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The KA^2 coupling reaction under green, solventless, heterogeneous catalysis

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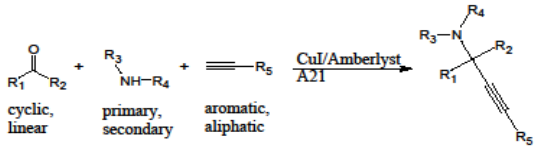
Graphical abstract



Highlights

- CuI on Amberlyst A-21 is a green efficient catalyst for the KA^2-coupling reaction
- Both primary and secondary amines can be used
- Aliphatic alkynes and linear ketones react successfully for the first time
- The catalyst is cheap and can be recycled and recovered easily
- Propargylamines obtained in good to excellent yields under heterogeneous catalysis

ABSTRACT: Amberlyst A-21 supported CuI was found to be highly efficient novel heterogeneous catalyst for the three-component reaction between ketones, amines and alkynes, commonly called KA^2-coupling. This inexpensive, easy-to-prepare, simple and recyclable catalyst has been employed in solventless conditions in the KA^2 coupling reaction involving both primary and secondary amines, ketones and various alkynes. The secondary and tertiary propargylamine products were obtained in good to excellent results in moderate reaction times.

KEYWORDS*: solventless, KA^2-coupling, multi-component, heterogeneous catalysis, copper(I) iodide - Amberlyst A-21*

1. Introduction

Propargylamines are key intermediates in the synthesis of biologically active compounds such as β-lactams, conformationally restricted peptides and drug molecules [1]. For example both aliphatic *N*-methyl propargylamines and primary propargylamines have been shown to be potent neural rescue agents that can help in the therapy of Parkinson's disease, Alzheimer's and other neurodegenerative diseases [1,2].

Such compounds are usually synthesized by the multi-component A^3-coupling reaction of an aldehyde, an amine and an alkyne to form a tertiary carbon centre. Initially, the latter reaction was catalysed by homogeneous catalysts containing metal ions that could activate the C_{sp}-H of the terminal alkyne. Examples of metal salts which have been used include: silver, gold, mercury, iridium, and copper salts [3-7]. However these reagents are usually moisture sensitive, require the use of an organic solvent and are not easily recoverable. Consequently, heterogeneous catalysts started to be employed such as polystyrene supported silver(I), lanthanum loaded copper(II) oxide, copper(0)-nanoparticles supported on montmorillonite, copper(II) exchanged molecular sieves, copper-aluminium nanocomposites, gold(III)-supported on ceria, nano-zinc sulfide particles among others [8-14].

Unlike aldehydes, ketones are much less reactive and have been rarely used in the synthesis of propargylamines which contain a quaternary carbon centre (Scheme 1). Most homogeneous and heterogeneous catalysts employed for the A^3-coupling were not extended to the KA^2 reaction or when utilised gave poor results. For example, the copper(II)-magnetite catalyst gave excellent yields for aldehydes after heating for 3 hours at 120 ^{0}C, but when ketones were employed poor yields were obtained after 7 days of reaction time [15]. The first major breakthrough in the KA^2 reaction happened when copper(I) iodide was employed in solventless conditions under microwave irradiation to obtain average to good results in short reaction times whilst employing primary amines and cyclohexanone derivatives [16]. When gold(III) bromide was used, it gave moderate to very good results in neat conditions even if only with secondary amines [17]. Copper(II) and copper(I) bromide (in the presence of molecular sieves) were two separate homogeneous catalysts that gave excellent yields [18,19]. Such homogeneous catalysts suffered from one or more of the following disadvantages: expensive, non-recoverable, required solvent and/or involved electromagnetic irradiation.

When heterogeneous catalysts were employed, varying results were obtained. Copper(II) chloride-supported on titania required 24 hours and dichloromethane solvent to give average results for two ketones only [20]. However both nano copper(I) oxide/zinc oxide and copper(I)-nano copper-magnetite gave excellent results in short reaction times in solventless conditions [21,22]. Despite this, both catalysts are expensive and preparation is not as simple. Moreover primary amines were not used or gave no products, no linear ketones were employed and only aromatic alkynes were involved.

In a previous study by our research group, copper(I) iodide was successfully loaded onto Amberlyst A-21 for the A^3-coupling (Figure 1); the catalyst is cheap, easily prepared, reusable and gave excellent results [23]. In continuation of our studies we have now employed this catalyst for the KA^2 reaction involving both primary and secondary amines, aliphatic and aromatic alkynes together with either cyclic or linear ketones in solventless conditions.

2. Experimental

2.1. Materials and methods

All commercially available chemicals were purchased from Aldrich and used without further purification. IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer calibrated against a 1602 cm^{-1} polystyrene absorbance spectra. Samples were analysed as a thin film or in a Nujol™ mull between sodium chloride plates. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD® NMR Spectrometer, equipped with an Ascend 500 11.75 Tesla Superconducting Magnet, operating at 500.13 MHz for ^1H and 125.76 MHz for ^{13}C, and a Multinuclear 5 mm PABBO Probe. Samples were dissolved in deuterated chloroform (with TMS). Mass spectra were performed using a Waters® ACQUITY® TQD system with a tandem quadrupole mass spectrometer after dissolving the sample in methanol. Reactions were monitored using TLC and GC on a Shimadzu GC-2010 *plus* gas chromatograph equipped with a flame ionisation detector and HiCap 5 GC column with dimensions of 0.32 mm (internal diameter) x 30 m (length) x 0.25 mm (film thickness), using nitrogen as carrier gas. The heterogeneity of the catalysis and copper(I) iodide loading on Amberlyst A-21 (A-21) was checked by performing flame atomic absorption spectroscopy (FAAS) using a contraAA® 700 High Resolution Continuum Source Atomic Absorption Spectrometer.

2.2 Preparation of Copper(I) iodide on Amberlyst A-21 (CuI /A-21)

Copper(I) iodide supported on Amberlyst A-21 was prepared by modifying a previously reported method [24]. A sample of dry Amberlyst A-21 was prepared by placing 10 g of the resin in 50 mL methanol and allowing it to stand for 30 minutes. After this, the mixture was filtered and washed with 20 mL methanol three times over. This procedure was then repeated in dichloromethane, and the resin was then placed in a vacuum desiccator to dry overnight. A solution of 2.285 g (12 mmol) of copper(I) iodide in 60 mL acetonitrile was then mixed with 4 g of dry Amberlyst A-21 and left stirring overnight at room temperature. Our method therefore used 3 mmol of copper(I) iodide per gram of Amberlyst A-21 instead of 2 mmol per gram. The solvent was subsequently evaporated off and the resulting light green resin was washed with two 15 mL aliquots of acetonitrile, followed by eight 15 mL aliquots of dichloromethane. The resin was dried overnight in a vacuum desiccator and, after confirming a stable weight, the loading of copper per gram of resin (1.64 mmol/g) was calculated by observing the weight increase of the final dried sample of CuI/A-21. This loading was also confirmed by performing an AAS study (see below).

2.3 Procedure for preparation of propargylamines by KA^2 coupling

A nitrogen-flushed 25 mL two-necked flask was loaded with 0.152 g (10 mol% CuI/A-21 with a loading in terms of copper(I) iodide of 1.64 mmol/g) to which the ketone (2.5 mmol), amine (3.0 mmol) and alkyne (3.75 mmol) were added. The mixture was stirred whilst heating in an oil bath at 98 ^0C in the presence of a nitrogen atmosphere. Upon completion, as judged by TLC which was stained with 2,4-dinitrophenylhydrazine, the reaction was allowed to cool down before the catalyst was filtered and washed with 5 x 2 mL diethyl ether. The crude reaction mixture was concentrated by rotary evaporation before being loaded to a silica-filled chromatographic column. The most common eluent mixtures used

were 9:1 or 8:2 *n*-hexane/ethyl acetate. The yields of the purified products were recorded and then IR and NMR spectroscopy and MS spectrometry were performed.

2.4 Flame atomic absorption spectroscopy

In order to confirm heterogeneity of the catalysis, the same procedure described in *Section 2.3* was followed up to the point when the catalyst was washed with diethyl ether (5 x 2 mL). Then the filtrate was concentrated by rotary evaporator and the crude reaction mixture was treated with 3 mL concentrated (70%) nitric(V) acid (trace grade) in order to oxidize copper(I) iodide and make it water soluble. Subsequently, the resulting mixture was treated with 15 – 20 mL of 1% HCl / 0.1% KCl (all trace grade) followed by 25 mL of ethyl acetate. The resulting immiscible mixture was shaken several times before separating the two layers. As a result, any leached copper ended up in the aqueous layer. Finally, the aqueous layer was made up to 45 mL and secured in a plastic container for analysis by the AAS spectrometer. The recovered catalyst was reused for further cycles repeating the same procedure. All samples were then analysed by AAS after plotting a calibration curve using a 5 ppm stock solution of copper (trace grade).

In order to calculate the exact loading of copper(I) iodide on A-21, 0.1 g of the prepared catalyst was weighed and treated with 3 mL of 70% nitric(V) acid (70%) followed by 3 mL of 34% hydrochloric acid (all trace grade). The copper(I) iodide became oxidized and leached out from the A-21 beads forming a yellow solution. Following filtration, the yellow solution was diluted to 200 mL using 1% HCl/0.1% KCl (all trace grade) and copper loading was checked by AAS. The concentration of copper in this solution was found to be 52.99 mg/L meaning that the amount of copper present in the 0.1 g sample was 10.598 mg. As a result, the loading of copper(I) iodide on Amberlyst A-21was found to be equal to 1.66 mmol /g.

2.5 Analytical data

The characterization of the products by ^{1}H NMR and ^{13}C NMR spectroscopy and MS spectrometry led to the following results.

(**4i**) ***N*-benzyl-1-(phenylethynyl)cyclohexanamine** [18]. Orange oil. IR (neat, cm^{-1}): 3307 (w), 3082 (w), 3061 (m), 3028 (m), 2929 (s), 2852 (s), 1702 (m), 1687 (m), 1597 (m), 1489 (s), 1450 (s), 1442 (s), 1357 (w), 1342 (w), 1290 (m), 1265 (m), 1157 (m), 1116 (m), 1070 (m), 1028 (m), 952 (w), 935 (w), 906 (w), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.48 - 7.44 (m, 2 H), 7.42 - 7.37 (m, 2 H), 7.38 - 7.29 (m, 6 H), 3.98 (s, 2 H), 1.98 (d, *J*=11.9Hz, 2 H), 1.79 - 1.62 (m, 5 H), 1.60-1.49 (m, 5 H).

(**4ii**) **4-[1-(phenylethynyl)cyclohexyl]pyrrolidine** [21]. Yellow orange oil.
IR (neat, cm^{-1}): 3078 (w), 3053 (w), 3030 (w), 3018 (w), 2960 (s), 2929 (s), 2870 (m), 2856 (m), 2806 (m), 1597 (m), 1558 (m), 1489 (s), 1442 (s), 1288 (m), 1263 (s), 1246 (s), 1199 (s), 1155 (w), 1126 (w), 1068 (w), 1028 (w), 912 (w), 882 (w), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.46 - 7.41 (m, 2 H), 7.32 - 7.27 (m, 3 H), 2.84 - 2.77 (m, 4 H), 2.04 (d, *J* = 12.2 Hz, 2 H), 1.82 - 1.77 (m, 4 H), 1.74 - 1.60 (m, 7 H), 1.58 - 1.48 (m, 2 H).

(**4iii**) **4-[1-(phenylethynyl)cyclohexyl]piperidine** [21]. Yellow oil. IR (neat, cm^{-1}): 3080 (w), 3061 (w), 3028 (w), 2931 (s), 2852 (s), 2802 (m), 2748 (w), 1739 (w), 1716 (w), 1597 (w), 1558 (w), 1489 (m), 1465 (w), 1452 (m), 1442 (m), 1292 (w), 1244 (w), 1157 (m), 1097 (m), 1068 (w), 966 (w), 910 (w),

862 (w), 756 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.47 - 7.40 (m, 2 H), 7.32 - 7.26 (m, 3 H), 2.67 (br. s., 4 H), 2.09 (d, *J* = 12.5 Hz, 2 H), 1.76 - 1.68 (m, 3 H), 1.66 - 1.57 (m, 7 H), 1.53 - 1.42 (m, 4 H).

(**4iv**) **4-[1-(phenylethynyl)cyclohexyl]morpholine** [21]. Yellow-orange solid. Melting point (98 ^{0}C). IR (neat, cm^{-1}): 3080 (w), 3035 (w), 3008 (m), 2931 (s), 2856 (s), 2818 (m), 1558 (m), 1489 (m), 1452 (m), 1442 (m), 1290 (w), 1269 (w), 1215 (m), 1116 (s), 1070 (w), 1028 (w), 972 (w), 921 (w), 881 (w), 754 (s), 690 (m), 667 (m). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.42 - 7.38 (m, 2 H), 7.28 - 7.25 (m, 3 H), 3.74 (t, *J* = 4.9 Hz, 4 H), 2.70 (t, *J* = 4.9 Hz, 4 H), 2.11 - 2.04 (m, 2 H), 1.92 - 1.83 (m, 2 H), 1.77 - 1.44 (m, 8 H).

(**4v**) ***N*-benzyl-*N*-methyl-1-(phenylethynyl)cyclohexanamine** [20]. Light yellow oil. IR (neat, cm^{-1}) 3080 (w), 3062 (m), 3028 (m), 2931 (s), 2852 (s), 2790 (s), 1597 (m), 1558 (m), 1489 (s), 1452 (s), 1361 (w), 1340 (w), 1290 (m), 1217 (m), 1157 (w), 1120 (w), 1070 (m), 1028 (m), 960 (w), 912 (w), 881 (w), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.51 - 7.44 (m, 2 H), 7.40 - 7.35 (m, 2 H), 7.34 - 7.28 (m, 6 H), 3.68 (s, 2 H), 2.20 (s, 3 H), 2.13 - 2.05 (m, 2 H), 1.83 - 1.58 (m, 7 H), 1.39 - 1.29 (m, 1 H).

(**4vi**) ***N*-(4-methoxybenzyl)-1-(phenylethynyl)cyclohexanamine** [16]. Orange oil. IR (neat, cm^{-1}): 3308 (w), 3057 (w), 3030 (w), 2995 (w), 2929 (s), 2852 (s), 2835 (m), 1610 (m), 1597 (m), 1585 (m), 1512 (s), 1442 (m), 1342 (w), 1300 (m), 1246 (s), 1176 (m), 1105 (w), 1070 (w), 1035 (m), 952 (w), 904 (w), 821 (m), 756 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.48 - 7.44 (m, 2 H), 7.34 - 7.29 (m, 5 H), 6.86 (d, *J*=8.5Hz, 2 H), 3.91 (s, 2 H), 3.79 (s, 3 H), 1.97 (d, *J* = 12.5 Hz, 2 H), 1.76 - 1.62 (m, 5 H), 1.61 - 1.46 (m, 5 H).

(**4vii**) **4-[1-(phenylethynyl)cyclopentyl]pyrrolidine** [21]. Yellow-orange oil. IR (neat, cm^{-1}): 3080 (w), 3053 (w), 3030 (w), 3020 (w), 2931 (s), 2852 (s), 2804 (m), 1597 (m), 1558 (s), 1489 (s), 1442 (m), 1348 (w), 1338 (w), 1288 (m), 1263 (m), 1157 (m), 1124 (m), 1068 (w), 912 (w), 881 (w), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.46 - 7.41 (m, 2 H), 7.32 - 7.27 (m, 3 H), 2.84 - 2.77 (m, 4 H), 2.04 (d, *J* = 12.2 Hz, 2 H), 1.82 - 1.77 (m, 4 H), 1.74 - 1.60 (m, 7 H), 1.58 - 1.48 (m, 2 H).

(**4viii**) **4-[1-(phenylethynyl)cyclopentyl]piperidine** [21]. Orange-brown oil. IR (neat, cm^{-1}): 3080 (m) , 3053 (m), 3030 (m), 3020 (m), 2964 (s), 2931 (s), 2848 (s), 2806 (s), 2748 (m), 2698 (m), 2673 (m), 1944 (w), 1874 (w), 1801 (w), 1597 (s), 1573 (m), 1489 (s), 1467 (m), 1454 (s), 1442 (s), 1382 (w), 1321 (w), 1288 (m), 1274 (m), 1271 (m), 1230 (m), 1195 (m), 1155 (m), 1107 (s), 1068 (m), 1037 (m), 1012 (m), 989 (m), 964 (w), 910 (m), 862 (m), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.42 - 7.38 (m, 2 H), 7.28 - 7.24 (m, 3 H), 2.69 - 2.58 (m, 4 H), 2.14 - 2.08 (m, 2 H), 1.91 - 1.82 (m, 2 H), 1.78 - 1.67 (m, 4 H), 1.63 - 1.57 (m, 6H).

(**4ix**) **4-[1-(phenylethynyl)cyclopentyl]morpholine** [21]. Orange solid. Melting point (75 ^{0}C). IR (neat, cm^{-1}): 3066 (w), 3062 (w), 3051 (w), 3030 (w), 2953 (m), 2860 (m), 2818 (m), 2762 (w), 2735 (w), 2688 (w), 2659 (w), 1990 (w), 1961 (w), 1732 (m), 1716 (m), 1683 (m), 1651 (m), 1597 (m), 1571 (m), 1489 (s), 1446 (s), 1392 (w), 1361 (w), 1271 (s), 1195 (m), 1138 (m), 1118 (s), 1103 (m), 1072 (m), 1020 (m), 991 (w), 920 (m), 871 (m), 761 (s), 692 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.42

- 7.38 (m, 2 H), 7.28 - 7.25 (m, 3 H), 3.74 (t, *J* = 4.9 Hz, 4 H), 2.70 (t, *J* = 4.9 Hz, 4 H), 2.11 - 2.04 (m, 2 H), 1.92 - 1.83 (m, 2 H), 1.82 - 1.76 (m, 2 H), 1.74 - 1.67 (m, 2 H).

(**4x**) ***N*-benzyl-*N*-methyl-1-(phenylethynyl)cyclopentanamine.** Novel compound. Light yellow oil. IR (neat, cm^{-1}): 3082 (m), 3061 (m), 3028 (m), 2958 (s), 2926 (s), 2852 (m), 2789 (m), 2698 (w), 1946 (w), 1874 (w), 1801 (w), 1597 (m), 1558 (s), 1489 (s), 1454 (s), 1361 (w), 1323 (w), 1296 (w), 1261 (w), 1219 (w), 1192 (w), 1141 (w), 1124 (w), 1068 (m), 1028 (m), 910 (w), 827 (w), 754 (s), 750 (m), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.51 - 7.44 (m, 2 H), 7.39 - 7.35 (m, 2 H), 7.34 - 7.28 (m, 5 H), 7.28 - 7.26 (m, 1 H), 3.65 (s, 2 H), 2.21 (s, 3 H), 2.20 - 2.12 (m, 2 H), 1.98 - 1.78 (m, 6 H). ^{13}C NMR (126MHz, CHLOROFORM-d) δ = 141.2, 131.8, 128.8, 128.3, 128.2, 127.7, 126.6, 123.8, 90.8, 85.6, 59.2, 55.7, 36.7, 35.4, 22.9. MS(ES+): m/z = 320 $[MH]^{+}$, 199, 120, 105, 91, 77.

(**4xiii**) **1-(3-methyl-1-phenylpent-1-yn-3-yl)pyrrolidine** [19]. Orange-brown oil. IR (neat, cm^{-1}): 3084 (m), 3061 (m), 3028 (m), 2933 (s), 2852 (m), 2802 (m), 2750 (w), 1681 (s), 1651 (s), 1635 (s), 1598 (m), 1558 (m), 1489 (m), 1454 (m), 1440 (m), 1357 (m), 1265 (m), 1205 (w), 1174 (w), 1155 (w), 1112 (w), 1099 (w), 1070 (w), 1033 (w), 1026 (w), 993 (w), 952 (w), 912 (w), 862 (w), 756 (s), 690 (s).^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.37 - 7.29 (m, 2 H), 7.29 - 7.26 (m, 3 H), 2.86 - 2.75 (m, 4 H), 1.81 (t, *J* = 6.6 Hz, 4 H), 1.74 - 1.61 (m, 2 H), 1.42 (s, 3 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

(4xvii) 1-(3-methyl-1-phenylhex-1-yn-3-yl)pyrrolidine [25]. Orange-brown oil. IR (neat, cm^{-1}): 3080 (w), 3061 (w), 3030 (w), 2960 (s), 2929 (s), 2872 (s), 2808 (s), 1741 (w), 1716 (w), 1683 (w), 1652 (w), 1597 (m), 1558 (s), 1489 (s), 1456 (m), 1442 (m), 1369 (m), 1313 (w), 1290 (w), 1253 (w), 1176 (m), 1147 (m), 1118 (m), 1085 (w), 1068 (w), 1029 (w), 995 (w), 912 (w), 754 (s), 690 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.43 - 7.39 (m, 2 H), 7.29 - 7.26 (m, 3 H), 2.82 - 2.75 (m, 4 H), 1.82 - 1.78 (m, 4 H), 1.67 - 1.57 (m, 4 H), 1.43 (s, 3 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

(**4xxii**) **1-[1-(oct-1-yn-1-yl)cyclohexyl]pyrrolidine** [18]. Yellow oil. IR (neat, cm^{-1}): 2929 (s), 2856 (s), 2806 (s), 1446 (m), 1377 (w), 1348 (w), 1328 (w), 1282 (m), 1263 (m), 1224 (w), 1161 (w), 1126 (m), 1078 (w), 1014 (w), 995 (w), 914 (w), 883 (w), 723 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 2.71 (t, *J* = 6.7 Hz, 4 H), 2.23 (t, *J* = 6.9 Hz, 2 H), 1.89 (d, *J* = 12.5 Hz, 2 H), 1.76 (td, *J* = 3.2, 7.0 Hz, 4 H), 1.59 - 1.13 (m, 16 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

(**4xxiii**) **1-[1-(oct-1-yn-1-yl)cyclohexyl]piperidine** [18]. Yellow oil. IR (neat, cm^{-1}): 2956 (s), 2931 (s), 2854 (m), 2802 (w), 1716 (m), 1465 (m), 1454 (m), 1361 (w), 1220 (w), 1159 (w), 1118 (w), 1101 (w), 1035 (w), 862 (w), 756 (m). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 2.58 (br. s., 4 H), 2.23 (t, *J* = 6.9 Hz, 2 H), 1.99 - 1.91 (m, 2 H), 1.69 - 1.23 (m, 25 H), 0.92 - 0.87 (m, 4 H).

(**4xxiv**) **1-[1-(oct-1-yn-1-yl)cyclohexyl]morpholine** [18]. Yellow oil. IR (neat, cm^{-1}): 2953 (m), 2929 (s), 2852 (s), 2837 (m), 1558 (w), 1494 (m), 1454 (m), 1377 (m), 1284 (w), 1269 (m), 1226 (w), 1163 (w), 1120 (m), 1070 (w), 1033 (w), 975 (m), 941 (w), 921 (w), 883 (m), 856 (w), 790 (w), 765 (w), 746 (w), 725 (w), 690 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 3.81 - 3.67 (m, 4 H), 2.69 - 2.55 (m, 4 H), 2.27 - 2.21 (m, 2 H), 1.89 (d, *J* = 12.8 Hz, 2 H), 1.74 - 1.17 (m, 16 H), 0.90 (t, *J* = 6.9 Hz, 3 H).

(**4xxv**) ***N*-benzyl-1-(oct-1-yn-1-yl)-*N*-methylcyclohexanamine** [18]. Light yellow oil. IR (neat, cm^{-1}): 3084 (w), 3062 (m), 3026 (m), 2926 (s), 2852 (s), 2790 (m), 1716 (s), 1602 (w), 1558 (m), 1494 (s), 1454 (s), 1357 (m), 1327 (w), 1284 (w), 1236 (w), 1217 (w), 1174 (w), 1161 (m), 1120 (m), 1074 (w), 1055 (m), 989 (w), 960 (m), 904 (w), 881 (w), 827 (w), 756 (s), 698 (s), 667 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.36 (d, *J* = 7.3 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 3.57 (s, 2 H), 2.26 (t, *J* = 6.9 Hz, 2 H), 2.11 (s, 3 H), 1.99 - 1.89 (m, 2 H), 1.76 - 1.67 (m, 2 H), 1.63 - 1.51 (m, 8 H), 1.50 - 1.42 (m, 3 H), 1.37 - 1.23 (m, 3 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

(**4xxvi**) ***N*-benzyl-1-(oct-1-yn-1-yl)cyclohexanamine** [18].Yellow-orange oil. IR (neat, cm^{-1}): 3304 (w), 3084 (w), 3061 (w), 3026 (w), 2931 (s), 2854 (s), 1712 (m), 1681 (w), 1604 (w), 1558 (w), 1494 (m), 1452 (s), 1377 (w), 1342 (w), 1340 (w), 1282 (w), 1261 (w), 1215 (w), 1172 (w), 1139 (w), 1118 (m), 1028 (w), 956 (w), 937 (w), 906 (w), 756 (s), 698 (s). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.37 (d, *J* = 6.9 Hz, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 3.88 (s, 2 H), 2.28 (t, *J* = 7.0 Hz, 2H), 1.83 (d, *J* = 12.8 Hz, 2 H), 1.70 - 1.58 (m, 6 H), 1.58 - 1.51 (m, 3 H), 1.49 - 1.38 (m, 5 H), 1.34 - 1.29 (m, 4 H), 0.92 - 0.88 (m, 3 H)

(**4xxvii**) ***N*-4-methoxybenzyl-1-(oct-1-yn-1-yl)cyclohexanamine** [18].Yellow oil. IR (neat, cm^{-1}): 3309 (w), 3101 (w), 3028 (w), 2995 (w), 2929 (s), 2854 (s), 1712 (s), 1681 (m), 1610 (s), 1602 (s), 1577 (m), 1512 (s), 1456 (s), 1300 (m), 1246 (s), 1172 (m), 1107 (w), 1035 (m), 904 (w), 858 (w), 829 (m), 763 (w), 642 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.28 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 3.82 (s, 2 H), 3.79 (s, 3 H), 2.26 (t, *J* = 7.0 Hz, 2 H), 1.84 - 1.82 (m, 2 H), 1.66 - 1.57 (m, 5 H), 1.56 - 1.52 (m, 2 H), 1.47 - 1.37 (m, 6 H), 1.33 - 1.30 (m, 3 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

(**4xxviii**) **1-[1-(oct-1-yn-1-yl)cyclopentyl]pyrrolidine**. Novel compound. Yellow-orange oil. IR (neat, cm^{-1}): 2966 (s), 2931 (s), 2872 (s), 2858 (s), 2810 (m), 1454 (m), 1377 (w), 1354 (w), 1321 (w), 1294 (w), 1234 (w), 1211 (w), 1147 (w), 1085 (w), 723 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) = 2.76 - 2.62 (m, 4 H), 2.20 (t, *J* = 6.9 Hz, 2 H), 1.95 - 1.87 (m, 2 H), 1.81 - 1.68 (m, 9 H), 1.53 - 1.24 (m, 11 H), 0.90 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126MHz, CHLOROFORM-d) δ = 84.7, 81.0, 65.2, 49.0, 40.6, 31.3, 29.2, 28.4, 23.6, 23.4, 22.6, 18.6, 14.0. MS(ES+): m/z = 248$[MH]^{+}$, 109, 95, 79, 72, 67.

(**4xxix**) **1-[1-(oct-1-yn-1-yl)cyclopentyl]piperidine.** Novel compound. Yellow oil. IR (neat, cm^{-1}): 2960 (s), 2929 (s), 2870 (m), 2856 (m), 2804 (m), 1651 (m), 1467 (m), 1452 (m), 1440 (m), 1379 (w), 1321 (w), 1273 (w), 1230 (w), 1155 (w), 1110 (w), 1037 (w), 1008 (w), 906 (w), 862 (w), 771 (m), 754 (w), 723 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 2.55 (br. s., 4 H), 2.21 (t, *J* = 6.9 Hz, 2 H), 2.02 - 1.94 (m, 2 H), 1.86 - 1.67 (m, 5 H), 1.67 - 1.56 (m, 9 H), 1.54 - 1.47 (m, 3 H), 1.47 - 1.39 (m, 4 H), 1.30 (td, *J* = 3.2, 7.2 Hz, 3 H), 0.92 - 0.88 (m, 3 H). ^{13}C NMR (126MHz, CHLOROFORM-d) δ = 84.9, 81.3, 67.1, 50.1, 40.0, 31.3, 29.3, 28.5, 26.2, 24.5, 23.2, 22.6, 18.7, 14.0. MS(ES+): m/z = 262 $[MH]^{+}$, 109, 95, 86, 79, 67.

(**4xxx**) **4-[1-(4-methylphenylethynyl)cyclohexyl]morpholine** [17]. Orange solid. Melting point (75 ^{0}C). IR (neat, cm-1): 3078 (w), 3024 (w), 2968 (w), 2947 (w), 2935 (w), 2920 (w), 2895 (w), 2856 (w), 2814 (w), 1734 (w), 1683 (s), 1652 (s), 1506 (s), 1456 (m), 1290 (w), 1271 (m), 1247 (w), 1157 (w), 1130 (w), 1114 (s), 1076 (w), 1031 (w), 970 (w), 920 (w), 879 (w), 812 (m), 783 (w), 750 (w), 715 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.33 (d, *J* = 7.9 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 3.76 (t, *J* = 4.5 Hz, 4 H), 2.73 (t, *J* = 4.5 Hz, 4 H), 2.34 (s, 3 H), 2.03 (d, *J* = 12.4 Hz, 2H), 1.78 - 1.68 (m, 2 H), 1.68 - 1.60 (m, 3 H), 1.53 - 1.43 (m, 2 H), 1.31 - 1.23 (m, 1 H).

(4xxxi) 4-[1-(4-methylphenylethynyl)cyclopentyl]morpholine. Novel compound. Orange solid. Melting point (69 ^{0}C). IR (neat, cm^{-1}): 3082 (w), 3037 (w), 3024 (w), 2962 (s), 2949 (s), 2850 (s), 2816 (s), 2742 (w), 2692 (w), 1683 (w), 1652 (s), 1508 (s), 1456 (s), 1325 (w), 1301 (w), 1273 (m), 1271 (s), 1197 (s), 1139 (s), 1116 (s), 1101 (s), 1078 (s), 1020 (s), 993 (m), 921 (s), 916 (w), 873 (m), 810 (s), 748 (w), 709 (w). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.31 (d, *J* = 7.9 Hz, 4 H), 7.10 (d, *J* = 7.9 Hz, 4 H), 3.76 (t, *J* = 4.5 Hz, 4 H), 2.71 (t, *J* = 4.5 Hz, 4 H), 2.34 (s, 3 H), 2.12 - 2.06 (m, 2 H), 1.94 - 1.84 (m, 2 H), 1.84 - 1.76 (m, 2 H), 1.76 - 1.67 (m, 2 H). ^{13}C NMR (126MHz, CHLOROFORM-d) δ = 137.8, 131.6, 129.2, 120.4, 89.7, 85.7, 67.3, 67.1, 49.5, 39.3, 23.3, 21.4. MS(ES+): m/z = 270 [MH]$^{+}$, 183, 155, 129, 105, 88.

3. Results and discussion

3.1 Catalyst screening and optimization

Despite the fact that the following study was going to serve as a continuation for the A^3 coupling catalyzed by CuI/A21 [23], some catalyst screening and optimization trials were performed. The reaction between, cyclohexanone (**1i**), the primary amine benzylamine (**2i**) and phenylacetylene (**3i**) was chosen as the model reaction (Scheme 2). In the first trial (entry 1, Table 1), copper(II) chloride was selected as a catalyst because it had previously been used by another research group in a similar reaction involving 1-octyne instead of phenylacetylene [18]. When used at the reported conditions, the product was only obtained at a yield of 44%.

Then some preliminary investigations were performed using copper(I) iodide supported onto Amberlyst A-21. Copper(I) iodide was chosen as the active component because of a series of reasons. Firstly, in a similar study with a model reaction involving cyclohexanone, *p*-methoxybenzylamine and phenylacetylene under neat but homogeneous conditions, copper(I) iodide was the only halide which gave the best result [16]. Contrastingly, copper(I) bromide performed worse [16]. In effect, when copper(I) bromide was used in a separate KA^2 study under homogeneous conditions, it required toluene solvent and 4Å molecular sieves in order to function [19]; a scenario which is not ideal in terms of green chemistry. In addition, to the best of our knowledge, copper(I) chloride has been used only for A^3-coupling and in reactions involving benzylamine, ethyl acetate solvent was required apart from the fact that it had to be used at a higher loading of 30 mol% [26]. Lastly, when in an attempt to prepare a similar catalyst, copper(II) chloride was loaded onto Amberlyst A21, whilst following the same method used for copper(I) iodide, the polymeric beads burst and a slurry was formed. In effect CuI was selected among other halides according to solubility tests in organic solvents to get the best efficient preparation of the copper halide/Amberlyst A-21 supported catalyst [24].

Initially, the same conditions as reported in our previous A^3-coupling study [23] were followed, that is using a reagents mole ratio between ketone, amine and alkyne of 1:1.2:1.5 and a loading of 1.38 mmol CuI/g, but we got side products difficult to isolate together with the target one. At this point, it is important to clarify that when molar percentages are mentioned, they are all in terms of the amount of copper(I) iodide relative to the amount of limiting starting material i.e. the ketone. So we decided to prepare and use a catalyst batch with an increased loading of copper(I) iodide per gram of Amberlyst A-21 (1.64 mmol CuI/g). Encouragingly, the product was obtained at a higher yield of 74% (entry 2, Table 1) even if the total amount of copper(I) iodide used was still 10 mol% (i.e. 0.25 mmol CuI when reaction was performed at a 2.5 mmol scale) as in our original A^3-coupling procedure. This can be explained in terms of the fact that by increasing the copper(I) iodide loading, the overall number of unchelated amine groups decreased and hence the overall basicity of the catalyst decreased as well

(refer to Figure 1). Consequently, side reactions which can take place under basic conditions became less favoured.

Using Montmorillonite K10 as a support resulted in a yield reduction to 71% (entry 3, Table 1). This could be explained in terms of the fact that when the catalyst was added, the reaction mixture dried up and a small amount of dichloromethane solvent had to be added to aid stirring. In addition, it must be stated that Montmorillonite K10 is a cation exchanger and hence when copper(I) iodide is added H+ ions exchange with copper(I) ions. That is to say that actual amount of copper(I) used in terms of molar percentage could not be known.

Two separate trials (entries 4 and 5, Table 1) involving Amberlyst A-21 and copper(I) iodide only yielded two different results. Amberlyst A-21 did not yield the product whilst when copper(I) iodide was used in homogeneous conditions, yield was lower than in entry 2. This showed that heterogenising the copper(I) iodide on a support resulted in a higher activity probably because of an increase in the surface area of the catalyst. Finally, when copper(II) and silver (I) (entries 6 and 7, Table 1) were exchanged into the acidic polymer support Amberlyst 15, yields were very poor.

In trials 8 – 11 (Table 1), some condition optimizations were performed. Increasing the temperature and reaction time resulted in a lowering of the yield probably because of product decomposition. It must be stated that reaction progress was difficult to monitor because ketone spot remained slight evident when TLC analysis using 2,4-dinitrophenylhydrazine as an indicator was performed. Unfortunately the model reaction could not be followed using GC because of the predicted high boiling point of the product, not compatible with our GC column. Upon lowering the reaction temperature yield decreased further despite increasing reaction time. Finally, doubling the catalyst amount (in terms of molar percentage) caused a decrease in the yield because of more side product formation and possibly also due to more product adsorbing onto catalyst.

3.2 Substrate Screening

Once the conditions were established, substrates were varied to obtain a wide scope. As shown in Table 2, the coupling of cyclic ketones, secondary amines and phenylacetylene gave the desired products in good to excellent yields (entries 1-4). Primary amines such as benzylamine and 4-methoxybenzylamine also reacted successfully albeit after longer reaction times (entries 5 and 6). In the reactions involving cyclopentanone (**1ii**) instead of cyclohexanone, secondary amines reacted much faster to give the products in higher yields (entries 6-10). However, the primary amines benzylamine (**2i**) and 4-methoxybenzylamine (**2vi**) formed products which decomposed after exposure to air during work up and column loading. In fact, for the product of benzylamine, two column chromatographies were performed to purify it. When the second one was performed, as the yellow-orange band of the product travelled down the column, it started to darken and ultimately became brown-black in colour.

Unlike previous studies employing heterogeneous catalysts, copper(I) iodide-Amberlyst A-21 managed to catalyse some reactions involving linear ketones. 2-Butanone and 2-pentanone reacted successfully with pyrrolidine (**2ii**) (Table 3, entries 1 and 5) but when coupled with other amines, several difficulties were encountered. In some cases, the product could not be separated from side products despite performing more than one column chromatography. In other cases, the product which was formed gave single spot on TLC after chromatography but then several side product peaks appeared in ^{1}H NMR spectra probably implying that the products were decomposed. The same arguments applied for the products of the reaction involving the aromatic ketone acetophenone (**1v**) (Table 3, entry 9). Despite managing to isolate the compound which gave single spot on TLC, ^{1}H NMR spectra showed uncharacteristic peaks.

Finally, to the best of our knowledge, this catalyst is the first heterogeneous catalyst which can be used to form the KA^2 products when an aliphatic alkyne, such as 1-octyne (**3ii**) (Table 4) is employed. Note worthily, the yields are less impressive than those involving phenylacetylene because the terminal hydrogen of an aromatic alkyne is more acidic than that of an aliphatic one. This is because of the negative inductive and mesomeric effects exerted by the aromatic ring. 4-Methyphenylacetylene (**3iii**) was then reacted with morpholine and cyclopentanone or cyclohexanone separately (Table 4, entries 9 and 10). Interestingly, unlike when phenylacetylene was used, cyclohexanone performed better. However, it must be noted that a significant amount of product decomposition probably took place as the reaction monitoring through GC showed.

3.3 Catalyst stability, recovery and recyclability

When copper(I) iodide was loaded onto the previously white spherical beads of Amberlyst A-21, they became light green in colour presumably because of the coordination between the amine moiety in the polymeric resin and the copper(I) ion [23]. The catalyst is stable in air and when it was left exposed

for a number of weeks and subsequently used for reactions it was still active. Another advantage of the catalyst is the easy recovery because of its physical form i.e. beads. It is also safe and easy to handle.

In order to check its recyclability, the reaction between morpholine (**2iv**), cyclopentanone (**1ii**) and phenylacetylene (**3i**) was chosen based on the fact that it could be followed through GC (Table 2, entry 8). When the reaction was performed, the catalyst was easily filtered and washed with a minimum amount of diethyl ether (15 mL). Then it was allowed to dry in a desiccator under vacuum overnight before it was reused. As Figure 2 shows, the catalyst could be recycled and reused for up to 4 times to still give respectable results. All reactions were allowed to take place for the same amount of time (i.e. 4 hours).

The heterogeneity of the catalysis was proved by following a modified version of the hot filtration test [28]. The reaction mixture (including the catalyst) was allowed to stir for 30 minutes at the ideal conditions and GC conversion was recorded at this point (35%). Subsequently, the catalyst was filtered using diethyl ether solvent for the workup. The reaction mixture was concentrated using a rotary evaporator (under vacuum) and a vacuum oil pump (30 minutes) to remove all solvent traces. Then the reaction mixture was left to stir once more whilst heating at 98 ^{0}C under Nitrogen in the absence of the catalyst and after 4 hours GC yield had remained approximately the same (38%). This further proved that no copper(I) iodide had actually leached from the catalyst and any yield reductions were probably because of product adsorption onto catalyst. In fact, the polymeric beads turned from green to light brown from the 1st to the 4th recycling trial.

AAS analysis of the filtrates obtained after each cycle for the reaction between morpholine (**2iv**), cyclopentanone (**1ii**) and phenylacetylene (**3i**) are reported in Table 5.

After the first trial, the amount of copper(I) iodide leached out was very small (0.74%) hence confirming why the yield value for the second reaction cycle (91%) was similar to the first one (95%). Contrastingly, the CuI leached out during the second cycle was substantially larger (5.68%) corresponding to the sudden drop in the yield (76%) for the third cycle. Leaching in the 3rd run decreased once more to 1.91% but a significant amount of leaching was observed in the 4th run (33.59%) showing why the catalyst could no longer be reused. A possible reason for this could have been the physical degradation of the beads due to heating.

4. Conclusions

Copper(I) iodide supported on Amberlyst A-21 is a cheap, safe, heterogeneous, easily prepared and easily recoverable, and recyclable catalyst which has already been utilised successfully for propargylamines synthesis through the A^3-coupling reaction. In this study we have shown that it can also be employed successfully for propargylamine derivatives synthesis through the KA^2-coupling reaction, using the less reactive ketones and confirming its efficient catalytic activity. So far the heterogeneous catalysts which have been employed were either very expensive or could not catalyse reactions involving primary amines, aliphatic alkynes and/or linear ketones. Yet, in this study we have shown that this is possible using the afore-mentioned catalyst so giving access to a wide range of primary and secondary propargylamines. All products were obtained in good to excellent yields when aromatic alkynes were used whilst aliphatic alkynes still gave respectable results.

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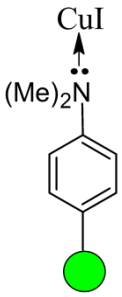


Figure 1. Structure of copper(I) iodide loaded onto Amberlyst A-21 polymer resin.

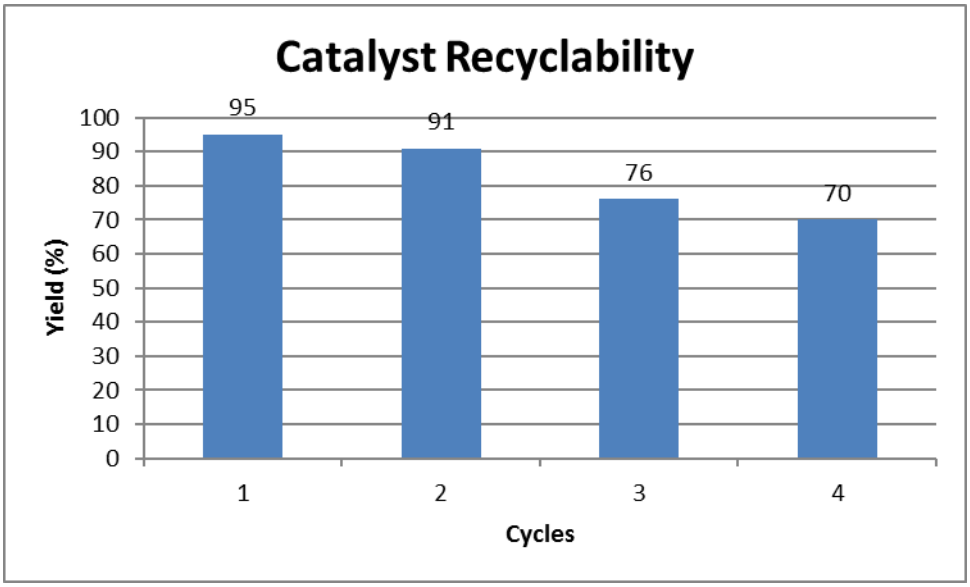
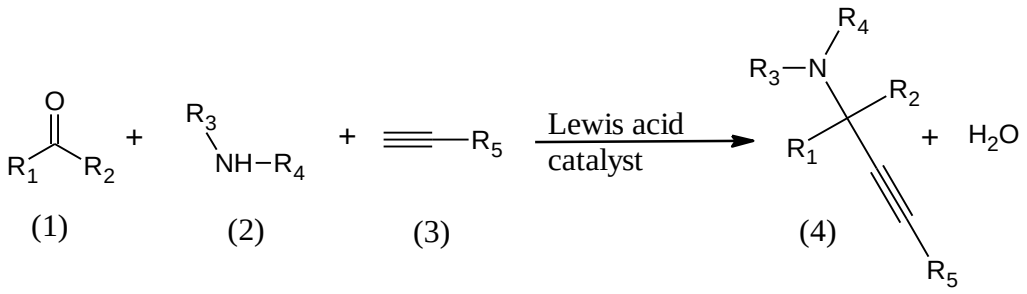
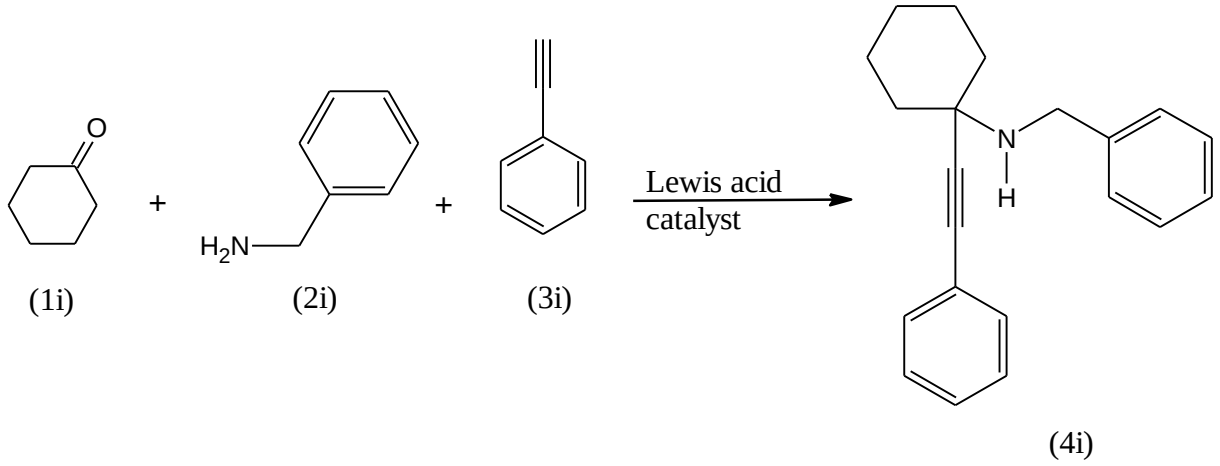


Figure 2. Recyclability runs for the catalyst CuI/A-21 in KA^2 coupling.



Scheme 1. Multicomponent coupling of a ketone (1), an amine (2) and an alkyne (3) (KA^2).



(1i) (2i) (3i) (4i)

Scheme 2. KA^2 Model reaction of cyclohexanone (1i), benzylamine (2i) and phenylacetylene (3i).

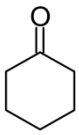
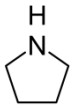
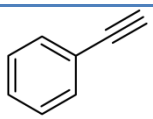
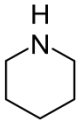
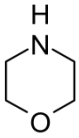
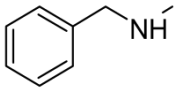
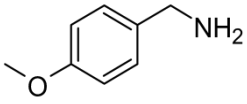
Table 1. Optimization trials and catalyst screening for the KA^2 -coupling reaction.

Entry	Temperature (^{0}C)	Reaction time (hrs)	Catalyst	mol %	Yield[a] (%)
1[b]	110	6	$CuCl_2$	5	44
2[c]	98	10	CuI/A-21	10	74
3[d]	98	15.5	Cu(I)-MK10[e]	-	71
4[f]	98	10	A-21	-	0
5[g]	98	10	CuI	10	62
6[g]	98	10	Cu(II)-A15[e]	10	44
7[g]	98	10	Ag(I)-A15[e]	10	13
8[g]	110	25	CuI/A-21	10	62
9[g]	98	24	CuI/A-21	10	76
10[g]	80	48	CuI/A-21	10	40
11[h]	98	10	CuI/A-21	20	68

[a] Pure isolated yield after column chromatography and drying in rotary evaporator
[b] Reaction conditions [18]: amine (2.5 mmol), ketone (2.5 mmol), alkyne (2.5 mmol), 110 ^{0}C, 0.0168 g (5 mol%) $CuCl_2$
[c] Reaction conditions: amine (3.0 mmol), ketone (2.5 mmol), alkyne (3.75 mmol), 98 ^{0}C, 0.152 g (10 mol%) CuI /A-21 (loading 1.64 mmol CuI/g)
[d] Reaction conditions: amine (3.0 mmol), ketone (2.5 mmol), alkyne (3.75 mmol), 98 ^{0}C, 0.2 g Cu(I)-Montmorillonite K10, 6 – 8 drops of dichloromethane
[e] Prepared following the method reported in [27]
[f] Reaction conditions: amine (3.0 mmol), ketone (2.5 mmol), alkyne (3.75 mmol), 98 ^{0}C, 0.2 g A-21

[g] Reaction conditions: amine (3.0 mmol), ketone (2.5 mmol), alkyne (3.75 mmol), 98 ^{0}C, 0.152 g (10 mol%) CuI/A-21 (loading 1.64 mmol CuI/g), N_2 atmosphere
([h] Reaction conditions: amine (3.0 mmol), ketone (2.5 mmol), alkyne (3.75 mmol), 98 ^{0}C, 0.304 g (10 mol%) CuI/A-21 loading 1.64 mmol CuI/g), N_2 atmosphere

Table 2. Three component coupling of cyclic ketones, primary and secondary amines and phenylacetylene.

Entry	Ketone	Amine	Alkyne	Product	Time (hours)[a]	Yield (%)[b] [TON][c]
1	 **1i**	 **(2ii)**	 **(3i)**	**4ii**	8	85 [8.5]
2	**1i**	 **(2iii)**	**3i**	**4iii**	8	85 [8.5]
3	**1i**	 **(2iv)**	**3i**	**4iv**	4	66 [6.6]
4	**1i**	 **(2v)**	**3i**	**4v**	23	62 [6.2]
5	**1i**	 **(2vi)**	**3i**	**4vi**	48	60 [6.0]
6	 **1ii**	**2ii**	**3i**	**4vii**	1.5	71 [7.1]

7	**1ii**	**2iii**	**3i**	**4viii**	3	98 [9.8]
8	**1ii**	**2iv**	**3i**	**4ix**	4	95 [9.5]
9	**1ii**	**2v**	**3i**	**4x**	4	96 [9.6]
10	**1ii**	**2i**	**3i**	**4xi**	-	-[d]
11	**1ii**	**2vi**	**3i**	**4xii**	-	-[d]

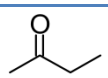
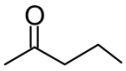
[a] Reaction conditions: ketone (2.5 mmol), amine (3.0 mmol), alkyne (3.75 mmol), 0.152 g CuI/A-21 (10 mol%), 98 ^{0}C, Nitrogen atmosphere

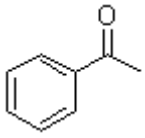
[b] Pure isolated yield

[c] TON (Turnover number) was calculated as follows: total number of moles of product/number of moles of active catalyst i.e. number of moles of copper(I) iodide present in 0.152 g of 1.64 mmol/g CuI/A21

[d] Product decomposed during column chromatography.

Table 3. Three component coupling of linear ketones, amines and phenylacetylene.

Entry	Ketone	Amine	Alkyne	Product	Time (hours)[a]	Yield (%)[b] [TON][c]
1	 **(1iii)**	**2ii**	**3i**	**4xiii**	4	70 [7.0]
2	**1iii**	**2iii**	**3i**	**4xiv**	11.5	-[d]
3	**1iii**	**2iv**	**3i**	**4xv**	4	-[d]
4	**1iii**	**2v**	**3i**	**4xvi**	4	-[d]
5	 **1iv**	**2ii**	**3i**	**4xvii**	3.5	81 [8.1]
6	**1iv**	**2iii**	**3i**	**4xviii**	3, 6, 10	-[d, e]
7	**1iv**	**2iv**	**3i**	**4xix**	24	-[d]
8	**1iv**	**2v**	**3i**	**4xx**	9	-[d]

9	 **1v**	**2ii**	**3i**	**4xxi**	17	-[d]

[a] Reaction conditions: ketone (2.5 mmol), amine (3.0 mmol), alkyne (3.75 mmol), 0.152 g of CuI/A-21 (10 mol%), 98 ^{0}C, Nitrogen atmosphere

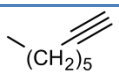
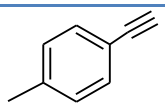
[b] Pure isolated yield after column chromatography

[c] TON (Turnover number) was calculated as follows: total number of moles of product/number of moles of active catalyst i.e. number of moles of copper(I) iodide present in 0.152 g of 1.64 mmol/g CuI/A21

[d] Product was formed but could not be separated from side products by column chromatography or it started to decompose to form other side products. This was confirmed by ^{1}H-NMR which showed characteristic peaks and other unexpected ones.

[e] Reaction was allowed to take place for different periods to try to avoid product decomposition but product obtained was never pure

Table 4. Three component coupling of ketones, amines and other alkynes (aliphatic and aromatic).

Entry	Ketone	Amine	Alkyne	Product	Time (hours)[a]	Yield (%)[b] [TON][c]
1	**1i**	**2ii**	 **3ii**	**4xxii**	3	81 [8.1]
2	**1i**	**2iii**	**3ii**	**4xxiii**	15	48 [4.8]
3	**1i**	**2iv**	**3ii**	**4xxiv**	9	46 [4.6]
4	**1i**	**2v**	**3ii**	**4xxv**	5	65 [6.5]
5	**1i**	**2i**	**3ii**	**4xxvi**	12.5	22 [2.2]
6	**1i**	**2vi**	**3ii**	**4xxvii**	6	61 [6.1]
7	**1ii**	**2vi**	**3ii**	**4xxviii**	2	81 [8.1]
8	**1ii**	**2vii**	**3ii**	**4xxix**	7	49 [4.9]
9	**1i**	**2iv**	 **3iii**	**4xxx**	8	71 [7.1]

10	**1ii**	**2iv**	**3iii**	**4xxxi**	4	61 [6.1]

[a] Reaction conditions: ketone (2.5 mmol), amine (3 mmol), alkyne (3.75 mmol), 0.152 g CuI /A-21 (10 mol%), 98 ^{0}C, Nitrogen atmosphere

[b] Pure isolated yield

Table 5 - Copper leaching values for the filtrates obtained after each recycling cycle

Cycle Number	Concentration of copper in 45 mL extract (mg/L)	Mass of copper(I) iodide leached out into reaction mixture (mg)	Percentage amount of copper(I) iodide leached out (%)[a]
1	2.638	0.356	0.7404
2	20.26	2.732	5.686
3	6.811	0.9186	1.912
4	119.7	16.14	33.59

[a] Values are based on the reaction performed at the following conditions: ketone (2.5 mmol), amine (3 mmol), alkyne (3.75 mmol), 0.152 g CuI /A-21 (10 mol%), 98 ^{0}C, Nitrogen atmosphere. Hence, amount of copper(I) iodide present initially was 48.050 mg and percentages in last column are calculated referring to this initial value, which remained unchanged.