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Ionic liquid assisted silver-catalyzed one-pot A^3-coupling reactions for the synthesis of propargylamines

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ABSTRACT

A series of ionic liquids with different cations and anions were synthesized and their performances for the silver catalyzed one-pot A^3-coupling reactions were investigated. The selection showed that the combination of $AgNO_3$ and ionic liquid [TMG][TFA] showed highest catalytic activity. This catalytic system was then utilized for the production a series of propargylamines with satisfactory isolated yields. This reaction system is very simple and easy to be conducted because no inert gases or any other additional solvents, basic additives are needed. This also led to the convenience of the following work-up procedures and the recycle and reutilization for the catalytic system. The ionic liquid was believed to be involved in the catalytic procedure through the interaction with substrates or catalysts as co-catalyst and ligands.

1. Introduction

Multicomponent reactions (MCRs) have been considered as ideal reactions to synthesized large compound libraries in organic or medical chemistry, and have been widely utilized in target-oriented synthesis [1,2]. MCRs can be conducted as one-pot processes or through a sequential-addition procedure in a single solvent system. Ionic liquids which are composed with organic cations and organic or inorganic anions give an excellent reaction platform for MCRs due to its high and adjustable solutilities for different kinds of compounds such as organics, inorganics or even metal salts [3–5]. Additionally, the functionalization of ionic liquids has endowed them different features as catalyst, co-catalyst or separating assistants in a reaction procedure [6–11].

Propargylamines are recurrent moieties in many biological active compounds [12–14], and due to the existence of the amine group on the β-position of alkyne moiety, they have been used as important synthetic precursors for a large number of heterocycles such as oxazoles, imidazoles, pyrazoles, and quinolines [15–17]. The wide utilization of these compounds in synthetic chemistry, pharmacological and pharmaceutical chemistry leads to the rapid expansion of their synthetic method [18]. Transition metal catalyzed A^3 coupling is one of the most intriguing protocols for propargylamines synthesis and various catalytic systems involving Cu(I) [19–21], Au [22–25], Fe [26–28], In [29,30], Zn [31,32], Ni [33,34], Co [35,36], have been reported. These catalytic systems often benefit to the transformation of aromatic aldehydes and the aliphatic aldehydes often suffered from low conversions. Li and other researchers found that Ag salts catalyzed A^3 reactions have great improvement in the substrate scope and many catalytic systems have been developed [37–42]. However, most of these reported reaction systems suffered from the necessary of inert gas environment and toxic organic solvents, tedious synthesis of complex ligands, high reaction temperature, long reaction time and the difficulty to recycle the catalyst. The application of ionic liquids as solvent in the A^3 coupling reactions has showed good potentials to facilitate the reutilization of Cu or Au catalyst [43,44].

Herein, a series of ionic liquids with different cations and anions were synthesized and utilized for the synthesis of propargylamines. The results showed that the ionic liquid and silver salts have synergetic effect to promote the reactions and the combination of $AgNO_3$ and ionic liquid [TMG][TFA] lead to the satisfactory catalytic performance for the one-pot A^3 coupling reactions, especially for the reaction involving aliphalic aldehydes. This reaction system is very simple and easy to be conducted because no inert gases or any other additional solvents, basic additives are needed, this also lead to the convenience of the following work-up procedures and the recycle and reutilization for the catalytic system. The ionic liquid was believed to be involved in the catalytic procedure through the interaction with substrates or catalysts as co-catalyst and ligands.

2. Experimental section

2.1. Synthesis of functional ionic liquids

0.1 mol carboxyl acid dissolved in 10 ml methanol was drop-wise added to the 100 ml flask containing 0.1 mol corresponding amines in

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10 ml methanol under stirring in ice bath. The solution was then stirred at 40 °C for 48 h. after the completion of the reaction, and then the methanol was evaporated at 50 °C to get the functional ionic liquids.

2.2. General procedures for the synthesis of propargylamine

In a 10 ml round bottom flask, the mixture of [TMG][TFA] (0.6 mmol), $AgNO_3$ (0.006 mmol), aldehyde (0.6 mmol), secondary amine (0.72 mmol) and alkyne (0.72 mmol) was stirred at 70 °C for the desired time. The reaction process was monitored by TLC (the solvent for the TLC is the mixture of ethyl acetate and petroleum ether). After the completion of reaction, the reaction mixture was extracted with diethyl ether. The organic layer was evaporated and the residue was subjected to a silica gel column with EA/Petroleum ether as eluent to give the target *propargylamines.*

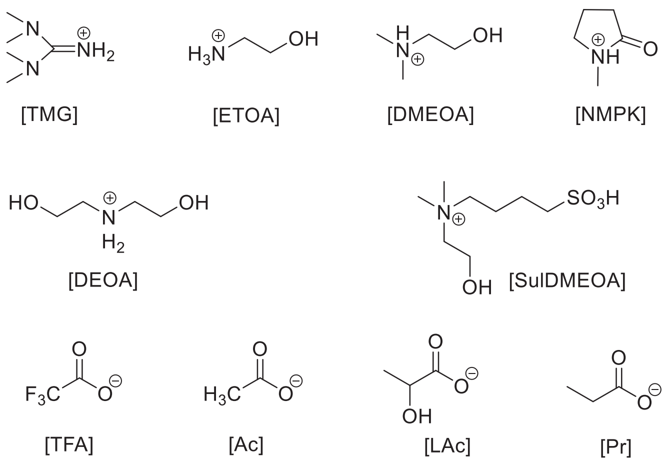
2.3. Reutilization of the catalyst system

After the completion of the reactions, the product was extracted from the reaction mixtures by the addition of diethyl ether. The upper ether layer was decanted, leaving the ionic liquid and silver salts insoluble, which was then evaporated and used for the following catalytic cycles directly without additional activation.

3. Results and discussion

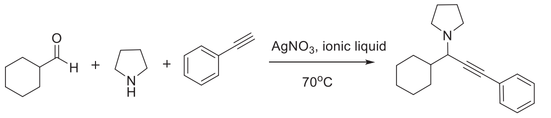
A series of ionic liquids with different cations and anions were synthesized and their structures were illustrated in Scheme 1. Their performances in different silver salts catalyzed A^3 coupling reactions were investigated using the reaction among cyclohexanecarboxaldehyde, pyrrolidine and phenylethynyl as a model. The results were collected in Table 1. From the Table 1 it can be seen that the presence of ionic liquid and silver salt both promoted the target A^3 coupling reaction. (Entries 1–3, Table 1). The structures of ionic liquids and the types of silver salts both influenced the production of target propargylamine (Entries 3, 8–18, Table 1). Then the influences of the loading of silver salts were investigated using $AgNO_3$. It was shown that when the $AgNO_3$ dosage increased from 0 to 1% mole benefit to the reaction, but further increase of its amount to 5% mole had negligible effect(Entries 3, 19–21, Table 1). So, 1% mole $AgNO_3$ based on cyclohexanecarboxaldehyde was selected as the optimal catalyst amount. Then the influence of the amount of ionic liquid on the model reaction was investigated under the optimized amount of $AgNO_3$. It is clear that 1.5 eq [TMG][TFA] based on cyclohexanecarboxaldehyde is the most favorable ionic liquid amount(Entries 20, 22–24, Table 1).

Then the influence of the reaction temperature on the model reaction was investigated under the optimized silver salt and ionic liquid. The results were collected in Table 2. It is clear that 70 °C is the most favorable reaction temperature.



Scheme 1. The cations and anions structures of ionic liquids.

Table 1
Influences of silver salts and ionic liquids.



Entry[a,b]	Ag(I)/(loading)	Ionic liquid/(molar ratio)	Isolated yield
1	$AgNO_3$/0%	[TMG][TFA]/1.5	20
2	$AgNO_3$/5%	[TMG][TFA]/0	65
3	$AgNO_3$/5%	[TMG][TFA]/1.5	89
4	Ag_2CO_3/5%	[TMG][TFA]/1.5	70
5	AgOAc/5%	[TMG][TFA]/1.5	65
6	$AgCF_3COO$/5%	[TMG][TFA]/1.5	70
7	AgI/5%	[TMG][TFA]/1.5	86
8	$AgNO_3$/5%	[DMEOA][TFA]/1.5	58
9	$AgNO_3$/5%	[ETOA][TFA]/1.5	69
10	$AgNO_3$/5%	[DEOA][TFA]/1.5	77
11	$AgNO_3$/5%	[NMPK][TFA]/1.5	48
12	$AgNO_3$/5%	[SulDMEOA][TFA]/1.5	23
13	$AgNO_3$/5%	[DMEOA][Ac]/1.5	56
14	$AgNO_3$/5%	[TMG][Ac]/1.5	65
15	$AgNO_3$/5%	[NMPK][Ac]/1.5	52
16	$AgNO_3$/5%	[TMG][Lac]/1.5	69
17	$AgNO_3$/5%	[NMPK][Lac]/1.5	47
18	$AgNO_3$/5%	[TMG][Pr]/1.5	52
19	$AgNO_3$/5%	[TMG][NO_3]/1.5	70
20	$AgNO_3$/0.5%	[TMG][TFA]/1.5	84
21	$AgNO_3$/1%	[TMG][TFA]/1.5	90
22	$AgNO_3$/3%	[TMG][TFA]/1.5	87
23	$AgNO_3$/1%	[TMG][TFA]/0.5	85
24	$AgNO_3$/1%	[TMG][TFA]/1	88
25	$AgNO_3$/1%	[TMG][TFA]/2	90

[a] 0.6 mmol cyclohexanecarboxaldehyde, 0.72 mmol pyrrolidine, 0.72 mmol phenylethynyl, $AgNO_3$ and ionic liquid were mixed and heated at 70 °C for 2 h.

[b] Isolated yields.

Next, the substrate tolerance of this catalytic system for the synthesis of propargylamine analogues through the one-pot multi-component A^3 reactions was investigated using different aldehydes, alkynes and pyrrolidine/piperidine under optimized conditions, and the results were collected in Table 3. It is evident that various aromatic alkynes with electro-donating or electro-withdrawing groups and other alkynyl compounds, such as 2-pyridylacetylene, 1, 9-decadiyne, propargyl ethers could react with cyclohexanecarboxaldehyde and pyrrolidine smoothly to give the target compounds with good to excellent isolated yields(entries 1–14, Table 2). Other aliphatic aldehydes like n-hexaldehyde, 3-phenylpropionaldehyde and 2-ethylbutanal could also be converted to the corresponding propargylamine analogues with excellent isolated yields within 6 h(entries 15–17, Table 2). The reaction among cyclohexanecarboxaldehyde, Piperidine, and aromatic alkyne with different substitutes can also give propargylamines with satisfactory yields(entries 21–24, Table 2). The corresponding reactions using aromatic aldehydes showed lower conversions(entries 18–20, Table 2)

Table 2
Influence of reaction temperature on the model reaction.

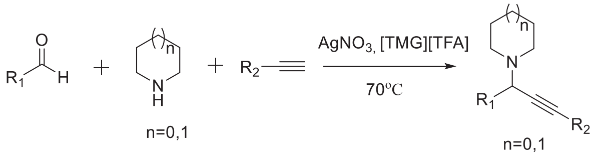
Entry[a]	Temperature(°C)	Time(h)	Yield(%)[c]
1	25	4	68
2	50	4	80
3	70	2	90
4[b]	90	2	90

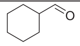
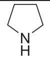
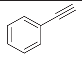
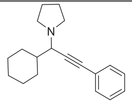
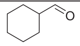
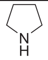
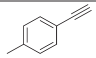
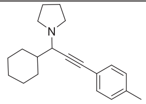
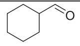
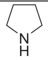
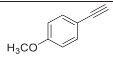
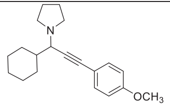
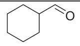
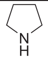
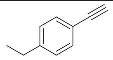
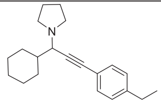
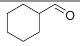
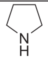
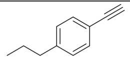
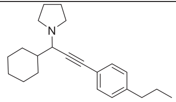
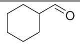
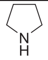
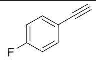
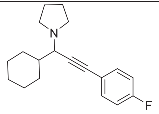
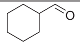
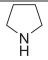
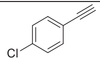
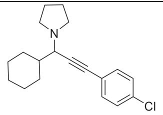
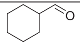
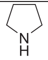
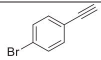
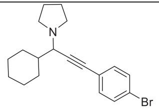
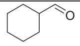
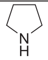
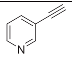
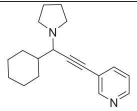
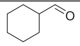
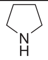
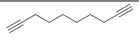
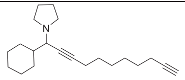
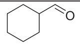
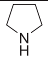
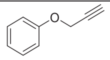
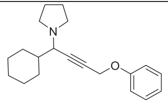
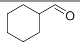
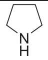
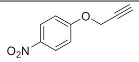
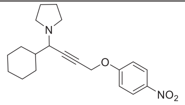
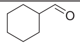
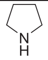
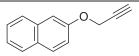
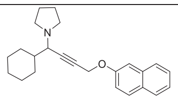
[a] 0.6 mmol cyclohexanecarboxaldehyde, 0.72 mmol pyrrolidine, 0.72 mmol phenylethynyl, 1 mol% $AgNO_3$ and 1.5 eq [TMG][TFA] were mixed and heated at corresponding reaction temperature for the desired reaction time.

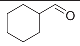
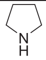
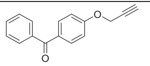
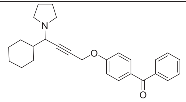
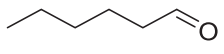
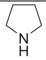
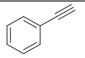
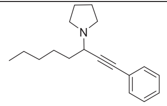
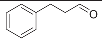
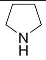
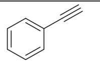
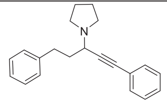
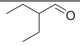
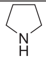
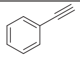
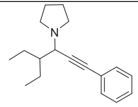
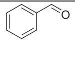
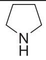
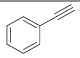
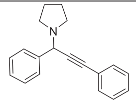
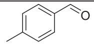
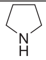
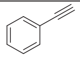
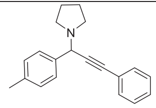
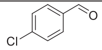
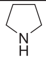
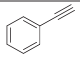
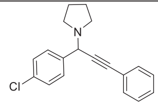
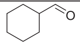
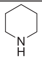
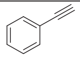
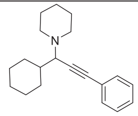
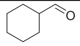
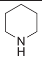
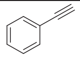
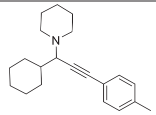
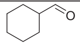
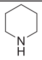
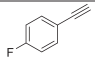
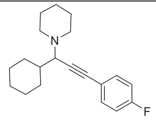
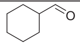
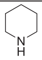
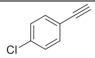
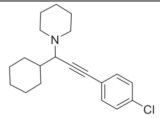
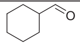
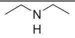
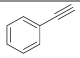
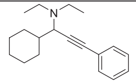
[b] Reflux.

[c] Isolated yields.

Table 3
$AgNO_3$-[TMG][TFA] catalyzed synthesis of propargylamines.



Entry[a]	Aldehyde	Amine	Alkyne	Product	Yield(%)[d]
1					90
2					85
3					92
4					87
5					89
6					87
7					80
8					70
9					69
10					70
11					89
12					85
13					90

14					80
15[b]					75
16[b]					85
17[b]					80
18[c]					54
19[c]					66
20[c]					50
21					80
22					82
23					72
24					60
25					70

[a] 0.6 mmol aldehyde, 0.72 mmol amine, 0.72 mmol alkyne, 1 mol% $AgNO_3$ and 1.5 eq [TMG][TFA] were mixed and heated at 70 °C for 2 h.

[b] 6h.

[c] 12h.

[d] Isolated yields.

compared with their aliphatic components, suggesting that this catalytic system is more suitable for the conversion of aliphatic aldehydes.

The reusability of the silver salts and ionic liquids catalytic system was also investigated using the reaction among cyclohexanecarboxaldehyde, pyrrolidine and phenylethynyl as a model, and the results were illustrated in Fig. 1. It was shown that after five cycles the catalytic activity had a negligible decrease, suggesting the excellent recyclability of this catalytic system in multi-component A^3 reaction.

According to the literature report and our previous experience on the functional ionic liquids catalysis, a plausible reaction mechanism were proposed and illustrated in Scheme 2. The silver salt activates terminal alkyne and forms silver acetylide, releasing $[H]^+$. The NH_2 on the cation of ionic liquid activates the C=O of aldehyde as hydrogen bond donor, while the anion of ionic liquid activate N—H of amine as hydrogen bond acceptor. The activated aldehyde and amine were then reacted under the presence of $[H]^+$ to produce iminium ion and the

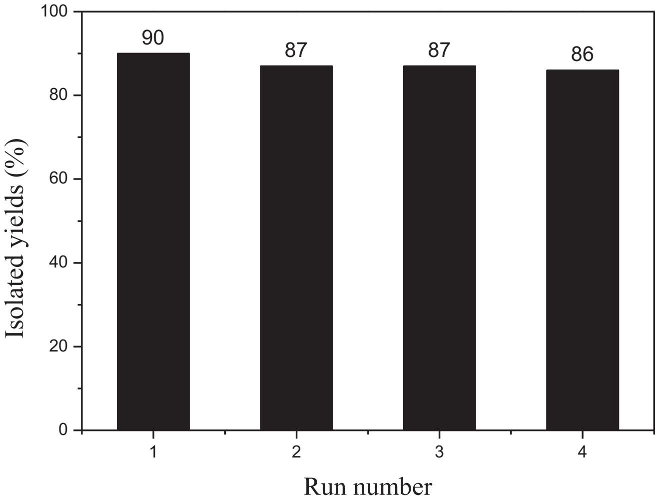
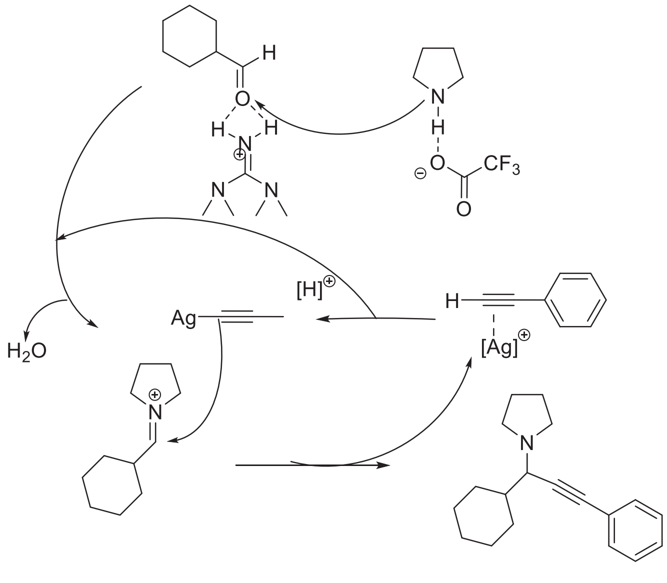


Fig. 1. Recyclability of ionic liquid catalyst.

only by-product water. The iminium ion was then attacked by silver acetylide, giving the target propargylamine and reproduced the silver salt.

4. Conclusions

This work has developed an efficient silver salt and ionic liquid combined catalytic system, $AgNO_3$-[TMG][TFA], for the one-pot A^3-coupling reactions. Various aromatic alkynes with different substitute groups including electro-donating or electro-withdrawing groups, diynes, heteroaromatic alkynes and propargyl ethers could react with different aldehyde and pyrrolidine and piperidine to give the target propargylamines with good to excellent isolated yields. These reactions can be conducted without inert gases and additional bases, solvents or any other additives. This makes the reaction and work-up procedures very simple and easy to be conducted. The silver salt and the ionic liquid were believed to have synergetic effect on the catalytic synthesis of propargylamines.



Scheme 2. Plausible reaction mechanism for the Ag/ionic liquid catalyzed multi-component A^3 reaction.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2019.01.142.

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