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(54) Title: PROPARGYLAMINE SYNTHESIS USING A COPPER (I) CATALYSED THREE COMPONENT COUPLING REACTION

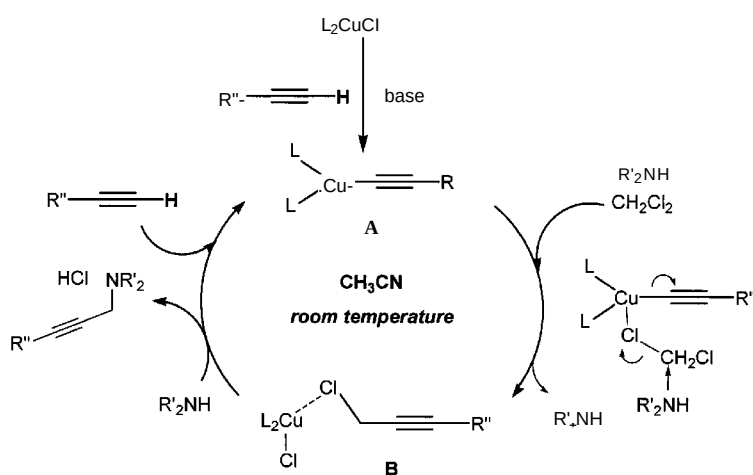


Figure 3

(57) Abstract: The present invention relates to a three component coupling reaction. In this reaction a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine are reacted in the presence of a copper (I) catalyst to produce a propargylamine.

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THREE COMPONENT COUPLING REACTION

Technical Field

The present invention relates to a three component coupling reaction to produce propargylamines.

Priority

This application claims priority from Singaporean application 201004888-2, filed on 7 July 2010, the entire contents of which are incorporated herein by cross-reference.

Background of the Invention

The direct C-H activation for C-C bond-formation is one of the most interest reactions for organic chemistry. C-C bond formation using alkynes as a carbon nucleophilic source is a very useful method in synthesis. However, the reactive alkynilides are typically prepared by using sensitive organometallic reagents such as BuLi, EtMgBr or metal hydride in a separate step rather than by a more versatile and elegant catalytic C-H activation process.

Recently, a three-component coupling of an aldehyde, an alkyne, and an amine (A^3 -coupling) reaction has been developed and well documented, in which the terminal alkyne is used as a carbon nucleophilic source via C-H activation (a) Wei, C ; Zhang, L.; Li, C. J. *Synlett* **2004**, 1472; b) Patil, M. K.; Keller, M.; Reddy, B. M.; Pale, P.; Sommer, J. *Eur. J. Org. Chem.* **2008**, 4440; c) Zhang, X.; Corma, A. *Angew. Chem. Int. Ed.* **2008**, 47, 4358; d) Zhang, Y.; Li, P.; Wang, M.; Wang, L. *J. Org. Chem.* **2009**, 74, 4364; e) Gommermann, N.; Koradin, C ; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, 42, 5763; f) Knopfel, T. F.; Aschwanden, P. A.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004**, 116, 6097; g) Bisai, K. A.; Singh, V. K. *Org. Lett.* **2006**, 8, 2405). Highly reactive organometallic reagents are avoided in this reaction. A^3 -coupling reactions, as an excellent example of multi-component reactions (MCRs), provide an elegant method for synthesis of propargylamines. These structures are commonly found skeletons and synthetically versatile key intermediates for the preparation of many nitrogen-containing biologically active compounds. From a mechanistic point of view, A^3 -coupling reaction is an extension of well known alkynylation of imines with terminal alkynes. A disadvantage of the A^3 -coupling reaction is that aldehyde functionality in the starting materials can participate in the reaction even when this is not desired.

Summary of the Invention

In a first aspect of the invention there is provided a process for producing a propargylamine comprising reacting a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine in the presence of a copper (I) catalyst.

5 The following options may be used in conjunction with the first aspect, either individually or in any suitable combination.

The geminal dihalide may have structure CA_2X_2 , wherein each A is independently hydrogen or deuterium and each X is independently chloride, bromide or iodide. It may be $CH_2C_1H_2$ or CH_2I_2 .

10 The amine may be such that the nitrogen atom is not directly attached to or part of an aromatic ring. It may be a non-aromatic amine. It may be an aliphatic amine.

The copper (I) catalyst may be a copper (I) halide such as copper (I) chloride.

The process may be conducted under non-acidic conditions. It may be conducted in the presence of a base. The base may be used in at least about 50 mol% relative to the geminal dihalide. In a particular embodiment, the base is an inorganic base, or is absent, and the terminal alkyne or salt thereof is acetylene ($HC\equiv CH$) or an acetylide salt (C_2A or HC_2B , where A is a divalent cation and B is a monovalent cation), whereby the product is a 1,4-diamino-2-alkyne. In this embodiment, the molar ratio of acetylene or acetylide salt to geminal dihalide and the molar ratio of acetylene or acetylide salt to amine may each be, independently, about 1:1.5 to about 1:2.5

Both the mole ratio of alkyne or salt thereof to geminal dihalide and the mole ratio of geminal dihalide to amine may be, independently, between about 0.8:1 and 1.2:1.

The process may be conducted under an inert atmosphere.

25 In an embodiment there is provided a process for producing a propargylamine comprising reacting a terminal alkyne or a salt thereof, a methylene dihalide and a primary or secondary aliphatic amine in the presence of a base and of a copper (I) halide catalyst.

In a second aspect of the invention there is provided a propargylamine made by the process of the first aspect.

30 In a third aspect of the invention there is provided use of a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine for making a propargylamine.

In a fourth aspect of the invention there is provided use of a copper (I) catalyst for catalysing the reaction of a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine to a propargylamine.

Brief Description of the Drawings

Embodiments of the present invention will now be described, by way of example only, with reference to the accompanying drawings wherein:

Figure 1 shows a comparison between the present AHA coupling and the A^3 coupling;

Figure 2 shows the reaction of an acetylide in the reaction of the invention; and

Figure 3 shows a proposed mechanistic scheme for the reaction.

Detailed Description

The present invention relates to a copper catalysed reaction of a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine in the presence of a copper (I) catalyst to produce a propargylamine. Details of the various materials in this reaction are set out below.

terminal alkyne: this has structure $R-C\equiv C-H$. R may be an alkyl group, a cyclic group, an aryl group, a heteroaryl group or may be hydrogen. R may optionally be substituted, e.g. with one or more alkyl groups, cyclic groups, aryl groups, heteroaryl groups, ether groups, ester groups etc. The terminal alkyne may be present as its anion ($R-C\equiv C^-$) or, in the case where R is hydrogen (including deuterium), its dianion (C_2^{2-}). The counterion may be a +1 cation, e.g. sodium, potassium etc. or may be a +2 cation, e.g. calcium, magnesium etc.

In the context of the present specification (here and elsewhere unless otherwise indicated), an alkyl group may be linear or branched. It may be C1 to C12 or may be greater than C12, and may in some cases be oligomeric or polymeric. It may be substituted or may be unsubstituted (e.g. with cyclic groups, aromatic groups etc.). It may be C1 to C6, C1 to C3, C3 to C6 or C6 to C12, e.g. C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11 or C12 provided that, if it is branched it is greater than C2.

In the context of the present specification (here and elsewhere unless otherwise indicated), a cyclic group refers to a non-aromatic ring structure. It may have from 3 to 8 atoms in the ring. Each may, independently, be C, O, N or S (provided that the N is tertiary). It may for example be a cyclohexyl group, a tetrahydrofuryl group, a tetrahydropyranyl group, an N-methylpiperidinyl group, an N-methylmorpholinyl group etc.

In the context of the present specification (here and elsewhere unless otherwise indicated), an aryl group may be monocyclic, bicyclic, tricyclic or may have more than 3 rings. The rings may be fused or linked directly or linked by a linker group (e.g. ether, alkyl etc.) and combinations of these structures (e.g. naphthyloxyphenyl) are also envisaged.

In the context of the present specification (here and elsewhere unless otherwise indicated), a heteroaryl group may be monocyclic, bicyclic, tricyclic or may have more than 3 rings. The rings may be fused or linked directly or linked by a linker group (e.g. ether, alkyl etc.) and combinations of these structures are also envisaged. Each ring, independently, may have 1, 2 or 3 heteroatoms. Each heteroatom may, independently, be N, S or O. Each ring may, independently, be 5, 6 or 7 membered.

geminal dihalide: this has structure $R'R''CXX'$, where R' and R'' are each, independently, hydrogen (including deuterium), alkyl, a cyclic group, aryl or heteroaryl, where these are as defined above. X and X' are each halides, which may be the same or may be different.

They may each, independently, be chloride, bromide or iodide. Particular examples of the geminal dihalide include CH_2C_{12} , CD_2C_{12} , CH_2I_2 , benzal chloride ($PhCHCl_2$).

amine: the amine may be a non-aromatic amine. In this context, this is taken to indicate that the amine nitrogen is not part of an aromatic system (e.g. pyridine) or attached directly to an aromatic system (e.g. aniline), however it may be attached indirectly to an aromatic system, for example by a methylene group or a longer chain alkyl group (e.g. the amine may be benzylamine). In some embodiments the amine is not a secondary amine having two arylmethyl substituents. The amine may be an aliphatic amine. It may have no substituents having aromatic groups therein. The amine may be primary or may be secondary, i.e. it may have structure $R^1NH R^2$, where R^1 and R^2 are each, independently, hydrogen or an alkyl group or a cyclic group as defined above. It may be a cyclic amine, in which the nitrogen is part of a non-aromatic ring (e.g. morpholine, piperidine etc.). In this case R^1 and R^2 are joined so as to form a ring structure. In some embodiments at least one of R^1 and R^2 is not H.

catalyst: the catalyst for the reaction is a copper (I) catalyst. It may be a copper (I) salt, e.g. a copper (I) halide. It may for example be copper (I) chloride.

solvent: the reaction may be conducted in a solvent. It may be a solvent for some of the materials used in the reaction or in some cases for all of these materials. In some instances the geminal dihalide itself may be used as a solvent. In other cases a separate solvent may be used. The solvent may be an aprotic solvent. It may be polar or may be non-polar. It

may be for example DMSO, DMF, HMPA, HMPT, THF, diethyl ether, dioxane, tetrahydropyran, toluene, benzene, acetonitrile or some other suitable solvent. It may be a solvent which is inert to the reaction conditions, or one or more of the materials used in the reaction may be used as a solvent. Mixtures of such suitable solvents may also be used. The solvent may be a dry solvent, i.e. an anhydrous solvent. It may have less than about 0.1% water by weight, or less than about 0.05, 0.01, 0.005 or 0.001% by weight.

base: if used, the base may be an inorganic base or an organic base. It may be for example a carbonate, a bicarbonate, a phosphate or some other base. It may be a base capable of scavenging acid generated in the reaction. It may be an amine. In some instances the amine of the reaction may also function as a base. An excess of that amine may be used in such cases. Alternatively a separate amine which can not participate in the reaction may be used. Such amines include anilines, secondary aromatic amines and tertiary amines. Suitable amines which may be used as the base include diazabicyclononene, diazabicycloundecene, triethylamine, pyridine, α -methyl benzylamine etc. The base may be soluble in the solvent or it may be insoluble in the solvent, or it may be sparingly soluble in the solvent. In some instances the selection of base can control the product obtained. Thus when using acetylene or a salt thereof as the alkyne, use of an inorganic base may result in disubstitution to produce a 1,4-diamino-2-butyne and use of an organic base (or no added base) may result in monosubstitution to produce a propargylamine (i.e. a 3-amino-1-propyne). The base, if used, may be soluble in the solvent or may be insoluble therein.

atmosphere: the reaction may be conducted under a non-oxidising atmosphere. It may be conducted under an inert atmosphere. The atmosphere may be a dry atmosphere. It may be for example carbon dioxide, nitrogen, helium, argon or a mixture of any two or more of these.

product: the product of the reaction is a propargylamine, i.e. a 3-amino-1-propyne. As noted above, double addition can occur under some conditions to acetylene to generate a 1,4-diamino-2-butyne. In its most general form, reaction of a terminal acetylene $R-C\equiv CH$ with a geminal dihalide $R'R''CXX'$ and an amine R^1NH^2 will produce $R-C\equiv C-C(R'R'')N(R^1)R^2$. R , R' , R'' , R^1 and R^2 are as defined above. In the event that R is H (or a negative charge), the product may be $R^1(R^2)NC(R'R'')-C\equiv C-C(R'R'')N(R^1)R^2$, or may be $H-C\equiv C-C(R'R'')N(R^1)R^2$.

The reaction is commonly conducted at about 40 to about 80°C, or about 40 to 60, 60 to 80 or 50 to 70°C, e.g. about 40, 50, 60, 70 or 80°C. It may be conducted for

sufficient time for substantially all of at least one of the amine, the alkyne or the dihalide to be consumed. The time will depend in part on the temperature at which the reaction is conducted. Indicative times are from about 1 to about 24 hours, or about 1 to 12, 1 to 6, 6 to 24, 12 to 24, 12 to 18 or 10 to 15 hours, e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours.

The mole ratio of alkyne to halide may be about 0.8 to about 1.2 (i.e. about 0.8:1 to about 1.2:1), or about 1 to 1.2, 0.8 to 1 or 0.9 to 1.1, e.g. about 0.8, 0.85, 0.9, 0.95, 1, 1.05, 1.1, 1.15 or 1.2. There may be a slight molar excess of halide over alkyne, e.g. about 1 to about 10%, or about 1 to 5 or 5 to 10%, e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10%. The mole ratio of alkyne to amine may be about 0.7 to about 1.1 (i.e. about 0.7:1 to about 1.1:1) or about 0.7 to 1, 0.7 to 0.9, 0.9 to 1.1 or 1 to 1.1, e.g. about 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 1, 1.05 or 1.1. There may be a slight molar excess of amine over alkyne, e.g. about 5 to 25%, or about 10 to 25, 15 to 25, 5 to 20 or 10 to 20%, e.g. about 5, 10, 15, 20 or 25%. There may be a slight molar excess of amine over halide, e.g. about e.g. about 1 to about 10%, or about 1 to 5 or 5 to 10%, e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10%. In cases where double addition to an acetylene or salt thereof is desired, the ratios of amine and dihalide may be higher, e.g. double. Each may independently be in a molar ratio to the acetylene or salt thereof of about 1.5 to about 2.5 (i.e. about 1.5:1 to about 2.5:1), or about 1.5 to 2, 1 to 2.5 or 1.7 to 2.2, e.g. about 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4 or 2.5.

The catalyst may be present in a molar ratio to the acetylene of about 1 to about 10%, or about 1 to 5, 5 to 10 or 3 to 7%, e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10%.

If present, the base may be used in a molar ratio to the dihalide of at least about 50%, or at least about 60, 70, 80, 90 or 100%, or of about 50 to about 200%, or of about 50 to 100, 100 to 150 or 150 to 200%, e.g. about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200%.

The concentration of the alkyne in the solvent, if solvent is used, may be about 1 to about 10% w/v, or about 1 to 5, 5 to 10 or 3 to 7%, e.g. about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10%. Indicative concentrations of other reagents and of the catalyst may be derived from the concentration of the alkyne using the above indicative molar ratios.

The reaction may be achieve yields (based on alkyne or salt thereof) of at least about 30%, or at least about 40, 50, 60, 70, 80 or 90%. Under optimum conditions, yields of over 90% are commonly achievable.

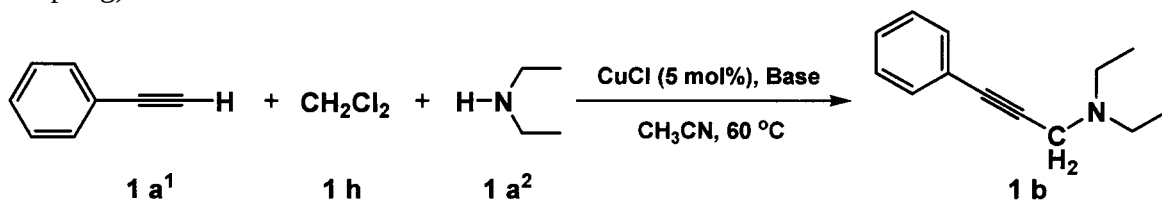
In common embodiments, the present invention relates to an efficient copper catalyzed three-component coupling reaction of terminal alkynes, dihalomethanes and amines through C-H and C-halide activation to form propargylamines under mild conditions. The reactions described herein commonly generate propargylamines in high yields and are applicable to both aromatic and aliphatic alkynes. This reaction differs from current methods of synthesis of propargylamines by A^3 coupling reaction with alkyne, aldehyde and amine in that it is tolerant to aldehyde functionality in the reagents and is generally conducted under milder conditions. Compared to other systems, such as the A^3 coupling reaction, this new approach is attractive for its mild reaction conditions, simple operation, low cost and tolerance to a wide range of substrates.

The chemistry presented herein offers not only a new approach to propargylamines with new C-C and C-N bonds formation through C-H and C-halide activation, but also provides valuable mechanistic insight into the novel multi-component reactions (MCRs).

Examples

The three-component coupling of terminal alkynes, dihalomethanes and amines (referred to herein as "AHA-coupling") was typically carried with CuCl (5 mol%) catalyst at 60 °C and afforded the desired propargylamines in good to excellent yield (Fig. 1). The optimum ratio of alkyne, dihalomethane and amine was found to be generally about 1:1.1:1.2. Reaction conditions were optimized by the variation of bases and solvents. The three-component coupling (AHA) reaction of phenylacetylene, dichloromethane and diethylamine was taken as an example for the optimization of the reaction conditions, Table 1.

Table 1. Effect of bases on copper catalyzed three-component coupling reaction (AHA-coupling).



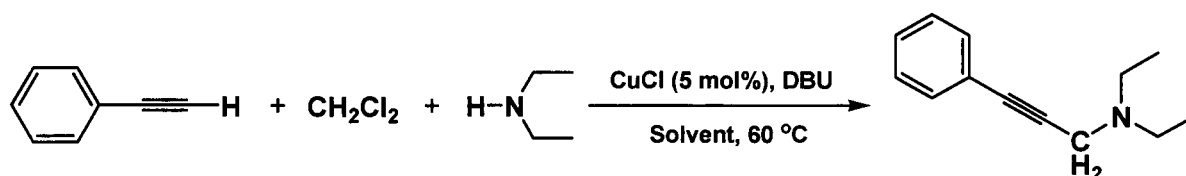
Entry	Base (mol %)	Reaction Time (h)	Isolated Yield (%)
1	K ₂ CO ₃ (100)	14	80
2	Cs ₂ CO ₃ (100)	14	82
3	Na ₂ CO ₃ (100)	14	77
4	NaHCO ₃ (100)	14	70
5	K ₃ PO ₄ (100)	14	75
6	TEA (100)	14	88
7	DBU(100)	14	95
8	DBU (50)	24	80
9	DBU(20)	24	60
10	DBU (0)	36	30

Reaction conditions: 1-ethynylbenzene (1.0 mmol), dichloromethane (1.1 mmol), diethylamine (1.2 mmol), CuCl (5.0 mol %), base, CH₃CN (2 ml), 60 °C.

5 A control experiment without any additional base additives was performed. Under this condition **1b** was obtained with a yield of merely 30 % (Table 1, entry 10). From the equation of the reaction, there will be two equivalents of HCl generated during the reaction.



10 The amine (ether reactant or product) may function as one equivalent of base and therefore an additional equivalent of base is necessary in order to neutralize the acid byproduct and to promote the reaction. This may explain the results of experiments in Table 1, entries 7-10. Without any additional base additive, 30% of yield was obtained and as increasing amounts of base (2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine
15 (DBU)) were added, from 0.2 to 1 equivalent, the yield of propargylamine was increased to 60 to 95%. The reaction was also conducted using inorganic bases such as Na₂CO₃, NaHCO₃, K₂CO₃, Cs₂CO₃ and K₃PO₄, providing yields between 70-82% of **1b** yields (Table 1, entries 1-5). Organic bases such as DBU and triethylamine (Et₃N) were observed to be more effective than inorganic bases (Table 1, entries 6, 7). The new AHA-coupling
20 reaction generally worked well in various common organic solvents, Table 2.

Table 2. Effect of solvents on copper catalyzed AHA-coupling reaction.

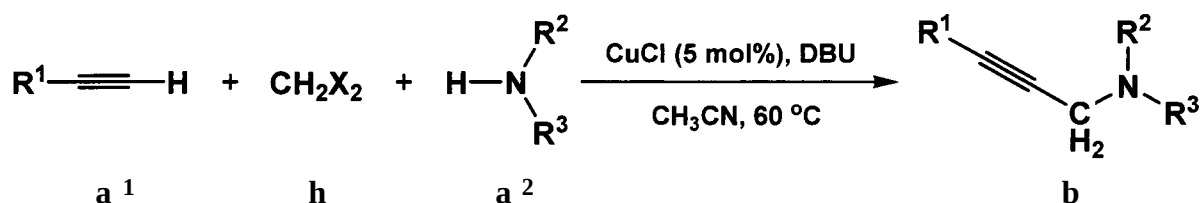
Entry	Solvent	Reaction Time (hour)	Isolated Yield (%)
1	DMSO	16	92
2	CH ₃ CN	14	95
3	DMF	16	80
4	THF	20	75
5	Toluene	24	70
6	CH ₂ Cl ₂	24	70

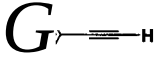
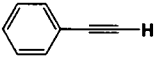
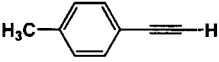
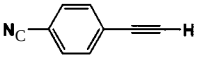
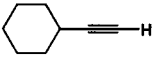
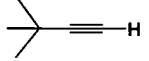
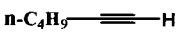
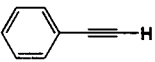
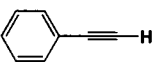
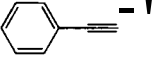
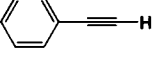
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Reaction conditions: 1-ethynylbenzene (1.0 mmol), dichloromethane (1.1 mmol), diethylamine (1.2 mmol), CuCl (5.0 mol %), DBU (2.0 mmol), solvent (2 ml), 60 °C.

The reaction in CH₃CN gave highest yield of product **1b** while the reaction in other solvent, such as DMSO, DMF, THF toluene and CH₂Cl₂ also gave good to excellent yields under similar conditions (Table 2, entries 2-6).

With the optimized reaction conditions of 5.0 mol % CuCl, 100 mol % DBU in CH₃CN for 14 hours at 60 °C, the substrate scope of the reaction was evaluated, Table 3.

15 **Table 3.** Copper catalyzed AHA-coupling reaction.^a

Entry	Alkyne (a ¹)	Dihalomethane (h)	Amine (a ²)	Yield (%) (b)
1		CH ₂ Cl ₂		95
2		CH ₂ I ₂		95
3		CH ₂ Cl ₂		95
4		CH ₂ Cl ₂		90
5		CH ₂ Cl ₂		88
6		CH ₂ Cl ₂		85
7		CH ₂ Cl ₂		87
8		CH ₂ Cl ₂		93
9		CH ₂ Cl ₂		93
10		CH ₂ Cl ₂		90
11		CD ₂ Cl ₂		95 ^b

^a Reaction conditions: alkyne (1.0 mmol), dihalomethane (1.1 mmol), amine (1.2 mmol), CuCl (5.0 mol %), DBU (2.0 mmol), CH₃CN (2 ml), 60 °C. ^b PhCC-CD₂-N(Et)₂.

5 Firstly, it was found that ether dichloromethane or diiodomethane were effective in this three-component coupling reaction, Table 3, entries 1-2. Remarkably, both aryl alkynes and alkyl alkynes were active in this reaction and gave excellent yield of corresponding propargylamines, Table 3. Aromatic alkynes, either with electron donating groups or with electron withdrawing group were able to undergo AHA-coupling smoothly and generate the corresponding propargylamines in excellent yields (Table 3, entries 1-4).
 10 On the other hand, cyclic, branched and linear aliphatic alkynes also gave the corresponding propargylamines in good yields (Table 3, entries 5-7). It is worth noting that acetylene and calcium carbide also undergo this coupling reaction to give mono- or bispropargylamine products under different reaction conditions, Fig. 2.

It was found that cyclic, heterocyclic, and acyclic secondary aliphatic amines gave excellent yields of products under the standard reaction conditions. However, no AHA-coupling product was isolated when an arylmethyl secondary amine, such as N-di-p-tolylamine or N-methyl(phenyl)methanamine, was used as amine substrate.

5 A tentative mechanism is proposed in Fig. 3, involving the activation of the C-H bond of alkyne by a Cu(I) species. In the proposed mechanism, the copper acetylide intermediate A reacts with dichloromethane, which might be activated by the amine, to form a propargylchloride intermediate B. The intermediate B rapidly reacts with amine to generate propargylamine product. The reaction between propargylchloride and amine to
10 form propargylamine under current conditions was confirmed by a separate control reaction. It is known that sp-sp³ Sonogashira reaction between terminal alkynes and haloalkanes can occur only with Pd/Cu or Ni/Cu bi-metal catalysts systems. In a control experiment, it was found that the reaction of alkyne with dichloromethane or iodomethane under current (copper(I) only) conditions without amine did not proceed. Methylene
15 chloride is a volatile but relatively inert organic liquid that is used extensively as a solvent in small and large scale synthesis and extraction processes. It is known that amines can be alkylated by methylene chloride, but the reaction is very slow with half-lives of many weeks to several months or under strong base condition. No reaction occurred between dichloromethane and amine without alkyne under current conditions. The reaction with
20 deuterated methylenechloride (CD₂Cl₂) was also conducted and the result clearly showed that CD₂ was incorporated into the propargylamine structure. Based on these observations it is proposed that the presently described AHA coupling reaction is a unique three component co-effected catalytic reaction.

In summary, an efficient CuCl catalyzed three-component coupling reaction of
25 alkynes, dihalomethanes and amines through C-H and C-halide activation to form propargylamines under mild conditions has been developed. The reaction generates corresponding propargylamines in high yields and is applicable to both aromatic and aliphatic alkynes. This chemistry offered not only a new approach to propargylamine but also valuable mechanistic insight into novel multiple component reactions.

30 **Experimental details**

Materials

All starting materials were commercial and were used as received, unless otherwise indicated. Solvents were anhydrous and were purchased from Sigma-Aldrich® (99.8%).

All reactions were performed in oven-dried (140°C) or flame-dried glassware under an inert atmosphere of dry N₂ or Ar.

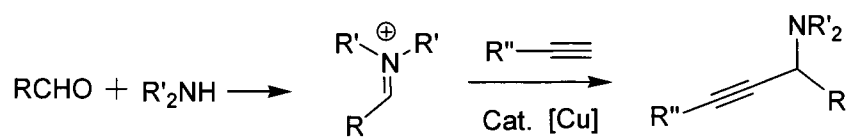
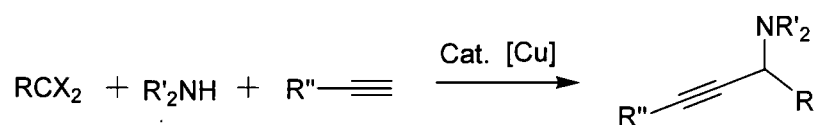
General procedure for production of propargylamines (lb as example)

5 A mixture of phenylacetylene (1.0 mmol, 102 mg), dichloromethane (1.1 mmol, 93.5 mg), diethylamine (1.2 mmol, 86.5 mg), DBU (1.0 mmol, 152.0 mg) and CuCl catalyst (5.0 mg, 5.0 mol %) was added in the reaction tube (10 mL) with 2 mL CH₃CN. After stirring at 60 °C for 14 hours, the mixture was diluted with H₂O (10 mL) and the aqueous layers were extracted with diethyl ether (2 × 10 mL), dried over Na₂SO₄ and concentrated to give the crude product which was further purified by column
10 chromatography on silica gel (ethyl acetate / dichloromethane = 1: 4) to afford the corresponding pure propargylamine.

Claims:

1. A process for producing a propargylamine comprising reacting a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine in the presence of a copper (I) catalyst.
- 5 2. The process of claim 1 wherein the geminal dihalide has structure CA_2X_2 , wherein each A is independently hydrogen or deuterium and each X is independently chloride, bromide or iodide.
3. The process of claim 2 wherein the geminal dihalide is CH_2Cl_2 or CH_2I_2 .
4. The process of any one of claims 1 to 3 wherein the amine is such that the
10 nitrogen atom is not directly attached to or part of an aromatic ring.
5. The process of any one of claims 1 to 4 wherein the copper (I) catalyst is a copper (I) halide.
6. The process of any one of claims 1 to 5 which is conducted under non-acidic conditions.
- 15 7. The process of claim 6 which is conducted in the presence of a base.
8. The process of claim 7 wherein the base is used in at least about 50 mol% relative to the geminal dihalide.
9. The process of claim 7 or claim 8 wherein the base is an inorganic base or is absent and the terminal alkyne or salt thereof is acetylene or an acetylide salt, whereby
20 the product is a 1,4-diamino-2-alkyne.
10. The process of claim 9 wherein both the molar ratio of acetylene or acetylide salt to geminal dihalide and the molar ratio of acetylene or acetylide salt to amine are about 1:1.5 to about 1:2.5
11. The process of any one of claims 1 to 9 wherein both the mole ratio of alkyne
25 or salt thereof to geminal dihalide and the mole ratio of geminal dihalide to amine are between about 0.8:1 and 1.2:1.
12. The process of any one of claims 1 to 11 which is conducted under an inert atmosphere.
13. A propargylamine made by the process of any one of claims 1 to 12.
- 30 14. Use of a terminal alkyne or a salt thereof, a geminal dihalide and a primary and secondary amine for making a propargylamine.
15. Use of a copper (I) catalyst for catalysing the reaction of a terminal alkyne or a salt thereof, a geminal dihalide and a primary or secondary amine to a propargylamine.

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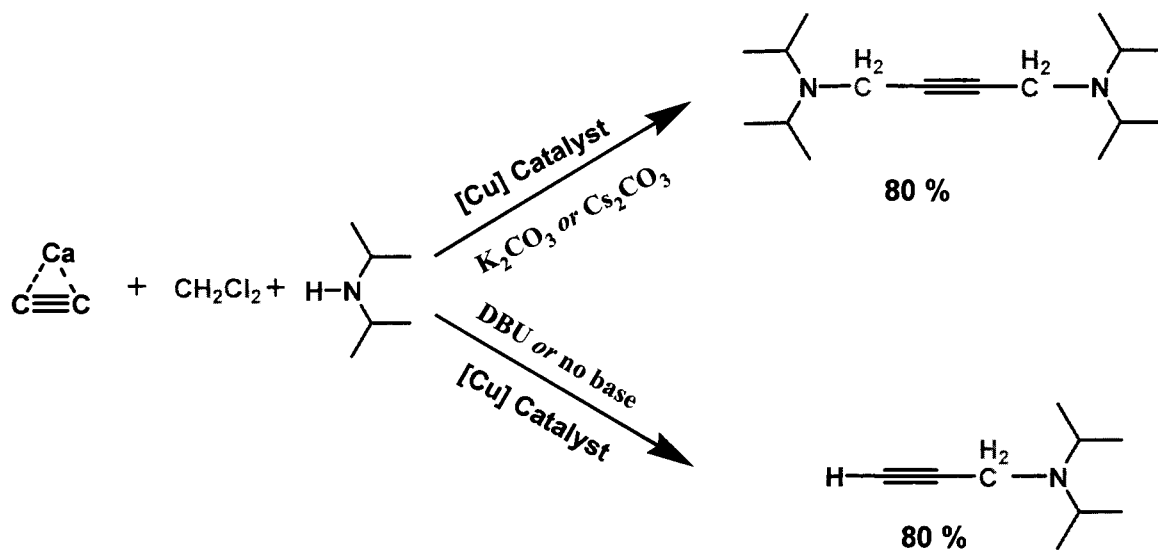
**Alkyne Aldehyde Amine (A³) coupling****Alkyne Haloalkane Amine (AHA) coupling****Figure 1**

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**Figure 2**

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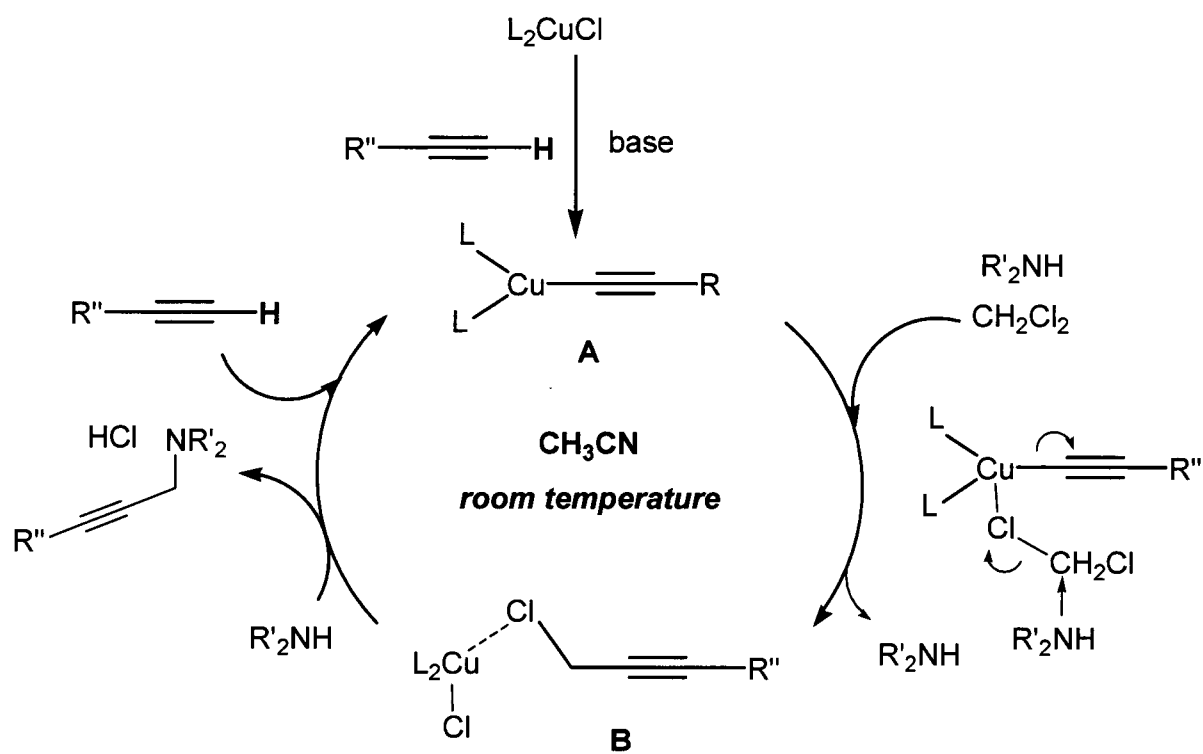


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT /SG201 1/000237

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07C 209/66 (2006.01)

C07C 211/25 (2006.01)

C07C 211/35 (2006.01)

C07C 211/23 (2006.01)

C07C 211/26 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASREACT: Reaction search based on three reaction components. CAPLUS: Keywords: propargyl amine, multicomponent reaction, synthesis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Aguilar, D. <i>et al</i> , "Mechanistic Insights into the One-Pot Synthesis of Propargylamines from Terminal Alkynes and Amines in Chlorinated Solvents Catalyzed by Gold Compounds and Nanoparticles", <i>Chemistry: A European Journal</i> , 2010, 16, 9287-9296, published online 25 June 2010. Whole document, in particular scheme 2, scheme 7 and table 2	13, 14
X	Aschwanden, P. <i>et al</i> , "Highly Enantioselective Access to Primary Propargylamines: 4-Piperidinone as a Convenient Protecting Group", <i>Organic Letters</i> , 2006, 8 (11), 2437-2440. Table 1	13, 14



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"I"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent but published on or after the international filing date

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&"

document member of the same patent family

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Date of the actual completion of the international search

24 August 2011

Date of mailing of the international search report

19/09/2011

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Shao, Z. <i>et al</i> , "Copper(I)-Catalyzed Three-Component Coupling Leading to an Efficient Synthesis of β,γ -Alkynyl α -Amino Acid Derivatives", <i>Synthesis</i> , 2008, 18, 2868-2870. Table 2.	13, 14
X	Gorske, B. C. <i>et al</i> , "Regio- and Stereoselective Synthesis of Fluoroalkenes by Directed Au(I) Catalysis", <i>Organic Letters</i> , 2009, 11 (19), 4318-4321. Table 1 and page S-12 of Supporting Information.	13, 14
P,X	Yu, D. <i>et al</i> , "Copper-Catalyzed Three-Component Coupling of Terminal Alkyne, Dihalomethane and Amine to Propargylic Amines", <i>Advanced Synthesis and Catalysis</i> , 2011, 353, 163-169. The whole document.	1-15
A	Vechorkin, O. <i>et al</i> , "Ni-Catalyzed Sonogashira Coupling of Nonactivated Alkyl Halides: Orthogonal Functionalization of Alkyl Iodides, Bromides, and Chlorides", <i>Journal of the American Chemical Society</i> , 2009, 131, 12078-12079. Introduction and tables 1-2.	