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## A walk around A<sup>3</sup> Coupling for the synthesis of Propargylamines

**Jasmine Gupta and Rashmi**

### Abstract

Propargylamines are a versatile class of compounds which find broad application in many fields of chemistry. This review aims to describe the different strategies developed so far for the synthesis of propargylamines and their derivatives as well as to highlight their reactivity and use as building blocks in the synthesis of chemically relevant organic compounds. In this review, the different synthetic approaches to synthesize propargylamines using different metal and metal ion immobilized ionic liquids and metal catalyst free such as A<sup>3</sup> couplings and C–H functionalization of alkynes, have been described and organized on the basis of the catalysts employed in the syntheses. A metal-free and straightforward greener protocol for the preparation of propargylamine has been reported.

**Keywords:** A<sup>3</sup> coupling; Immobilized metal catalysts; Ionic liquids; Metal catalyst free, Propargylamines

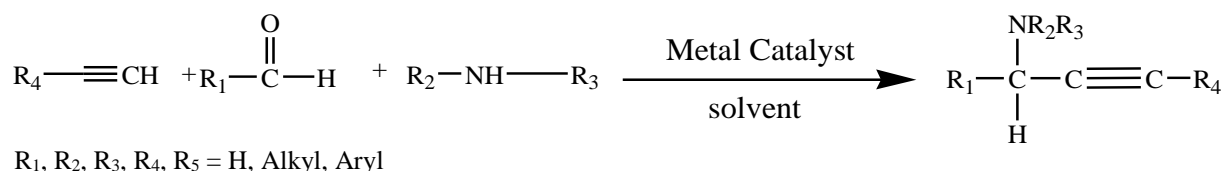
### Introduction

Propargylamines are highly versatile building blocks in organic synthesis <sup>[1]</sup> and their structural unit has been found in various natural products <sup>[2, 3]</sup> and in compounds of pharmaceutical <sup>[4-10]</sup>, phytoprotective <sup>[5]</sup> or biological importance. The propargylamines obtained by A<sup>3</sup> coupling reactions of an aldehyde, amine and alkyne, are high-value synthetic intermediates for biologically active compounds such as β-lactams, conformationally restricted peptides, isosteres, natural products and therapeutic drug molecules. Developing the synthetic strategies for C–H bond activation has claimed one of the most important areas in organic chemistry <sup>[11, 12]</sup>. C–C bond formation using alkynes as a carbon nucleophile source is a very useful method in synthesis. However, a more versatile process has also been established, in which an excellent three-component coupling of an aldehyde, an alkyne and an amine (A<sup>3</sup>coupling) is performed using the terminal alkyne as a carbon nucleophile source via C–H activation <sup>[13-17]</sup>. A<sup>3</sup> coupling reactions, as an excellent example of MCRs, provide an elegant method for the synthesis of propargylamines which are frequent skeletal components and synthetically versatile key intermediates for the preparation of many nitrogen-containing biologically active compounds <sup>[18-24]</sup>. As far as the mechanism is concerned, A<sup>3</sup> coupling reactions are extension of well-known alkylation of imines with terminal alkynes.

### Discussion

One of the most challenging tasks in organic synthesis is the efficient preparation of complex molecules starting from easily available small molecules i.e. the raw materials. Especially attractive are multicomponent reactions which allow the formation of several bonds including new C–C bonds in a one-pot, single-step procedure <sup>[25-27]</sup>. This type of reaction has a wide scope in modern organic chemistry, since it exhibits generally a high atom economy <sup>[28]</sup> and selectivity, as well as lesser formation of by-products as compared with classical stepwise synthesis. Propargylamines can be obtained by the reaction of alkynes to imines, but as imines are easily formed from aldehydes and amines, three component versions of the reaction are known, either as such <sup>[29-30]</sup> or promoted by various transition metals <sup>[31-32]</sup> (as shown in scheme 1 and 2).

### General Reaction

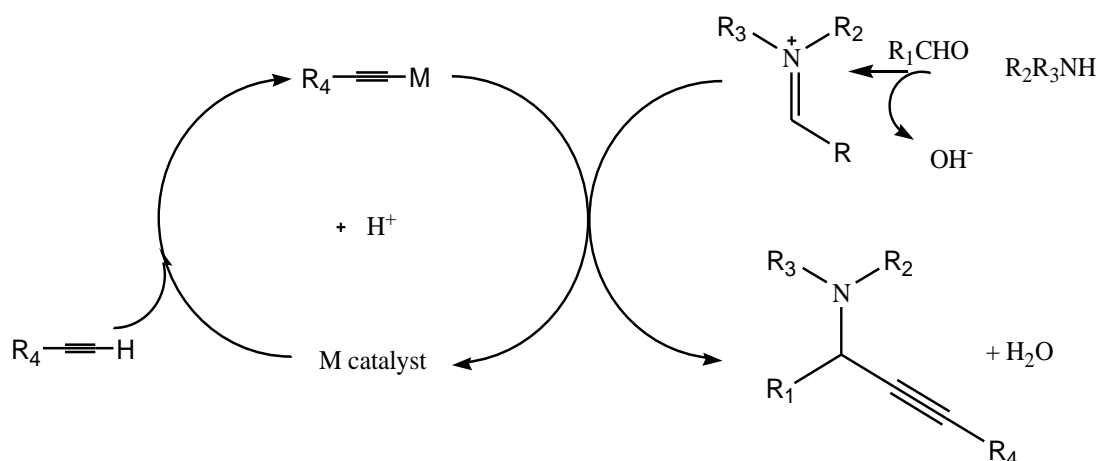


Scheme 1

### General Mechanism

In the  $A^3$  coupling, the role of the metal catalyst is believed to activate the terminal acetylene primarily, which then

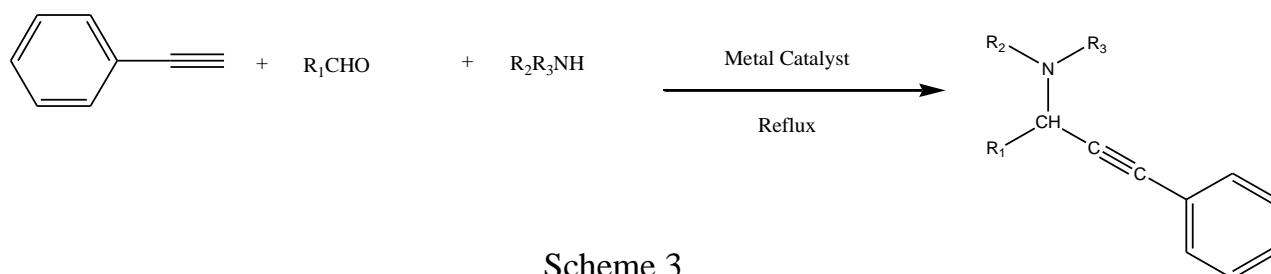
undergoes a nucleophilic addition to the iminium electrophile generated from the aldehyde and the amine as shown in scheme 2.



Scheme 2

The  $A^3$  coupling reaction in the presence of traditional -metal-catalyst like copper, zinc, nickel, gold, silver, iron, cobalt, iridium has already been reported [33-43]. Metal catalysed synthesis of propargylamines from aromatic aldehydes,

amines and phenylacetylene in the presence of various metal catalyst at room temperature and reflux condition in various solvents ( as shown in Scheme 3 and Table 1).



Scheme 3

Table 1:

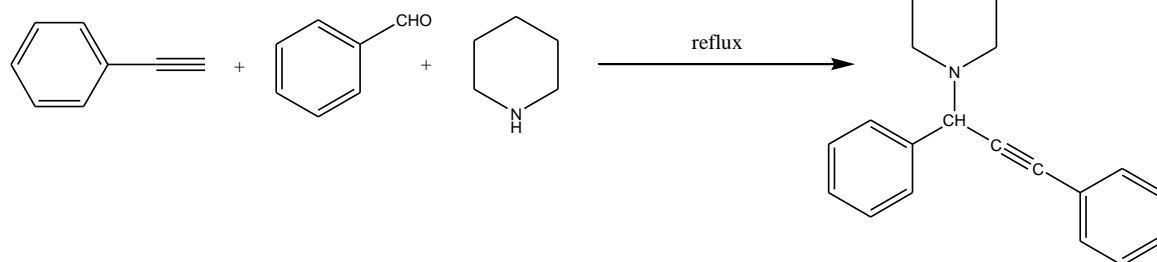
Metal catalyst	Solvent	Time (h)/Yield (%) Room Temperature	Time (h)/Yield (%) Reflux
BiCl <sub>3</sub> (10 mol%)	H <sub>2</sub> O	10/0	5/75
	EtOH	10/0	5/90
	MeOH	10/0	5/70
	THF	10/0	5/45
	Toulene	10/0	5/35
[Ag(I)(Pc-L)] <sup>+</sup> BF <sub>4</sub> <sup>-</sup> (3mol%)	H <sub>2</sub> O		4/65
	MeOH		4/62
	Toulene	90/31	4/60
[Ag(I)(Pc-L)] <sup>+</sup> OTf (6 mol%)	Toulene		4.5/96
[Ag(I)(Pc-L)] <sup>+</sup> OTf (3 mol%)	Toulene		0.25/96*

\* Microwave screw capped tube, mW, 150 °C.

To extend the scope of the reaction, various cyclic secondary amines such as pyrrolidine, piperidine, hexamethyleneimine, morpholine, pyrrolidine, N-methyl piperazine, and 4-methyl piperidine, were used. For minimizing the environmental pollution caused by solvents, the chemists are more concerned

for developing environment-friendly synthetic procedures. This initiative, has result into the development of new strategies in solid-solid reactions has prompted them to develop sufficiently valuable methodologies to achieve organic synthesis under solvent-free condition. Especially,

multicomponent reactions that provide poly-functionalized heterocyclic scaffolds in single operation and in stereo-specific manner are of great importance in synthetic organic



**Scheme 4:** Reaction b/w- Phenylacetylene: piperidine: benzaldehyde (1.3:1:1)

**Table 2**

Solvent	LiOTf (20mol %)	Temp@/time(h)	Yield (%)
Toulene	-	90/5	84
EtOH	-	90/12	25
H <sub>2</sub> O	-	100/24	<10
Neat	30mol%	90/1	90
Neat	40mol%	90/1	90
Neat	05mol%	90/2	72

Despite the widespread use of metal catalysed reactions, a series of drawbacks, such as product isolation, catalyst recovery and the use of large amount of ionic liquids in biphasic systems, which is costly and may cause toxicological concerns, still exist. The other way of using metal catalysts is immobilizing them over some polymer supports which gives a chance to reuse the supported catalyst and leads to lesser waste creation. Although these supported catalysts are easily recoverable by simple filtration but were not reusable, as the metal ions leached out of the supports just after a single use. This happened because the metal ions were bound to support only via physical adsorption, agitation due to stirring and heating lead to desorption. Solution to this problem is the chemical immobilization of the metal catalysts over supports. Solution to this problem is the chemical immobilization of the metal catalysts over supports. Chemically immobilization of copper chloride ions into imidazolium-based ionic liquids has been reported over activated SiO<sub>2</sub>, and used it as heterogeneous catalysts for the synthesis of propargyl amines. First catalyst prepared under this category was [SiO<sub>2</sub>-Pmim]<sup>+</sup>½CuCl<sub>4</sub><sup>2-</sup> which gave very good conversion without any leaching of the metal ions. To study any more scope of further increasing the reaction conversion a silica-grafted imidazolium-based IL having an additional acidic functional

and medicinal chemistry. Synthesis of propargylamines using LiOTf and Gold under neat conditions gave very good results [44] (as shown in Scheme 4 and Table 2).

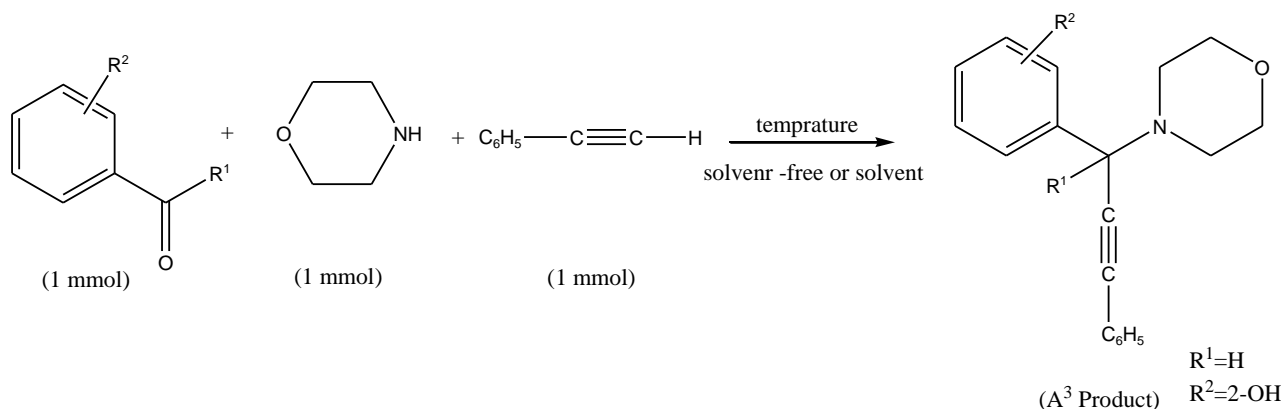
group which may further speed up the imine formation and thus the overall reaction was used. A new silica-grafted imidazolium-based ionic liquid containing CuCl<sub>4</sub><sup>2-</sup> counter ion and -SO<sub>3</sub>H group i.e. [SiO<sub>2</sub>-PimSO<sub>3</sub>H]<sup>+</sup>½CuCl<sub>4</sub><sup>2-</sup> has been prepared<sup>45</sup> and investigated for further reactions. Scanning of different Cu catalyst for the synthesis of propargyl amines is shown in Table 3.

**Table 3**

S. No.	Cu Catalyst	Time(hrs)	C (%)
1.	Resin-Cu(II)	5	81
2.	SiO <sub>2</sub> -Cu(II)	5	80
3.	Al <sub>2</sub> O <sub>3</sub> -Cu(II)	12	-----
4.	[SiO <sub>2</sub> -Pmim] <sup>+</sup> ½CuCl <sub>4</sub> <sup>2-</sup>	4	87
5.	[SiO <sub>2</sub> -PmimSO <sub>3</sub> H] <sup>+</sup> ½CuCl <sub>4</sub> <sup>2-</sup>	2	96

Immobilized ionic liquids combine the benefits of ionic liquids and heterogeneous catalysts such as high design ability, high solubility of catalytic site, ease of handling, separation and recycling.

The synthesis of propargylamines via A<sup>3</sup> coupling mostly under metal-catalyzed procedures has been discussed so far but Ghosh and his coworkers [46] invented an unprecedented effect of salicylaldehyde, one of the A<sup>3</sup> coupling partners, which lead to the formation of propargylamine in the absence of any metal catalyst and under mild conditions. The role of the hydroxy group in *ortho* position of salicylaldehyde has been explored, which presumably activates the C<sub>sp</sub>-H bond of the terminal alkyne leading to the formation of propargylamines in good to excellent yields, thus negating the function of the metal catalyst (as shown in scheme 5 and Table 4).



**Scheme 5:** Optimization of metal-catalyst-free A<sup>3</sup> coupling reaction.

**Table 4:** <sup>a</sup>Yield of product after purification by column chromatography; <sup>b</sup>using a mixture of CuI and 1,3-dithiane ligand [1-(3-(*p*-tolylthio)propylthio)-4-methylbenzene] in 1:2 ratios (1 mol %); <sup>c</sup>2 mL of solvent was taken; <sup>d</sup>cyclohexylamine (1 mmol) was used instead of morpholine; <sup>e</sup>benzylamine (1 mmol) was used instead of morpholine.

Entry	R <sup>1</sup>	R <sup>2</sup>	Temperature (°C)	Time (h)	Solvent	Yield (%) <sup>a</sup>
1 <sup>b</sup>	H	2-OH	80	4	neat	89
2	H	2-OH	80	4	neat	90
3	H	2-OMe	80	4	neat	no reaction
4	H	2-OH	rt	24	neat	Traces (<10%)
5 <sup>c</sup>	H	2-OH	80	4	MeCN	85
6 <sup>c</sup>	H	2-OH	80	4	toluene	88
7 <sup>d</sup>	H	2-OH	80	10	neat	no A <sup>3</sup> product, only imine formation
8 <sup>e</sup>	H	2-OH	80	10	neat	no A <sup>3</sup> product, only imine formation

After the successful optimization, further extension of the reaction protocol was made by varying the other two components viz. the secondary cyclic amine and the terminal alkyne and worked efficiently to produce the corresponding propargylamine derivatives.

### Conclusion

In conclusion, the review demonstrates a walk around A<sup>3</sup> coupling for the synthesis of propargylamines but an unusual added role of the hydroxy group of salicylaldehyde, which paves the way to develop metal-free as well as solvent-free A<sup>3</sup> coupling reactions leading to the formation of propargylamine – the useful synthetic intermediate and an important unit of many bio-active compounds. The reaction conditions are straightforward and products are obtained in good to excellent yields. The metal-free approach also offers the advantages of avoiding any possible byproduct arising out from the contamination with metal species. Thus the present reaction from easily available A<sup>3</sup> components leading to the formation of propargylamine under metal-catalyst-free and solvent-free conditions could attract the interest of synthetic and medicinal chemists.

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