


Cite this: *RSC Adv.*, 2018, 8, 32942

Recyclable Cu/C₃N₄ composite catalyzed AHA/A³ coupling reactions for the synthesis of propargylamines†

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The heterogeneous Cu/C₃N₄ catalyst was found to be efficient for the synthesis of propargylamines using a three-component coupling reaction of alkynes, CH₂Cl₂ and amines (AHA) without additional base. Moreover, the catalyst also showed highly catalytic activity in the synthesis of C1-alkynylated tetrahydroisoquinolines (THIQs) *via* an A³ reaction of alkynes, aldehydes and THIQ. The Cu/C₃N₄-catalyzed multicomponent reactions exhibited good functional group tolerance in most examples. Furthermore, the easily prepared Cu/C₃N₄ catalyst could be recovered and reused conveniently over 5 times without losing catalytic activities.

Received 6th August 2018
Accepted 18th September 2018

DOI: 10.1039/c8ra06613b

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Introduction

Multicomponent reactions (MCRs) are pretty important and effective in carbon–carbon bond formation because of their considerable economic and ecological merits.¹ A lot of organic compounds could be produced *via* MCRs, for example, propargylamines.

Propargylamines are very essential in pharmaceuticals due to their special nitrogen-containing biologically active structure, and have wide application in synthetic chemistry.² Traditionally, propargylamines were synthesized by stoichiometric nucleophilic attack of metal acetylides on imines³ or through the amination of propargylic halides⁴ and propargylic triflates.⁵ In the last decade, a catalytic three-component coupling reaction of alkynes, aldehydes and amines (A³ reaction) was developed as an efficient synthetic methodology for propargylamines, and many metal catalysts were utilized successfully.⁶ Meanwhile, another multicomponent reaction for the synthesis of propargylamines was also achieved through the coupling of alkynes, dihalomethane and amines (AHA reaction). Remarkable efforts on this method have been made by utilizing effective catalysts such as CuCl,⁷ nano-In₂O₃,⁸ FeCl₃,⁹ AgOAc,¹⁰ CoBr₂,¹¹ Nipy₄Cl₂,¹² Au NPs¹³ and K[AuCl₄].¹⁴ However, in most of the examples above, additional strong bases and additional solvents have to be required. In our previous work, a Cu NPs-catalyzed AHA reaction was accomplished

in CH₂Cl₂ solution.¹⁵ Although a highly catalytic activity was observed, additional strong base (Cs₂CO₃) was also required in the reaction and only low recyclability of the Cu NPs catalyst was observed. On the other hand, a metal-free AHA reaction was also developed, but only moderate yields were obtained.¹⁶

Moreover, as a special secondary amine, tetrahydroisoquinolines (THIQs) are found widely existed in natural products and have many biological activities.¹⁷ Thus, many novel and valid methods were developed to synthesize THIQ derivatives, and most of them focused on the activation of THIQ's C1 atom.¹⁸ Recently, an efficient C1-alkynylation method for THIQs was developed through the A³ coupling reaction of THIQ, aldehydes and alkynes, in which AgOAc,¹⁹ CuI,²⁰ and CuBr²¹ were reported as efficient catalysts. To develop greener approaches for the reaction, some efforts on the catalyst's immobilization were also tried, and polymers²² or magnetic materials²³ supported copper species were reported. However, both of them have to suffer lowered catalytic efficiency as well as complicated preparing procedure for immobilized catalysts.

N-doped carbon materials are a kind of novel superior materials and have been widely used as electrode materials because of its porous structure and amine-containing molecules.²⁴ The materials have also come into the view of organic chemists in recent years due to their superior performance and easy preparation.²⁵ Very recently, we reported a Cu/C₃N₄ composite-catalyzed homo- & cross-coupling reaction of terminal alkynes,²⁶ in which the easily prepared composite catalyst showed much higher catalytic activity than Cu NPs with excellent recyclability.

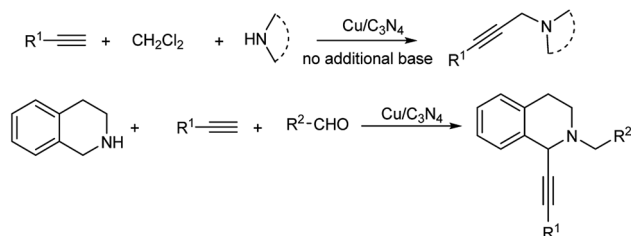
Since the Cu/C₃N₄ composite shows highly catalytic activity in Glaser–Hay reaction involving the activation of terminal alkynes, herein, we hope to investigate its application in AHA reaction of alkynes, dihaloalkanes and amines, and A³ coupling reaction of THIQ, aldehydes and alkynes (Scheme 1). The Cu/

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra06613b





Scheme 1 Synthesis of propargylamines via AHA/A³ reaction.

C₃N₄ catalyst exhibited excellent catalytic activities as well as good functional group tolerance in most examples. Furthermore, excellent recyclability of the catalyst was also achieved.

Experimental

Synthesis of Cu/C₃N₄ compounds

The Cu/C₃N₄ catalyst was synthesized following the reported method. Typically, melamine (2 g) was uniformly mixed with copper(II) acetate (625 mg). The resulting mixture was then heated to 550 °C with 2 °C min⁻¹ in a tube furnace under N₂ atmosphere and kept for 2 h. After cooling to room temperature, the final solid product (Cu/C₃N₄) was collected without further purification.

Typical procedure for Cu/C₃N₄-catalyzed AHA reaction of dichloromethane, alkynes and amines

The mixture of *p*-bromophenylacetylene (0.15 mmol) and piperidine (0.45 mmol), 20% Cu/C₃N₄ (9.6 mg, 20 mol%) in anhydrous DCM (0.5 mL) was heated at 50 °C for 24 h under nitrogen atmosphere. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 5 : 1) to give the desired product.

The detailed characterization data for 2a–2u are provided in the ESI.†

Typical procedure for Cu/C₃N₄-catalyzed A³ reaction of alkynes, aldehydes and THIQ

The mixture of benzaldehyde (0.2 mmol), phenylacetylene (0.3 mmol), THIQ (0.25 mmol), 5% Cu/C₃N₄ (6.4 mg, 2.5 mol%) and 4 Å MS (25 mg) in anhydrous toluene (0.5 mL) was heated at 70 °C for 12 h under nitrogen atmosphere. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 30 : 1) to give the desired product.

The detailed characterization data for 4a–4o are provided in the ESI.†

The experiments of catalyst recycle in AHA reaction

p-Bromophenylacetylene (1.0 mmol), piperidine (3.0 mmol), 20% Cu/C₃N₄ (64.0 mg), and 2 mL of CH₂Cl₂ were added into a 30 mL sealed tube under N₂. The mixture was stirred at 50 °C for 24 hours. After completion of the reaction, the catalyst was separated by centrifugation and washed by water, ethanol and

ether, and then, dried under vacuum at 60 °C. The recovered catalyst was reused for the next cycle with fresh starting materials and solvent.

The experiments of catalyst recycle in A³ reaction

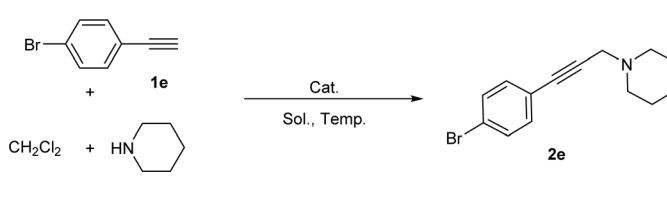
Phenylacetylene (2.0 mmol), benzaldehyde (1.0 mmol), THIQ (1.5 mmol), 5% Cu/C₃N₄ (32.0 mg), 4 Å MS (125 mg), and 2 mL of toluene were added into a 30 mL sealed tube under N₂. The mixture was stirred at 70 °C for 12 hours. After completion of the reaction, the catalyst was separated by centrifugation and washed by water, ethanol and ether, and then, dried under vacuum at 60 °C. The recovered catalyst was reused for the next cycle with fresh starting materials and solvent.

Results and discussion

With the Cu/C₃N₄ composite as catalyst, the AHA coupling reaction of *p*-bromophenylacetylene, dichloromethane and piperidine was selected as the prototype to start our investigation for the optimized reaction conditions, and the results were summarized in Table 1.

At the beginning, the reaction was carried out with Cu/C₃N₄ as catalyst and Cs₂CO₃ as base under N₂ atmosphere at 50 °C for 24 hours, and a moderate yield was observed (entry 1, Table 1). When DBU was used as base, 87% of 2e was obtained (entry 2).

Table 1 The optimization of Cu/C₃N₄ catalyzed AHA coupling reaction^a



Entry	Catalyst	T/°C	Base	Yield ^b (%)
1	20% Cu/C ₃ N ₄ (20 mol%)	50	Cs ₂ CO ₃	74
2	20% Cu/C ₃ N ₄ (20 mol%)	50	DBU	87
3 ^c	20% Cu/C ₃ N ₄ (20 mol%)	50	None	92
4 ^c	10% Cu/C ₃ N ₄ (20 mol%)	50	None	77
5 ^c	5% Cu/C ₃ N ₄ (20 mol%)	50	None	57
6 ^c	20% Cu/C ₃ N ₄ (10 mol%)	50	None	85
7 ^c	20% Cu/C ₃ N ₄ (5 mol%)	50	None	75
8 ^d	20% Cu/C ₃ N ₄ (20 mol%)	50	None	61
9 ^e	20% Cu/C ₃ N ₄ (20 mol%)	50	None	69
10 ^c	20% Cu/C ₃ N ₄ (20 mol%)	30	None	35
11 ^c	20% Cu/C ₃ N ₄ (20 mol%)	60	None	92
12 ^c	Cu NPs (20 mol%)	50	None	30
13 ^c	None	50	None	Trace

^a Reaction conditions: *p*-bromophenylacetylene (0.15 mmol), piperidine (0.15 mmol), base (0.3 mmol) and dichloromethane 0.5 mL as solvent under N₂ at 50 °C for 24 h. ^b Isolated yield. ^c Reaction conditions: *p*-bromophenylacetylene (0.15 mmol), piperidine (0.45 mmol) and dichloromethane 0.5 mL as solvent under N₂ at 50 °C for 24 h.

^d Reaction conditions: *p*-bromophenylacetylene (0.15 mmol), piperidine (0.45 mmol) and dichloromethane (0.3 mmol) in 0.5 mL CH₃CN under N₂ at 50 °C for 24 h. ^e Reaction conditions: *p*-bromophenylacetylene (0.15 mmol), piperidine (0.45 mmol) and dichloromethane (0.3 mmol) in 0.5 mL toluene under N₂ at 50 °C for 24 h.



Noteworthy, an up to 92% of yield was achieved with 3.0 equiv. of piperidine introduced as reactant & base (entry 3). The copper loading amount in catalyst was then evaluated. As can be seen, decreasing the copper loading resulted in worse yields (entries 4 and 5 vs. entry 3). The yields were also decreased with reducing catalyst loading (entries 6 and 7). Other solvents, such as CH₃CN and toluene, were ineffective in this catalytic system (entries 8 and 9).

Moreover, the influence of temperature was also investigated. The yield of **2e** decreased sharply at 30 °C, while the yield was not changed when the reaction temperature was increased to 60 °C (entries 10 and 11 vs. entry 3).

To understand the effect of C₃N₄ support on the catalytic activity, a controlled experiment was carried out, in which Cu NPs was used as catalyst. Obviously, without additional strong base,¹⁵ much worse result was observed (entry 12). This result might indicate that the C₃N₄ support increased the catalytic activity of copper species successfully under current conditions. On the other hand, there was no progress of reaction under a catalyst-free condition (entry 13).

Thus, the optimal conditions involved the following parameters: 20 mol% of 20% Cu/C₃N₄ and 3.0 equiv. of amines in 0.5 mL of dichloromethane at 50 °C under nitrogen for 24 h.

Under the optimized reaction conditions, we then tested the scope of AHA reaction of alkynes, dichloromethane, and amines. As shown in Table 2, aromatic acetylene derivatives underwent the coupling with dichloromethane and piperidine smoothly to afford the respective propargylamines in excellent yields of 85–94% (**2a–2g**). Less reactive aliphatic alkyne, 1-hexyne, was also suitable for this reaction, and a moderate yield was

observed (**2h**). Moreover, the AHA coupling reaction of alkynes, dichloromethane and pyrrole was also investigated, and good yields were obtained (**2i–2m**). Delightfully, acyclic secondary amine like diethylamine was also efficiently converted into the corresponding propargylamines in good yields (**2n–2s**). However, morpholine and diisopropylamine seem not be good substrates in current reaction (**2t–2u**).

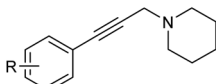
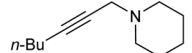
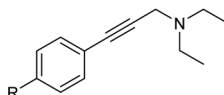
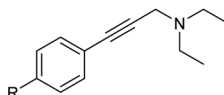
As known to all, one of the advantages of heterogeneous catalysts is their easy separation from the reaction mixture. Without the distribution from additional base, the catalyst could be separated and recovered easily by centrifugation from the reaction mixture, and then, fresh substrates were added to set up a new reaction. Following this procedure, the recyclability of Cu/C₃N₄ was also investigated. It can be seen from Fig. 1 that the yields were kept in 91–88% in 5 recycles. There was only *ca.* 1–4% yield decrease compared with the fresh reaction.

As can be seen from above results, the Cu/C₃N₄ catalyst showed great catalytic activities in AHA coupling reaction as well as good recyclability without additional base. With this catalyst in hand, therefore, we also examined its utilization in A³ coupling reaction of alkynes, aldehydes and THIQ.

At the beginning of the investigation, excess amounts of THIQ and phenylacetylene were used in order to consume all of benzaldehyde, which was inseparable from products **4a** and **5a** by column chromatography. Firstly, the A³ reaction was carried out in various solvents, with 5% Cu/C₃N₄ (2.5 mol%) as catalyst, under N₂ atmosphere at 70 °C for 24 h. When the reaction was carried in water, a moderate yield of **5a** was obtained as the single product (entry 1, Table 3). Both EtOH and isopropanol (IPA) could be processed effectively to afford **4a** as the major product (entries 2 and 3). Apparently, an enhanced reaction yield and regioselectivity was obtained in the presence of additional 4 Å MS (entry 4 vs. 3). To our delight, in toluene with 4 Å MS, a regiospecific reaction to **4a** was accomplished with excellent yield (entry 5).

From these results above, water is the key factor affecting the reaction selectivity. Following the mechanism described in Scheme 2,²¹ iminium **B** was formed firstly following the dehydrogenation of intermediate **A**, and then, **B** was isomerized to give iminium **C** as the key intermediate to the desired product **4a**. Obviously, in the presence of water, the formation of iminium **B** might be hindered, as a result, the isomerization

Table 2 The scope of the AHA reactions ^a

$R_1-C\equiv C + CH_2Cl_2 + HN \xrightarrow[50\text{ }^\circ\text{C, N}_2, 24\text{ h}]{20\% \text{ Cu/C}_3\text{N}_4} R_1-C\equiv C-N$	
	
<p>R = 4-H, 2a, 94% R = 4-Me, 2b, 91% R = 4-Et, 2c, 88% R = 4-F, 2d, 85% R = 4-Br, 2e, 92% R = 4-CF₃, 2f, 90% R = 3-Me, 2g, 95%</p>	<p>R = H, 2i, 85% R = Me, 2j, 81% R = Et, 2k, 78% R = OMe, 2l, 84% R = Br, 2m, 81%</p>
	
<p>R = H, 2n, 90% R = Me, 2o, 90% R = Et, 2p, 82% R = OMe, 2q, 85% R = F, 2r, 86% R = Br, 2s, 88%</p>	<p>2t, 46% 2u, 20%</p>

^a Reaction conditions: alkynes (0.15 mmol), amines (0.45 mmol) and dichloromethane 0.5 mL as solvent with 20% Cu/C₃N₄ (20 mol%) under N₂ at 50 °C for 24 h; isolated yield.

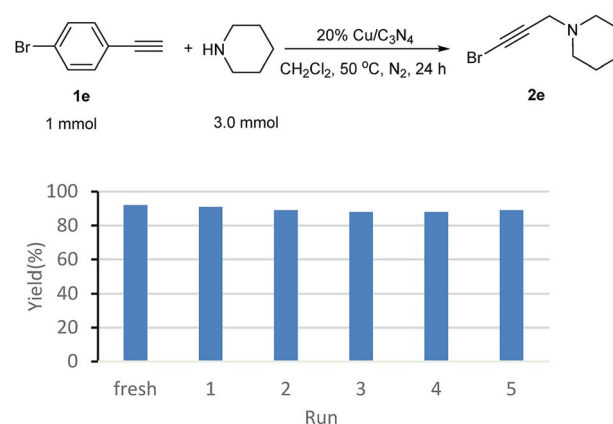
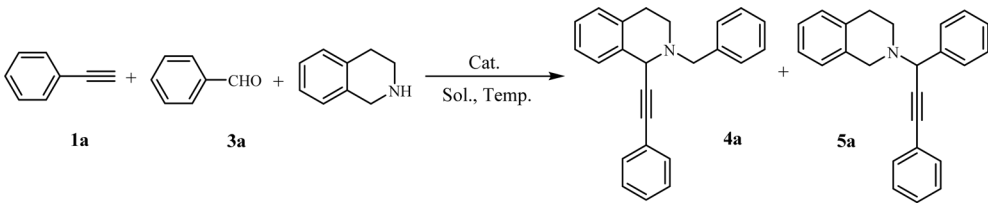


Fig. 1 AHA reaction catalyzed by recycled Cu/C₃N₄ catalyst.



Table 3 The optimization of Cu/C₃N₄ catalyzed A³ coupling reaction^a

					
Entry	Catalyst	T/°C	Solvent	Yield ^b (%) 4a + 5a	Ratio ^c 4a/5a
1	5% Cu/C ₃ N ₄ (2.5 mol%)	70	H ₂ O	46	0 : 1
2	5% Cu/C ₃ N ₄ (2.5 mol%)	70	EtOH	54	3 : 1
3	5% Cu/C ₃ N ₄ (2.5 mol%)	70	IPA	50	1.6 : 1
4 ^d	5% Cu/C ₃ N ₄ (2.5 mol%)	70	EtOH	62	7 : 1
5 ^d	5% Cu/C ₃ N ₄ (2.5 mol%)	70	Toluene	97	1 : 0
6 ^d	20% Cu/C ₃ N ₄ (2.5 mol%)	70	Toluene	90	1 : 0
7 ^d	Cu NPs (2.5 mol%)	70	Toluene	70	1 : 0
8 ^d	5% Cu/C ₃ N ₄ (1.25 mol%)	70	Toluene	85	1 : 0
9 ^d	5% Cu/C ₃ N ₄ (5 mol%)	70	Toluene	97	1 : 0
10 ^d	5% Cu/C ₃ N ₄ (2.5% mol%)	50	Toluene	76	1 : 0
11 ^d	5% Cu/C ₃ N ₄ (2.5% mol%)	25	Toluene	35	1 : 0
12 ^{d,e}	5% Cu/C ₃ N ₄ (2.5 mol%)	70	Toluene	97	1 : 0
13 ^{d,f}	5% Cu/C ₃ N ₄ (2.5 mol%)	70	Toluene	78	1 : 0

^a Reaction conditions unless otherwise noted: benzaldehyde **3a** (0.2 mmol), phenylacetylene **1a** (0.3 mmol), THIQ (0.25 mmol), solvent (0.5 mL), reaction time 24 h in cube with N₂. ^b Isolated combined yield of **4a** and **5a**. ^c Ratio was determined by NMR prior to purification. ^d 4 Å MS (25 mg) was added. ^e 12 h. ^f 8 h.

procedure would be prohibited as well. Therefore, **5a** was observed as the single product in water solution.

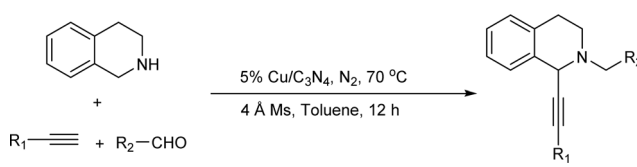
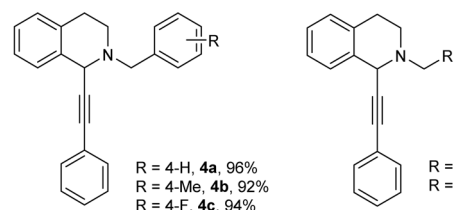
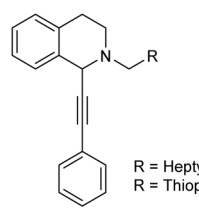
Other heterogeneous copper catalysts, such as 20% Cu/C₃N₄ and Cu NPs were also tested, the yields were decreased obviously (entries 6 and 7).

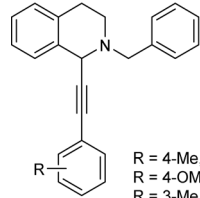
Decreasing the loading of catalyst resulted in worse yield, but the yield was not changed when the loading of catalyst enhanced (entries 8 and 9). Lowering the reaction temperature to 50 °C or 30 °C resulted in decreased yields (entries 10 and 11). When the reaction time was shortened to 12 h, the yield was not changed. However, when the reaction time was further shortened to 8 h, only 78% of **4a** was obtained (entries 12 and 13).

Thus, the optimized reaction conditions for A³ coupling reaction were 5% Cu/C₃N₄ (2.5 mol%) in toluene with 4 Å MS at 70 °C for 12 h under N₂ atmosphere.

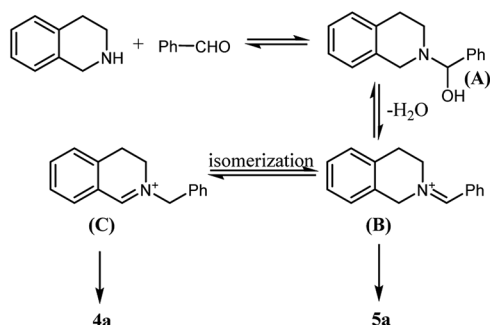
Under the optimized reaction conditions, a series of terminal alkynes and aldehydes were explored. The results were

Table 4 The scope of the A³ reactions^a

	
	R = 4-H, 4a , 96% R = 4-Me, 4b , 92% R = 4-F, 4c , 94% R = 4-Br, 4d , 96% R = 3-Me, 4e , 95% R = 2-Me, 4f , 95% R = 2-Br, 4g , 91%
	R = Heptyl, 4h , 72% R = Thiophen-2-yl, 4i , 95% R = Cyclohexyl, 4n , 99% R = <i>n</i> -Butyl, 4o , 92%

	R = 4-Me, 4j , 99% R = 4-OMe, 4k , 93% R = 3-Me, 4l , 99% R = 4-F, 4m , 90%
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^a Reaction condition: aldehydes (0.2 mmol), alkynes (0.3 mmol), THIQ (0.25 mmol), 4 Å MS (25 mg), toluene (0.5 mL), reaction time 12 h, 70 °C; isolated yield.

Scheme 2 The proposed mechanism of A³ coupling reaction.

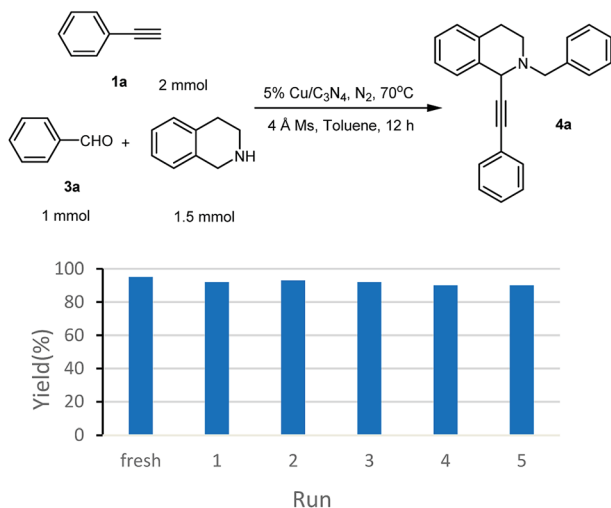


Fig. 2 A³ reaction catalyzed by recycled Cu/C₃N₄ catalyst.

listed in Table 4. Aromatic aldehydes with electron-donating groups and electron-withdrawing groups worked well to generate the corresponding products in excellent yields (4a–4g). Aliphatic aldehyde like *n*-caprylic aldehyde could be converted into the desired product with a 72% of yield (4h).

Thiophene-2-carbaldehyde was also applicable under the optimized reaction conditions to afford the corresponding product 4i in 95% yield. Various terminal alkynes were then examined for the target reaction. Phenylacetylenes bearing electron-donating groups such as methyl, methoxy at the *para* or *meta* positions, underwent the reaction to provide the corresponding products in excellent yields (4j–4l). Aliphatic alkynes, such as ethynylcyclohexane and 1-hexyne, were also suitable for this reaction, and good yields were observed (4n–4o).

Moreover, the recyclability of the Cu/C₃N₄ catalyst in this reaction was then investigated. Similar to that in AHA reaction, good recyclability was achieved and no significant decrease in yield was observed after 5 recycles (Fig. 2).²⁷

Conclusions

In conclusion, with Cu/C₃N₄ composite as catalyst, a facile, efficient, and environmental friendly synthetic strategy for propargylic amines was developed by the three-component coupling reaction of alkynes, CH₂Cl₂ and amines. Good functional group tolerance and high yields were accomplished without additional base required. Moreover, the A³ coupling reaction of alkynes, aldehydes and THIQ for the synthesis of C1-alkynylated tetrahydroisoquinolines (THIQs) could also be achieved by utilizing Cu/C₃N₄ as catalyst. The Cu/C₃N₄ catalyst was tolerant of a wide variety of functional groups and good to excellent yields were achieved in most examples. Moreover, the heterogeneous catalyst could be recovered and reused conveniently for several times with satisfactory yields in both of the reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the financial support from National Natural Science Foundation of China (21472092 to XY). This is a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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