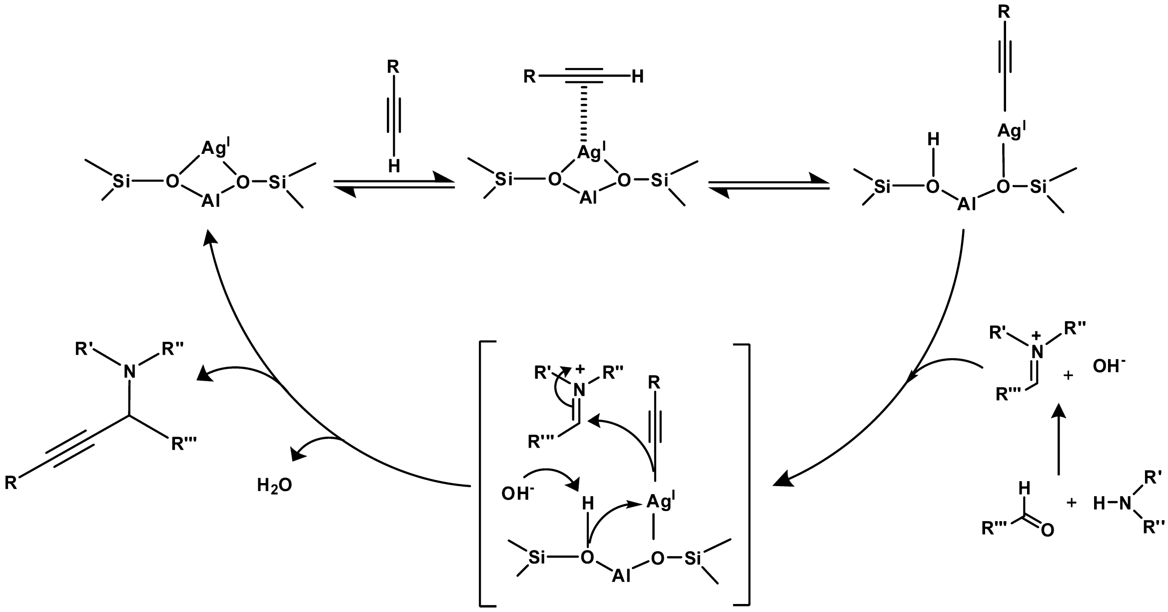
Ag^{I}−K10 clay is found to be a highly efficient catalyst for the synthesis of propargylamines from alkynes, aldehydes, and amines in water as well as under neat conditions. The process is

Table 5. A^3 Coupling Reaction of Substituted Alkynes, Aliphatic/Aromatic Aldehydes, and Pyrrolidine Catalyzed by Ag^I–K10

entry	alkyne	aldehyde	amine	isolated yield (%)
1[a]	phenylacetylene	benzaldehyde	pyrrolidine	85
2[a]	phenylacetylene	3-chlorobenzaldehyde	pyrrolidine	88
3[a]	phenylacetylene	2-methylbenzaldehyde	pyrrolidine	85
4[a]	3-methylphenylacetylene	4-methylbenzaldehyde	pyrrolidine	89
5[a]	phenylacetylene	benzaldehyde	aniline	–
6[a]	phenylacetylene	benzaldehyde	*N*-methylaniline	–
7[b]	phenylacetylene	cyclopropanecarbaldehyde	pyrrolidine	87
8[b]	3-methylphenylacetylene	cyclopropanecarbaldehyde	pyrrolidine	90
9[b]	4-methoxyphenylacetylene	cyclopropanecarbaldehyde	pyrrolidine	92
10[b]	phenylacetylene	Isobutyraldehyde	pyrrolidine	80
11[b]	2-ethynylpyridine	Isobutyraldehyde	pyrrolidine	88
12[b]	3-methylphenylacetylene	Isobutyraldehyde	pyrrolidine	81
13[b]	phenylacetylene	3,3-dimethylbutyraldehyde	pyrrolidine	75

[a] Reaction conditions: alkyne (1 mmol), aldehyde (1 mmol), amine (1 mmol), and Ag^I–K10 (50 mg) at 100 °C for 20 h under neat condition. [b] Reaction conditions: alkyne (1 mmol), aldehyde (1 mmol), amine (1 mmol), and Ag^I–K10 (50 mg) at room temperature for 15 h under neat condition.

Scheme 1. Plausible Mechanism for Three-Component Coupling Catalyzed by Ag^I–K10 as Catalyst



simple and allows the synthesis of a diverse range of propargylamines in high yields. Moreover, no solvent is required when aromatic aldehyde is used as one of the components. The reaction is also successful with formaldehyde and aromatic and aliphatic aldehydes with substituted amines/alkynes. The solid catalyst can be readily recovered by filtration and reused several times without any significant decay in its activity, thus making this procedure more environmentally benign. The other advantages of the present methodology are the absence of side reactions such as aldehyde/alkyne cyclization and no base or other co-catalysts are needed. Further, heterogeneity tests show evidence for the absence of leaching, and thus, the catalyst enjoys stability under the present experimental conditions. Consequently, this protocol offers a new approach for the synthesis of propargylamines using a layered aluminosilicate as catalyst for the first time under mild reaction conditions.

■ EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz Bruker spectrometers, respectively. Coupling constants were reported in hertz (Hz). Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Reactions were carried out in an oven-dried, three-necked, round-bottomed flask. Yields reported here correspond to isolated yield of compounds as determined by ^{1}H and ^{13}C NMR analyses.

Preparation of Ag^I–K10 Clay. K10 montmorillonite clay (Fluka) was used as received. The silver ions were exchanged into K10 montmorillonite clay (5 g) by stirring with silver nitrate (1 M in 25 mL of water for 1 g of clay) solution at room temperature for 72 h. The clay was filtered and washed thoroughly with distilled water. This was dried at 100 °C under vacuum drying overnight. The BET surface area of K10 and Ag^I–K10 clay were 224 and 182 m^2/g, respectively. In addition, Ag^I–K10 clay was characterized by powder XRD, SEM with EDX, and UV-DRS analyses.

Typical Procedure of A^3 Coupling Reaction Catalyzed by Ag^I–K10 Clay. To a stirred solution of alkyne (1 mmol), formaldehyde (37% aqueous solution) (0.2 mL), and amine (1.1 mmol) in water (5 mL), 50 mg of Ag^I–K10 clay was added. The reaction mixture was stirred at room temperature for 8 or 12 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and then filtered. The ethyl acetate layer was concentrated to obtain a crude product. This was purified by column chromatography by using n-hexane/ethyl acetate (15% ethyl acetate in n-hexane) as an eluent to afford propargylamine. The recovered catalyst was thoroughly washed with acetone, dried, and used for the next run. A similar reaction procedure was followed for the reactions wherein aromatic aldehydes were used as substrates, and the corresponding reaction conditions are given in Tables 4 and 5.

■ ASSOCIATED CONTENT

Supporting Information

This document describes the synthesis of various metal ion-exchanged clays and zeolites. The detailed characterization of Ag^{I}−K10 clay is presented. The characterization of all the products by ^{1}H and ^{13}C NMR spectra are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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