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PAPER

Polystyrene supported N-phenylpiperazine-Cu(II) complex: An efficient and reusable catalyst for KA^2-coupling reaction under solvent-free conditions

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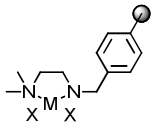
A new polystyrene supported N-phenylpiperazine-Cu(II) complex **4c** was found to be an efficient, simple, versatile catalyst for the selective multicomponent reaction of terminal alkynes, ketones, and secondary amines to give the corresponding propargylamines. The coupled products were formed in excellent yields at low catalyst loadings (0.2 mol % of metal) under solvent free conditions at 110 °C. Further, this heterogeneous catalyst showed excellent recyclability without any significant loss in its activity upto five times.

Introduction.

Propargylamines are highly versatile intermediates in organic synthesis[1] and key structural elements in natural products and drug molecules.[2] In addition they have found broad application as synthetic precursors of various nitrogen-heterocycles, such as pyrrolidines, pyrroles and oxazoles.[3] Furthermore some propargylic amine derivatives were found to possess interesting biological properties.[4] The most direct generally applicable protocol to access propargylamines is the multi-component coupling (MCC) of an aldehyde, amine and alkyne in one pot, three component synthesis referred as A^3 coupling.[5] This method has been widely investigated as it circumvents isolation of imine intermediate compared to ketones in MCC reaction.[6]

The three-component coupling with ketone–amine–alkyne is known as KA^2 coupling reaction and the use of ketones remains as a synthetic challenge owing to its low reactivity. Due to the difficulty of incorporating ketones, very few methods have been reported for the propargylamine formation from ketones. This KA^2 coupling remains as green synthetic challenge viz to enhance the reactivity of the substrates, yields, lowering the reaction times and catalytic loadings with broad substrate scope. In view of this C. H. Larsen and co-workers employed (Ti(OEt)$_4$) as lewis acid to enhance the activity of ketones[7c] and also described neat KA^2 coupling reaction of acyclic and cyclic aliphatic ketones under solvent free conditions.[7] Vander Eycken reported microwave-assisted Cu(I)-catalyzed one-pot coupling of a ketone, an alkyne, and a primary amine.[8] S. Ma et. al developed CuBr catalyzed KA^2 coupling reaction of aliphatic ketones in toluene at 100 °C.[9]

In d-block elements only Cu transition metal is more active for MCC reactions of ketones but Chan et al. reported copper free $AuBr_3$ and M. H. Savari with ZnO for KA^2 coupling of ketones.[10–11] Moreover the reported homogeneous conditions require 5-20 mol % of metal catalyst for efficient coupling and the recovery of the catalyst is impossible. Ramon *et al.* has reported the first recyclable heterogeneous catalyst Cu(OH)x–Fe_3O_4 (0.1 mol % of catalyst used) for MCC reaction of 3-pentanone with phenylacetylene and piperidine with considerably low yields and prolonged reaction times.[12] To till date, very few heterogeneous copper systems have been reported for KA^2 coupling reactions.[12–14] To achieve the eco-friendly protocol for KA^2 reaction the primary goal is to develop an economical, more benign recyclable catalyst, efficient even with low catalytic loadings. Therefore making the process more viable compared to homogeneous conditions. Thus there is a wide scope for improvement of heterogeneous copper catalysts (HCC) for this KA^2 coupling transformations.



4a: M = Cu; X = Br
4b: M = Pd; X = Cl

Fig. 1 Polymer supported copper and palladium complexes (**4a** and **4b**).

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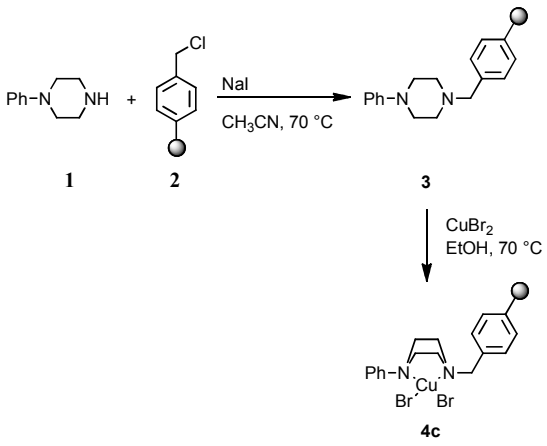
The most significant advantage of heterogeneous catalysts is recyclability and easy separation.[15] Several heterogeneous catalysts have been synthesized and applied for multi-component A^3 coupling reactions.[16] Polystyrene is the most popular polymeric support used in the synthesis of heterogeneous catalysts because of its low cost, ready availability, chemical inertness and facile functionalization. A variety of polystyrene supported metal catalytic systems were reported in many organic transformations.[17] Recently, we have reported polystyrene-supported N,N-dimethylethylenediamine with Cu and Pd complexes (**4a** and **4b** in figure. 1) as catalysts for Sonogashira, Suzuki and A^3 coupling reactions.[18]

Herein, we report polymer supported N-phenylpiperazine-Cu(II) complex **4c** as an efficient and highly reusable heterogeneous catalyst for the synthesis of propargylamines from KA^2 coupling reaction under solvent free conditions. To the best of our knowledge, this is the first report on the application of polymer supported heterogeneous catalyst **4c** for KA^2 coupling reactions to generate propargylamines.

Results and discussion

The synthesis of polymer-supported N-phenylpiperazine Cu(II) complex **4c** is systematically represented in Scheme 1. N-phenylpiperazine functionalized polystyrene resin **3** was formed by heating a mixture of chloromethylated polystyrene and N-phenylpiperazine in CH_3CN at 70 °C for 48 h. This polymer-supported N-phenylpiperazine **3** is insoluble in common organic solvents. Reaction of polymer-bound N-phenylpiperazine with EtOH and $CuBr_2$ in 1 : 1 molar ratio for 24 h at 70 °C resulted in covalent attachment of copper to give functionalized polymer. This complex formation was confirmed by FT-IR analysis. In the FT-IR spectrum of polymer-bound N-phenylpiperazine, the absence of sharp C–Cl peak (due to CH_2Cl groups) at 1263 cm^{-1} of starting polymer indicates the introduction of nitrogen ligand on the polymer. In addition, the stretching vibration of the Cu–N bond peaks observed at 531 cm^{-1} corresponds to the formation of polystyrene-supported N-phenylpiperazine Cu(II) complex.[19]



Scheme 1 Synthesis of polymer-supported N-phenylpiperazine-Cu(II) complex **4c**.

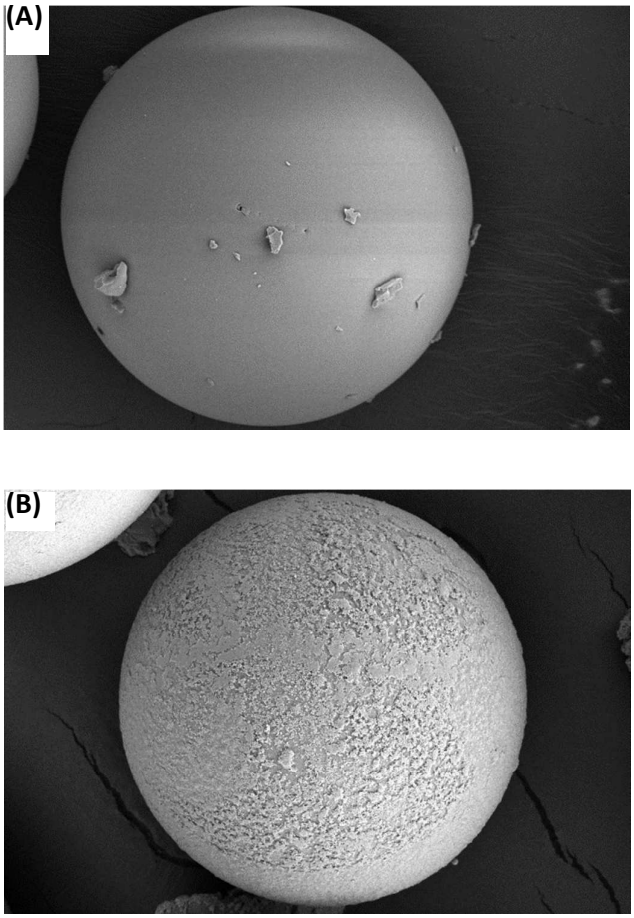


Fig. 2 SEM image of chloromethylated polystyrene (A) and N-phenylpiperazine-Cu(II) complex **4c** (B).

The scanning electron micrograph (SEM) images of the chloromethylated polystyrene and polymer supported N-phenylpiperazine Cu(II) complex **4c** shows the morphological changes. The change in the morphology of polystyrene surface indicates the formation of desired complex Fig. 2 (A and B). Energy dispersive X-ray spectroscopy (EDX) analysis data for the polymer anchored ligand and copper catalyst are given in Fig. 3 (I & II). The EDX spectrum clearly shows the presence of copper metal in the polymer complex. Thermal stability of the complex was investigated by TGA (Fig. 4). The complex is stable up to 372 °C and above this temperature it decomposes. The negligible weight loss below 200 °C is due to the physically adsorbed solvent molecules. The amount of copper incorporated into the polymer was also determined by inductively coupled plasma (ICP), which showed the value of 6.93% (1.09 mmol/g).

To begin our study, we examined the MCC reaction of ketones, amines and alkynes in the presence of polymer supported Cu(II) complex **4c** under a variety of reaction conditions. In order to establish the optimum conditions, we have chosen cyclohexanone, piperidine and phenylacetylene as model substrates (Table 1). The effect of different organic solvents on the catalytic activity of complex **4c** has been studied (entries 1–11). From the above tested

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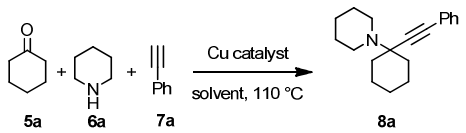
Table 1 Effect of solvent on the KA^2 coupling reaction[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	DCM	6	28
2	DCE	6	40
3	Dioxane	6	48
4	Toluene	6	91
5	THF	6	72
6	CH_3CN	6	60
7	DMF	12	31
8	DMSO	12	42
9	MeOH	12	15
10	EtOH	12	33
11	Water	12	Nr
12	_	6	94
13	_	10	64[c]
14	_	12	54[d]
15	_	12	Nr[e]

[a]Reaction conditions: cyclohexanone (1.0 mmol), phenylacetylene (1.0 mmol), piperidine (1.0 mmol), catalyst **4c** (0.2 mol % of Cu). [b]Isolated yield. [c]Reaction temperature 80 °C. [d]Reaction temperature 70 °C. [e]Without catalyst. Nr = no reaction.

solvents toluene showed excellent yield (91%) of KA^2 coupling product **8a** (entry 4). Polar aprotic solvents gave low to moderate yields (entries 5−8). No reaction or poor yields was observed in case of polar protic solvents like MeOH, EtOH and water (entries 9−11). From the results, polar aprotic solvents affect the reaction more than polar protic solvents. Next, we conducted solvent free MCC reaction, and the desired product was obtained in excellent yield (94%) in 6 h at 110 °C (entry 12). Further reducing the reaction temperature and catalyst loading led to a low yield of product and longer reaction times (entries 13 and 14). The KA^2 coupling was efficient at 110 °C and the catalytic activity of heterogeneous copper complex is better in solvent free conditions. As expected no product was observed in the absence of catalyst (entry 15). F. Alonso reported KA^2 coupling product **8a** (77% yield) with 0.5 mol % of CuNPs/TiO2-catalyst in dichloromethane at 70 °C for 24 h.[13] Here we employed only 0.2 mol % of copper for efficient KA^2 coupling reaction under solvent free conditions at 110 °C.

With the optimization conditions in hand, we examined the KA^2 coupling reaction of cyclohexanone with phenylacetylene and different secondary amines (Table 2). Six membered cyclic secondary amines piperidine **6a** and morpholine **6b** both was converted into the corresponding products **8a** and **8b** in excellent yields (entries 1 and 2). Diamine groups consisted piperazine **6c** produced 1,4-bis-propargylamine product **8c** in 90% yield under the

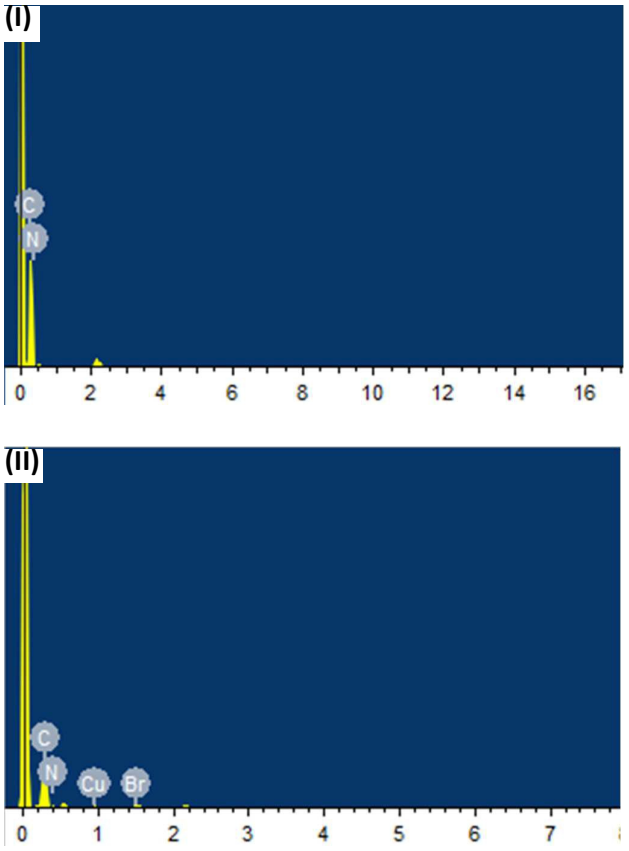


Fig. 3 EDX analysis of polystyrene-supported N-phenylpiperazine ligand **3** (I) and N-phenylpiperazine-Cu(II) complex **4c** (II).

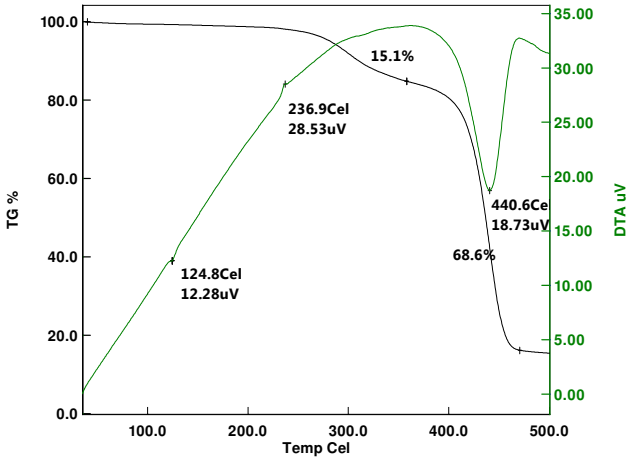


Fig. 4 Thermogravimetric analysis of polymer supported N-phenylpiperazine-Cu(II) complex **4c**.

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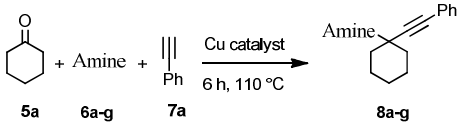
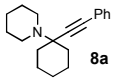
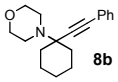
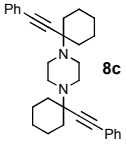
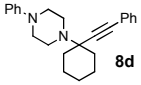
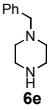
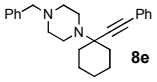
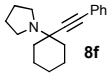
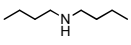
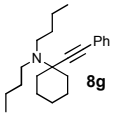
Table 2 Synthesis of propargylamines via KA^2 coupling reactions[a]



5a 6a-g 7a 8a-g

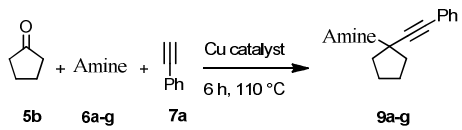
Entry	Amine	Product	Yield(%)[b]	Ref.
1	 6a	 8a	94	10
2	 6b	 8b	98	10
3	 6c	 8c	90[c]	-
4	 6d	 8d	92	-
5	 6e	 8e	95	-
6	 6f	 8f	89	14*a*
7	 6g	 8g	88	10

[a] Reaction conditions: cyclohexanone (1.0 mmol), phenylacetylene (1.0 mmol), amine (1.0 mmol), catalyst **4c** (0.2 mol % of Cu). [b] Isolated yield. [c] Cyclohexanone (2.0 mmol) and phenylacetylene (2.0 mmol) were used.

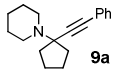
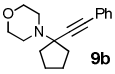
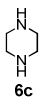
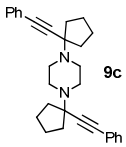
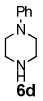
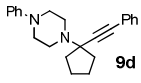
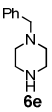
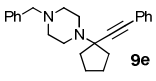
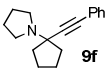
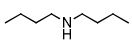
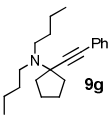
same reaction conditions by adding 2 equivalents of cyclohexanone and phenylacetylene (entry 3). 4-substituted phenyl and benzyl groups containing piperazine secondary amines **6d** and **6e** gave excellent yields (92 and 95%) of **8d** and **8e** (entries 4 and 5). Propargylamine **8f** formed in 89% yield from 5-membered cyclic secondary amine pyrrolidine **6f** (entry 6). Secondary N-dibutylamine **6g** afforded the corresponding coupling product **8g** in 88% yield (entry 7).

Next we extended the scope of this catalyst **4c** for KA^2 coupling reaction of cyclopentanone **5b** with phenylacetylene and variety of secondary amines under the above optimized conditions (Table 3). This proved to be an efficient catalytic method for KA^2 coupling reaction of cyclopentanone. All the amines reacted with cyclopentanone and phenylacetylene to produce tetrasubstituted propargylamine products **9a–g** in excellent yields (80–95%, entries 1–7). M. H. Sarvari recently reported cyclopentanone coupled products **9a**, **9b** and **9f** in 90–95% yield with excess nano copper(I) oxide–zinc oxide heterogeneous catalyst (0.073 mmol Cu and 0.033

Table 3 Synthesis of propargylamines via KA^2 coupling reactions piperazine[a]



5b 6a-g 7a 9a-g

Entry	Amine	Product	Yield(%)[b]	Ref.
1	 6a	 9a	92	14*a*
2	 6b	 9b	94	10
3	 6c	 9c	88[c]	-
4	 6d	 9d	92	-
5	 6e	 9e	95	-
6	 6f	 9f	92	14*a*
7	 6g	 9g	80	-

[a]Reaction conditions: cyclopentanone (1.0 mmol), phenylacetylene (1.0 mmol), amine (1.0 mmol), catalyst **4c** (0.2 mol % of Cu). [b] Isolated yield. [c] Cyclopentanone (2.0 mmol) and phenylacetylene (2.0 mmol) were used.

mmol Zn).[14a] However, in presence of our catalyst **4c** afforded excellent yields of the same products **9a**, **9b** and **9f** (92%, 94% and 92%) respectively (entries 1,2 and 6).

Encouraged by the above results, further we extended the scope of the MCC reaction to cyclohexanone and N-phenylpiperazine with various alkynes (Table 4). Electron withdrawing like *p*-CF_3O and *p*-Br substituted phenylacetylenes **7b** and **7c** afforded 86% and 89% yields of the corresponding products (**8h** and **8i** entries 1 and 2). 3-ethynylthiophene **7d** and but-3-yn-1-ylbenzene **7e** gave the coupled products **8j** and **8k** in moderate to good yields (entries 3 and 4). Ethynylcyclopentane **7f** coupled propargylamine product **8l** was obtained in 91% yield (entry 5). The reaction also extended to aliphatic acyclic terminal alkynes such as 1-hexyne **7g**, 1-heptyne **7h**, 1-octyne **7i** and 1-decyne **7j** which gave the corresponding products **8m–8p** in excellent yields (entries 6–9). All the new tetrasubstituted propargylamine products **8h–8p** of N-phenylpiperazine and cyclohexanone were obtained in excellent yields.

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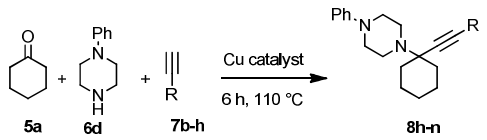
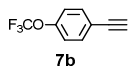
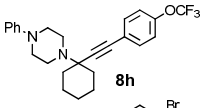
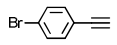
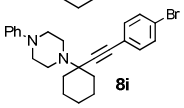
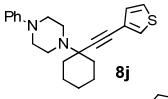
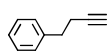
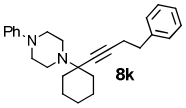
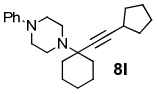
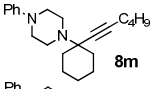
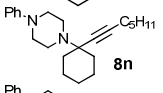
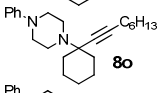
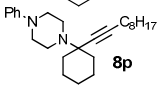
Table 4 KA^2 coupling reaction of cyclohexanone with phenylacetylene and amine.



5a 6d 7b-h 8h-n

Entry	R	Product	Yield(%)[b]	Ref.
1	 7b	 8h	86	-
2	 7c	 8i	89	-
3	 7d	 8j	80	-
4	 7e	 8k	75	-
5	 7f	 8l	91	-
6	C_4H_9 7g	 8m	90	-
7	C_5H_{11} 7h	 8n	93	-
8	C_6H_{13} 7i	 8o	96	-
9	C_8H_{17} 7j	 8p	92	-

a Reaction conditions: cyclohexanone (1.0 mmol), 1-alkyne (1.0 mmol), N-phenylpiperazine (1.0 mmol), catalyst **4c** (0.2 mol % of Cu). [b] Isolated yield.

The reusability of the heterogeneous catalyst is very important for economic point of view and in industrial applications. Therefore we have studied the reusability of the polymer supported catalyst for KA^2 coupling reactions of phenylacetylene with piperidine and cyclohexanone. After the completion of the reaction, the catalyst was easily separated from the reaction mixture by simple filtration, washing with acetonitrile and drying for further use. The activity of solid catalyst was not decreased considerably even after 5 cycles.

To find out the degree of leaching of the copper from the polymer supported N-phenylpiperazine, the catalyst was separated by filtration and the copper content of the filtrate was determined by ICP. During the course of multi-component coupling reactions, only 0.2% of copper was lost into solution after the first run. After five recycles loss of 8% was observed, which shows the average amount of leaching of copper per cycle is about 1.6%.

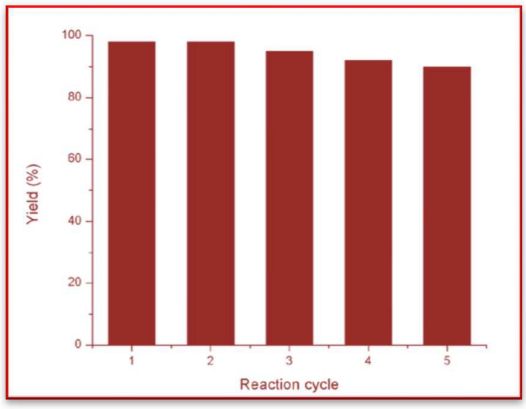
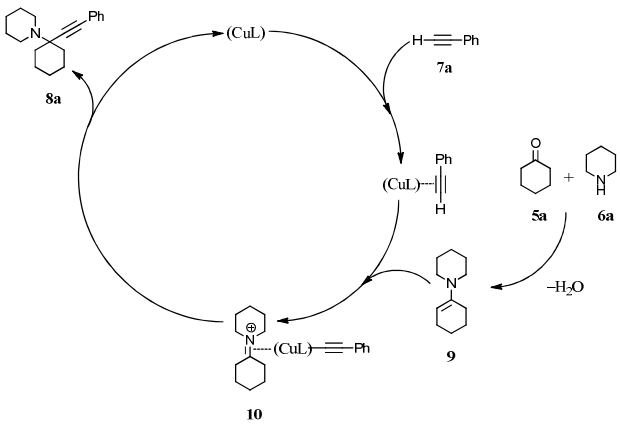


Fig. 5 Recyclability of catalyst **4c** for propargylamine synthesis.



Scheme 2 Proposed catalytic pathway for KA^2 coupling.

On the basis of the above described experiments we propose a reaction mechanism which involves complexation of copper with alkyne **7a** and enamine **9** (generated in situ from ketone **5a** and amine **6a**).[8] This results in the formation of intermediate **10** and intramolecular transfer of the alkyne moiety produces corresponding propargylamine **8a** with the regeneration of the copper catalyst (Scheme 2).

Conclusions

We have developed a highly efficient polymer supported N-phenylpiperazine-copper complex-catalyzed KA^2 coupling of ketone, alkyne and amine in 1 : 1 : 1 ratio under solvent free conditions. This method is simple and generates a diverse range of propargylamines in good to excellent yields of various substituted amines and terminal alkynes with cyclohexanone and cyclopentanone. This catalyst is superior in secondary amine

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participating solvent-free KA^2 coupling reactions compared to the earlier reports. Moreover, the catalyst can be reused for a reasonable number of consecutive cycles without a noticeable loss of its catalytic activity. These advantages make this protocol more viable from the cost and environmental point of view.

Experimental

General information

All materials were commercial reagent grade. Chloromethylated polystyrene (1% cross linked, 200-400 mesh with 1.0-1.3 mmol/g) was a product of Alfa-acer. Alkyne, ketone and amine compounds were obtained from Aldrich. $CuBr_2$ was procured from Merck and used without further purification. All solvents were dried and distilled by standard methods. Purification of products was carried out by column chromatography using commercial grade silica gel (60-120 mesh) using mixture of ethyl acetate and hexane as eluting agent. The ^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ and TMS as the internal standard. IR spectra were obtained using KBr pallets. ESI-MS spectra were determined on a LCQ ion trap mass spectrometer equipped with an ESI source.

Preparation of polymer supported N-phenylpiperazine (3)

To a 250-mL round bottom flask containing CH_3CN (50 mL), equipped with magnetic stirrer bar is added with chloromethylated polystyrene (1 g, 1.2 mmol/g of Cl) and N-phenylpiperazine (5 mmol) and NaI (0.1 mmol). The reaction mixture was stirred for 48 h at 70 °C and was subsequently filtered and washed thoroughly with CH_3CN, dried in oven at 80 °C for 24 h.

Preparation of polystyrene-supported Cu complex (4c)

To the EtOH solution polystyrene-supported N-phenylpiperazine ligand (1 g), and a solution of $CuBr_2$ (0.5 g) in EtOH (10 mL) were added, and the resulting mixture was allowed to stir at 70 ^{o}C for 24 h. This mixture was filtered and washed thoroughly with EtOH (3 × 30 mL) and finally dried in vacuum at 80 ^{o}C for 24 h (Scheme 1).

General experimental procedure for KA^2 coupling reaction

To a mixture of cyclohexanone (1.0 mmol), amine (1.0 mmol) and phenylacetylene (1.0 mmol), catalyst **4c** (20 mg, 0.02 mmol of Cu) and the solution was stirred at 110 °C for 6 h. After the completion of reaction (as monitored by TLC), the solvent EtOAc (10 mL) was added and the catalyst was separated out by filtration and the polymer was washed with acetonitrile. The Organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum. Then the crude mixture was purified by column chromatography (EtOAc/hexane) to afford the pure product. All the products were confirmed from ^{1}H and ^{13}C NMR and Mass spectral analysis.

New compounds characterization data

1,4-bis(1-(phenylethynyl)cyclohexyl)piperazine (8c): pale yellow solid, mp 199-201 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45-7.43 (m, 4H), 7.30-7.27 (m, 6H), 2.81 (s, 7H), 2.09 (d, *J* = 12.35 Hz, 4H), 1.75-1.70 (m, 4H), 1.67-1.59 (m, 6H), 1.53-1.47 (m, 4H), 1.25-1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.1, 127.6, 123.6, 90.2, 86.6, 58.8, 46.6, 35.5, 29.6, 25.6, 22.9; HRMS: exact mass calculated for $C_{32}H_{39}N_2$ $[M + H]^+$ = 451.3113, found m/z 451.3107.

1-phenyl-4-(1-(phenylethynyl)cyclohexyl)piperazine (8d): white solid, mp 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.43 (m, 2H), 7.28-7.25 (m, 5H), 6.95 (d, *J* = 8.69 Hz, 2H), 6.85 (t, *J* = 7.17 Hz, 1H), 3.25 (m, 4H), 2.91 (m, 4H), 2.12 (d, *J* = 12.20 Hz, 2H), 1.77-1.74 (m, 2H), 1.69-1.62 (m, 4H), 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 131.7, 129.0, 128.1, 127.7, 123.4, 119.5, 115.8, 89.8, 86.5, 58.7, 49.5, 46.1, 35.7, 25.6, 22.8; HRMS: exact mass calculated for $C_{24}H_{29}N_2$ $[M + H]^+$ = 345.2331, found m/z 345.2306.

1-benzyl-4-(1-(phenylethynyl)cyclohexyl)piperazine (8e): pale yellow solid, mp 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44-7.42 (m, 2H), 7.33-7.25 (m, 8H), 3.52 (s, 2H), 2.76 (m, 4H), 2.53 (m, 4H), 2.07 (m, 2H), 1.73-1.69 (m, 2H), 1.66-1.58 (m, 3H), 1.51-1.45 (m, 2H), 1.25 (m, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 131.7, 129.2, 128.0, 127.6, 126.9, 123.5, 90.2, 86.3, 63.0, 58.6, 53.6, 46.0, 35.7, 25.6, 22.8; HRMS: exact mass calculated for $C_{25}H_{31}N_2$ $[M + H]^+$ = 359.2487, found m/z 359.2467.

1-phenyl-4-(1-((4-(trifluoromethoxy)phenyl)ethynyl)cyclohexyl)piperazine (8h): pale yellow solid, mp 142-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46 (d, *J* = 8.85 Hz, 2H), 7.28-7.24 (m, 2H), 7.14 (d, *J* = 7.93 Hz, 2H), 6.95 (d, *J* = 7.93 Hz, 2H), 6.85 (t, *J* = 7.32 Hz, 1H), 3.24 (t, *J* = 5.03 Hz, 4H), 2.89 (t, *J* = 5.03 Hz, 4H), 2.11 (m, 2H), 1.77-1.75 (m, 2H), 1.65-1.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 148.5, 133.1, 129.0, 122.2, 120.7, 119.6, 115.8, 90.9, 85.1, 58.7, 49.5, 46.1, 35.6, 25.6, 22.7; HRMS: exact mass calculated for $C_{25}H_{28}ON_2F_3$ $[M + H]^+$ = 429.2154, found m/z 429.2122.

1-(1-((4-bromophenyl)ethynyl)cyclohexyl)-4-phenylpiperazine (8i): Pale yellow solid, mp: 169-171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42 (d, *J* = 8.55 Hz, 2H), 7.30-7.24 (m, 4H), 6.95 (d, *J* = 7.82 Hz, 2H), 6.85 (d, *J* = 7.33 Hz, 1H), 3.24 (t, *J* = 5.13 Hz, 4H), 2.88 (t, *J* = 5.01 Hz, 4H), 2.11 (m, 2H), 1.77-1.74 (m, 2H), 1.63-1.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 133.1, 131.3, 122.3, 121.8, 119.5, 115.8, 91.1, 85.4, 58.7, 49.5, 46.1, 35.5, 25.5, 22.7; HRMS: exact mass calculated for $C_{24}H_{28}N_2Br$ $[M + H]^+$ = 423.1426, found m/z = 423.1410.

1-phenyl-4-(1-(thiophen-3-ylethynyl)cyclohexyl)piperazine (8j): white solid, mp 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.39 (m, 1H), 7.28-7.22 (m, 3H), 7.10 (m, 1H), 6.95 (d, *J* = 7.82 Hz, 2H), 6.84 (t, *J* = 7.33 Hz, 1H), 3.24 (t, *J* = 5.13 Hz, 4H), 2.89 (t, *J* = 5.13 Hz, 4H), 2.10 (m, 2H), 1.77-1.72 (m, 2H), 1.65-1.55 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 130.1, 129.0, 127.9, 125.0, 122.3, 119.5, 115.8, 89.3, 81.3, 58.7, 49.5, 46.1, 35.7, 25.6, 22.7; HRMS: exact mass calculated for $C_{22}H_{27}N_2S$ $[M + H]^+$ = 351.1895, found m/z = 351.1873.

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1-phenyl-4-(1-(4-phenylbut-1-yn-1-yl)cyclohexyl)piperazine (8k): pale yellow solid, mp 78-79 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.29-7.23 (m, 5H), 7.21-7.18 (m, 2H), 6.94 (d, *J* = 7.82 Hz, 2H), 6.84 (t, *J* = 7.33 Hz, 1H), 3.19 (t, *J* = 5.13 Hz, 4H), 2.83 (t, *J* = 4.73 Hz, 2H), 2.74 (t, *J* = 5.13 Hz, 4H), 2.53 (t, *J* = 7.45 Hz, 2H), 1.93 (m, 2H), 1.66-1.61 (m, 3H), 1.56-1.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 140.7, 129.0, 128.5, 128.2, 126.0, 119.4, 115.8, 85.4, 80.6, 58.2, 49.4, 45.8, 35.6, 35.5, 25.6, 22.7, 20.7; HRMS: exact mass calculated for $C_{26}H_{33}N_2$ $[M + H]^+$ = 373.2644, found m/z = 373.2625.

1-(1-(cyclopentylethynyl)cyclohexyl)-4-phenylpiperazine (8l): white solid, mp 114-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (t, *J* = 8.31 Hz, 2H), 6.94 (d, *J* = 7.82 Hz, 2H), 6.83 (t, *J* = 7.33 Hz, 1H), 3.22 (t, *J* = 5.25 Hz, 4H), 2.79 (t, *J* = 5.13, Hz, 4H), 2.68-2.61 (m, 1H), 1.97 (m, 2H), 1.90-1.84 (m, 2H), 1.74-1.65 (m, 5H), 1.62-1.52 (m, 7H), 1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 129.0, 119.3, 115.7, 91.2, 79.1, 58.2, 49.4, 45.9, 35.8, 34.4, 30.2, 25.7, 24.8, 22.9; HRMS: exact mass calculated for $C_{23}H_{33}N_2$ $[M + H]^+$ = 337.2644, found m/z = 337.2622.

1-(1-(hex-1-yn-1-yl)cyclohexyl)-4-phenylpiperazine (8m): pale yellow solid, mp 101-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (t, *J* = 8.68 Hz, 2H), 6.94 (d, *J* = 7.94 Hz, 2H), 6.84 (t, *J* = 7.33 Hz, 1H), 3.22 (t, *J* = 5.13 Hz, 4H), 2.80 (t, *J* = 5.13, Hz, 4H), 2.22 (t, *J* = 7.09 Hz, 2H), 1.97 (d, *J* = 12.47 Hz, 2H), 1.70-1.67 (m, 2H), 1.59 (m, 3H), 1.52-1.39 (m, 7H), 0.91 (t, *J* = 7.21 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.0, 119.4, 115.8, 86.3, 79.6, 58.3, 49.4, 45.9, 35.8, 31.3, 25.7, 22.8, 21.9, 18.3, 13.6; HRMS: exact mass calculated for $C_{22}H_{33}N_2$ $[M + H]^+$ = 325.2644, found m/z = 325.2621.

1-(1-(hept-1-yn-1-yl)cyclohexyl)-4-phenylpiperazine (8n): Pale yellow solid, mp: 87-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (t, *J* = 8.39 Hz, 2H), 6.94 (d, *J* = 7.78 Hz, 2H), 6.83 (t, *J* = 7.32 Hz, 1H), 3.21 (t, *J* = 5.18 Hz, 4H), 2.80 (t, *J* = 5.18, Hz, 4H), 2.21 (t, *J* = 7.17 Hz, 2H), 1.97 (m, 2H), 1.70-1.67 (m, 3H), 1.62-1.57 (m, 3H), 1.54-1.48 (m, 2H), 1.44-1.40 (m, 2H), 1.39-1.35 (m, 2H), 1.34-1.28 (m, 2H), 0.89 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.0, 119.4, 115.8, 86.4, 79.7, 58.3, 49.5, 46.0, 35.8, 31.0, 28.9, 25.7, 22.8, 22.1, 18.6, 14.0; HRMS: exact mass calculated for $C_{23}H_{35}N_2$ $[M + H]^+$ = 339.2800, found m/z = 339.2777.

1-(1-(oct-1-yn-1-yl)cyclohexyl)-4-phenylpiperazine (8o): yellow solid, mp 82-84 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (t, *J* = 8.80 Hz, 2H), 6.94 (d, *J* = 7.82 Hz, 2H), 6.83 (t, *J* = 7.33 Hz, 1H), 3.21 (t, *J* = 5.13 Hz, 4H), 2.81 (t, *J* = 5.13, Hz, 4H), 2.21 (t, *J* = 7.09 Hz, 2H), 1.98 (d, *J* = 12.34 Hz, 2H), 1.70-1.67 (m, 2H), 1.59 (m, 3H), 1.58-1.36 (m, 7H), 1.33-1.28 (m, 4H), 0.88 (t, *J* = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.0, 119.4, 115.8, 86.4, 79.7, 58.3, 49.5, 46.0, 35.8, 31.2, 29.1, 28.5, 25.7, 22.8, 22.5, 18.6, 14.0; HRMS: exact mass calculated for $C_{24}H_{37}N_2$ $[M + H]^+$ = 353.2957, found m/z = 353.29367.

1-(1-(dec-1-yn-1-yl)cyclohexyl)-4-phenylpiperazine (8p): yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.25 (t, *J* = 8.31 Hz, 2H), 6.94 (d, *J* = 8.92 Hz, 2H), 6.84 (t, *J* = 7.33 Hz, 1H), 3.22 (t, *J* = 5.13 Hz, 4H), 2.81 (t, *J* = 5.13, Hz, 4H), 2.21 (t, *J* = 6.96 Hz, 2H), 1.98 (m, 2H), 1.70-1.67 (m, 3H), 1.59 (m, 3H), 1.43 (m, 4H), 1.28-1.25 (m, 10H), 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 129.0, 119.4, 115.8, 86.5, 79.6, 58.4, 49.4, 46.0, 35.8, 31.7, 29.6, 29.2, 29.0, 28.8, 25.6, 22.8, 22.6, 18.6, 14.0; HRMS: exact mass calculated for $C_{26}H_{41}N_2$ $[M + H]^+$ = 381.3252, found m/z = 381.3270.

1,4-bis(1-(phenylethynyl)cyclopentyl)piperazine (9c): white solid, mp 210-212 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.43-7.41 (m, 4H), 7.30-7.26 (m, 6H), 2.79 (s, 8H), 2.13-2.10 (m, 4H), 1.91-1.87 (m, 4H), 1.82-1.72 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.0, 127.5, 123.6, 91.1, 85.4, 66.7, 49.3, 39.6, 23.3; HRMS: exact mass calculated for $C_{30}H_{35}N_2$ $[M + H]^+$ = 423.2764, found m/z = 423.2764.

1-phenyl-4-(1-(phenylethynyl)cyclopentyl)piperazine (9d): white solid, mp 143-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42-7.41 (m, 2H), 7.29-7.24 (m, 5H), 6.95 (d, *J* = 7.93 Hz, 2H), 6.84 (d, *J* = 7.32 Hz, 1H), 3.25 (t, *J* = 5.03, Hz, 4H), 2.88 (t, *J* = 5.03 Hz, 4H), 2.18-2.15 (m, 2H), 1.93-1.91 (m, 2H), 1.83-1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 131.6, 129.0, 128.1, 127.6, 123.4, 119.5, 115.8, 90.5, 85.6, 66.8, 49.3, 49.1, 39.6, 23.3; HRMS: exact mass calculated for $C_{23}H_{27}N_2$ $[M + H]^+$ = 331.2174, found m/z = 331.2151.

1-benzyl-4-(1-(phenylethynyl)cyclopentyl)piperazine (9e): yellow solid, mp 81-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.43-7.41 (m, 2H), 7.33-7.22 (m, 8H), 3.52 (s, 2H), 2.74 (t, *J* = 4.83 Hz, 4H), 2.53 (m, 4H), 2.13-2.09 (m, 2H), 1.90-1.86 (m, 2H), 1.82-1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 131.6, 129.2, 128.0, 127.6, 126.9, 123.5, 90.9, 85.4, 66.7, 63.0, 53.2, 49.0, 39.6, 23.3; HRMS: exact mass calculated for $C_{24}H_{29}N_2$ $[M + H]^+$ = 345.2331, found m/z = 345.2309.

N,N-dibutyl-1-(phenylethynyl)cyclopentanamine (9g): yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40 (d, *J* = 7.93 Hz, 2H), 7.30-7.23 (m, 3H), 2.61 (t, *J* = 8.08 Hz, 4H), 2.08 (m, 2H), 1.85-1.76 (m, 6H), 1.53-1.47 (m, 4H), 1.34-1.25 (m, 4H), 0.92 (t, *J* = 7.32 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 128.1, 127.4, 124.0, 93.6, 83.4, 67.7, 53.0, 40.5, 32.4, 23.1, 20.7, 14.1; HRMS: exact mass calculated for $C_{21}H_{32}N$ $[M + H]^+$ = 298.2535, found m/z = 298.2511.

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Polystyrene supported N-phenylpiperazine-Cu(II) complex: An efficient and reusable catalyst for KA^2-coupling reaction under solvent-free conditions

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Propargylamines were synthesized in excellent yields from cyclohexanone and pentanone with variety of secondary amines and alkynes by employing new polystyrene supported N-phenylpiperazine-Cu(II) complex **4c**.