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Three-component coupling of aldehyde, alkyne, and amine catalyzed by silver in ionic liquid

Zigang Li,[a] Chunmei Wei,[a] Liang Chen,[a] Rajender S. Varma[b] and Chao-Jun Li[a,c,*]

[a]*Department of Chemistry, Tulane University, 6400 Freret, New Orleans, LA 70118, USA*
[b]*National Risk Management Research Lab, US Environmental Protection Agency, Cincinnati, OH 45268, USA*
[c]*Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal QC, Canada H3A 2K6*

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Abstract—A three-component coupling of aldehyde, alkyne, and amine was developed by using gold, copper, or silver as catalysts in ionic liquid.

The development of more efficient and more environmentally-benign processes for chemical synthesis has become increasingly important in the chemical community.[1] Barbier–Grignard type reactions in water are one of the most important area and some developments have been achieved during the past decade.[2] But the classical Barbier–Grignard type reactions are always atom economically inefficient with generating stoichiometric amounts of metal ions and halides as waste. An alternative suggestion to provide an atom-economical[3] approach is to perform this type of reaction via a catalytic reaction of C–H bonds.[4] Recently, we[5] and others[6] have reported the synthesis of propargyl alcohols and propargyl amines by direct addition of terminal alkynes to aldehydes and imines through the 'C–H' reactivity. A highly enantioselective imine addition in either water or organic solvent catalyzed by chiral copper catalyst[7] and highly efficient three-component coupling of aldehydes, alkynes, and amines catalyzed by gold and silver in water have been reported.[8]

Within the past few years, ionic liquids have emerged as a new class of 'green' solvents for chemical processes and chemical transformations and have attracted considerable attention. The nonvolatile nature of ionic liquids give them significant advantage in minimizing solvent consumption. Their polarity renders them good solvents for homogeneous catalysis.[9] Their unique solubility properties, that is, miscibility gap between water and organic solvents, have made them interesting candidates for separation processes by simple liquid–liquid extraction with either aqueous or conventional organic solvents and for immobilizing catalysts.[10] In many applications ionic liquid with weakly coordinating anions, such as BF_4^- and PF_6^-, together with suitably substituted cations often result in an altered chemical reactivity of the dissolved catalyst and therefore improve both reactivity and selectivity. Among the commonly used ionic liquids, 1-butyl-3-methyl-imidazolium hexafluorophosphate ($[Bmim]PF_6$) is a popular reaction medium for a wide variety of transition metal catalyzed organic transformations such as hydrogenation,[11] oxidation,[12] hydroformylation,[13] oligomerization,[14] etc. Previously, we reported an aldol-type as well as Mannich-type reaction between aldehydes and imines with allylic alcohol catalyzed by $RuCl_2(PPh_3)_3$ in an ionic liquid[15] and a direct formation of tetrahydropyranol.[16] Our continued interest in developing 'green' catalysis based on the reactivity of C–H bonds led us to explore other synthetically useful transformations. Herein, we wish to report a highly efficient silver-catalyzed three-component coupling reaction in ionic liquid, specifically butylmethyl-imidazolium hexafluorophosphate, $[Bmim][PF_6]$ to generate propargyl amines (Scheme 1).

Very recently, silver-catalyzed reactions such as aza-Diels–Alder reaction,[17] asymmetric aldol reaction,[18] addition,[19] coupling reaction,[20] cyclization,[21] and allylation[22] have received attention. In our attempt to

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Keywords: Silver; Alkyne; Imine; Catalysis; Ionic liquid.

* Corresponding author at present address: Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal QC, Canada H3A 2K6. Tel.: +1-504-8655573; fax: +1-504-8655596; e-mail address: cjli@tulane.edu; cj.li@mcgill.ca

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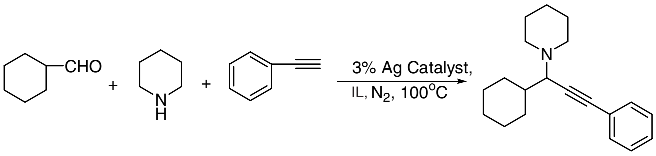


Scheme 1.

optimize the reaction shown in Scheme 1, various silver salts were utilized such as 3% $AgNO_3$, AgOTf, AgBr, and AgI. It was found that AgI provided the best result and additionally, no further additives are required. Subsequently, various aliphatic aldehydes, alkynes, and dialkyl amines were coupled with the yields ranging from moderate to excellent, with the results summarized in Table 1.

In an ionic liquid, the nature of the aldehyde influenced the reaction much more dramatically than the reactions in water. The reactions with aliphatic aldehydes were

Table 1. Three-component coupling of aliphatic aldehydes, amines, and alkynes in ionic liquid

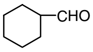
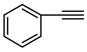
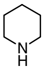
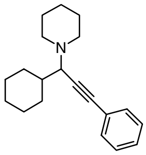
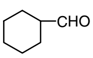
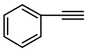
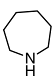
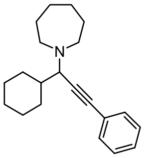
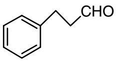
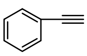
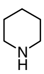
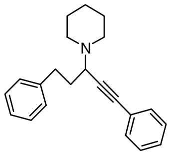
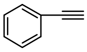
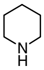
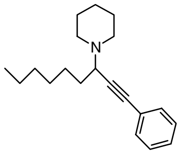
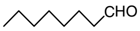
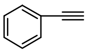
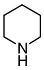
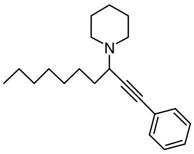
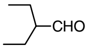
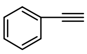
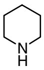
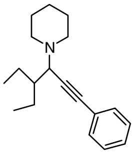
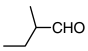
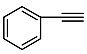
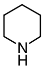
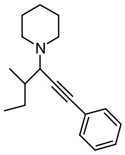
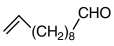
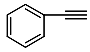
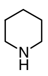
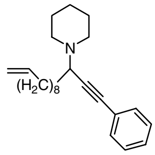
Entry	Aldehyde	Alkyne	Amine	Time (h)[a]	Product	Yield (%)[b]
1				16		86 (92[c])
2				16		90
3				16		81
4				16		74
5				16		80
6				16		91[d]
7				16		79[e]

Table 1 (*continued*)

Entry	Aldehyde	Alkyne	Amine	Time (h)[a]	Product	Yield (%)[b]
8				16		73

[a] Reaction time not optimized.

[b] Isolated yield based on aldehydes.

[c] Ionic liquid reused from the first trial.

[d] [Bmim][BF_4] was used.

[e] Yield of both *anti*- and *syn*-product (*anti*:*syn* = 76:24, determined by ^1H NMR).

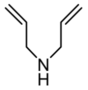
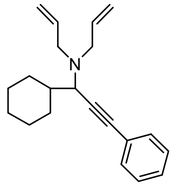
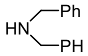
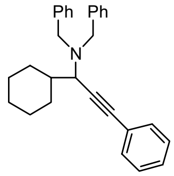
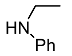
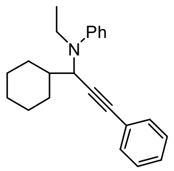
clean with high conversions and almost no trimer formation when compared with the reactions catalyzed by gold or copper; whereas the reactions with aromatic aldehydes were not clean, generating a variety of complex products. The reason may be due to the nature of the ionic liquid. In water, $AuBr_3$ can catalyze the addition of aromatic aldehydes to form propargyl amines in 2 h with a higher than 99% isolated yield; however in ionic liquid, both the conversion and the yield were low.

One limitation of this reaction in water is the low reactivity of aliphatic alkynes. In ionic liquid, the coupling of cyclohexylcarboxaldehyde, piperidine, and triethylsilylacetylene gave an isolated yield of 89% (Scheme 2, Eq. 1). In AgI catalyzed coupling reactions in water, the amines are mainly limited to piperidine analogues due to the poor reactivity of other amines. However, in ionic liquid, possibly because of homogenous nature, other dialkyl or alkylaryl amines also can react smoothly. In the coupling of cyclohexylcarboxaldehyde, diallylamine, and phenylacetylene, an isolated yield of 61% (Table 2, entry 1) was obtained. Perhaps due to the phenyl group, the reaction of cyclohexylcarboxaldehyde, ethylphenylamine, and phenylacetylene also had a good isolated yield of 83% (Table 2, entry 3). Noteworthy, the reaction between cyclohexylcarboxaldehyde, diallylamine, and triethylsilylacetylene also gives 30% isolated yield in ionic liquid (Scheme 3, reaction 2).

In conclusion, a silver-catalyzed synthesis of propargyl amines via a three-component reaction of aldehyde–alkyne–amine was developed in ionic liquid. The reaction can also be catalyzed by gold or copper, albeit less effectively. The mechanism, stereoselectivity, and synthetic applications are currently under further investigation.

General experimental process: To a sealed test tube charged with AgI (7 mg, 0.03 mmol, 3 mol%) in 0.3 mL ionic liquid under a nitrogen atmosphere, aldehyde (1 mmol), amine (1.2 mmol), and alkyne (1.3 mmol,

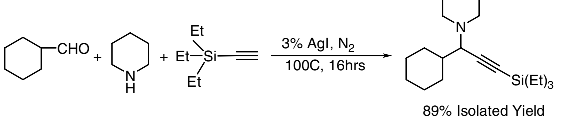
Table 2

Entry	Amine	Time (h)[a]	Product	Yield (%)[b]
1		16		61
2		16		57[c]
3		16		83[c]

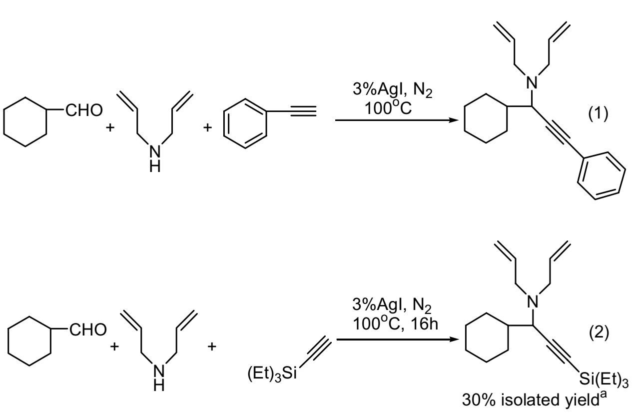
[a] Time not optimized.

[b] Isolated yield based on aldehyde.

[c] [Bmim][BF_4] was used.



Scheme 2. Reactivity of aliphatic alkynes.



a [Bmim][BF_4] was used.

Scheme 3. Reactivity with different amines.

1.5 mmol if aliphatic alkynes are used) were added. The reaction mixture was degassed under sonication for 10 min and allowed to react overnight at 100 °C (oil bath temperature). The reaction mixture was cooled and extracted with ether, and the organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude mixture was purified by flash chromatography on silica gel with eluent of hexanes–ethyl acetate 10:1.

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