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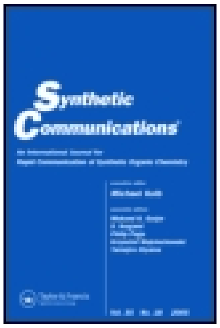

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Amanollah Zarei Ahmady [a] , Fariba Heidarizadeh [a] & Mosadegh Keshavarz [a]

[a] Chemistry Department, Faculty of Sciences, ShahidChamran University, Ahvaz 61357-4-3169, Iran

Accepted author version posted online: 26 Jan 2013.

To cite this article: Amanollah Zarei Ahmady , Fariba Heidarizadeh & Mosadegh Keshavarz (2013): Ionic Liquid Containing Copper (I): A New, Green, Homogeneous and Reusable Catalyst for Click Cyclization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI:10.1080/00397911.2012.687424

To link to this article: http://dx.doi.org/10.1080/00397911.2012.687424

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Ionic liquid containing Copper (I): a new, green, homogeneous and reusable catalyst for click cyclization

Amanollah Zarei Ahmady[1], Fariba Heidarizadeh[1,], Mosadegh Keshavarz[1]

[1]Chemistry Department, Faculty of Sciences, ShahidChamran University, Ahvaz 61357-4-3169, Iran

Corresponding author: Fariba Heidarizadeh, Chemistry department, College of Science, Shahid Chamran University, Ahvaz (6135743169), Iran, Tel.: +98-611 336 0018, Fax: +98-611333 7009, E-mail address: heidarizadeh@scu.ac.ir

Abstract

Ionic liquid containing copper (I) is introduced as a new, green, homogeneous and reusable catalyst for click synthesis of 1,4-disubstituted-1H-1,2,3-triazoles from α-azido ketones and terminal alkynes in various solvents especially in [bmim]BF_4. These cyclization reactions were efficiently performed in the presence of introduced ionic liquid catalyst with short reaction times and at high yields. This catalytic ionic liquid exhibitsexcellent activity and can be simply recovered and reused for at least five runs withoutany loss in its activity.

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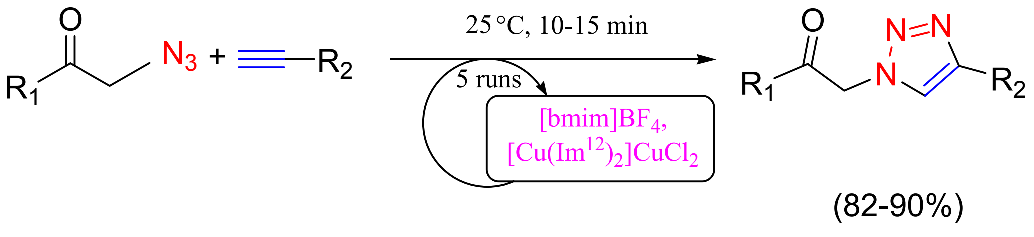

KEYWORDS: Ionic liquid, Multicomponent, Click chemistry, Triazole, Organic azide.

INTRODUCTION

Copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a widely utilized, reliable, and straightforward way for making covalent connections between building blocks containing various functional groups. It has been applied in various ways in organic synthesis, medicinal, surface, polymer and bioconjugation.[1–5]

Although many kinds of copper (I) have been introduced as catalyst for CuAAC reactions, the main decencies of these copper (I) catalysts are their instability and high tendency to oxidation which lead to catalytic inactivity. Almost all of them are applicable and suitable for certain kind of solvents. In fact, there is no copper (I) catalyst which can be employed for both organic and non-organic solvents due to their low solubility in all of these solvents. For instance, the simple coordination complexes $Cu(P(OMe)_3)_3Br$ [6] and $Cu(PPh_3)_3Br$ [7,8]are often used for reactions in organic solventswhere cuprous salts have limited solubility. There is research which describes the bis(phosphine) complex, $Cu(PPh_3)_2OAc$, as an excellent catalyst for the CuAAC reaction in toluene and dichloromethane.[9]Several Cu(I) complexes with N-heterocyclic carbene ligands have been described as CuAAC catalysts at elevated temperature in organic solvents or under heterogeneous aqueous conditions.[10–12]In situ prepared Cu (I) from Cu (II) using sodium ascorbate was introduced by Fokine and co-workers for click cyclization in water.[13]

Most of these catalysts have been less advised because of their thermodynamic instability, the formation of undesired alkyne-alkyne coupling and other byproducts which are sometimes observed in their presence.[14,15] It is noticeable that whensuch catalysts are soluble, cannot be recoverable and reusable. Although immobilizing of copper (I) on various supportsturns it intoa recoverable catalyst, the immobilized catalysts frequently suffer from leaching of the supported catalyst into the reaction mixture which leads to product contamination and catalyst deficiency during the recycling process.[16] These catalysts usually have low activity, low product yield, high reaction temperature and require additive.

Thispaper aims to illustrate that $[Cu(Im^{12})_2]CuCl_2$ is a versatile homogeneous and recyclable catalyst for the Huisgen preparation of 1,4-disubstituted 1,2,3-triazoles in various organic and non-organic solvents especially in $[bmim]BF_4$in accordance with the principles of green chemistry.

RESULTS AND DISCUSSION

The user friendly and adjustable properties of ionic liquids have prompted numerous applications, not only as environmentally benign reaction media, but also as catalysts,[17] task-specific reagents,[18] and chirality transfer media.[19] From this perspective, combining the synthetic potential of MCRs with the dual properties of RTILs as solvents and promoters has resulted in the development of new and promising eco-compatible organic transformations.[20] While some reports have been described the using of ionic liquids as green solvent for CuAAC reaction, these methods require additive for effective click cyclization and have long reaction times.[21,22] These reports do not represent the catalytic activity of ionic liquids and used only as suitable medium to increase the solubility of the reactants. With these respects, we became interested in investigating the effect of a new ionic liquid containing Cu (I), $[Cu(Im^{12})_2]CuCl_2$, as a new superior catalyst for CuAAC reaction. To achieve this, at the first step, the new ionic liquid containing Cu (I) catalyst was prepared according to the reported method (Scheme 1).[23]

To evaluate the efficiency of new introduced copper containing IL as catalyst for azide-alkyne cycloaddition reaction in various solvents, we turned to run the click cyclization between phenacylazide and phenyl acetylene in $[bmim]BF_4$, H_2O, $[bmim]BF_4/H_2O$, THF/H_2O, DMF/H_2O, dioxane/H_2O and CH_2Cl_2 as solvents. The results of using task-specific ionic liquid, $[Cu(Im^{12})_2]CuCl_2$, as catalyst are reported in Table 1.

It can be seen that the introduced task specific ionic liquid, ($[Cu(Im^{12})_2]CuCl_2$), works very well as a catalyst with various solvents even under neat conditions. This catalytic ionic liquid is the first type of ionic liquids which can promote click cyclization. The newly-introduced catalyst has removed the problems with the limited solubility of other copper (I) catalysts which has been one of the main deficiencies associated with all other kinds of copper (I) catalysts.Consequently, it can be employed in various types of organic and non-organic solvents

Although this catalyst constitutes a homogenous phase with all of these solvents and reduces the reaction times compared with the reported heterogeneous catalysts, it can be readily recovered and reused. While the introduced catalyst givesdesirable results using various solvents, $[bmim]BF_4$ evidently stands out as the solvent of choicewith its fast reaction rate, high yield and environmental acceptability.

To exploit the generality and scope of the reaction in [bmim][BF_4], the reaction was extended to various structurally diverse terminal alkynes and α-azido ketones(Scheme 2). The reaction progress was checked by TLC and the results are reported in table 2.

In all cases, click cyclization was completed in the course of a desirable and reasonable time and 1,2,3-triazole derivatives were isolated in high yields. These observations clearly indicate the generality and scope of the reaction with respect to various types of terminal alkynes and organic azides (Table 2). For example the using of 1,3-diethynylbenzene in click cyclizations led to the synthesis of interesting symmetrical bis-triazole~~s~~ (Table 2, entry 11 and Scheme 3).

Structural assignments of the products were confirmed by the appearance of a singletwithinthe range of 7.8 to 8.5 ppm in ^{1}H NMR spectra and indicated the regioselective synthesis of 1,4-disubstituted triazoleregioisomers.[24]

An efficient catalyst should be easily recovered and reused. To investigate these properties for our introduced catalyst, the reaction of phenacylazide with phenyl acetylene was selected again as the model reaction. After completion of click cyclization, the triazole product was easily extracted from the ionic liquids mixture using EtOAc. The recovered ionic liquids mixture was reused in the next run. A roughly-consistent activity was observed using [bmim]BF_4 as solvent and [Cu(Im^{12})$_2$]$CuCl_2$ as catalyst over five runs (Figure 1). The yield difference between the first and fifth runs was only 3% which indicates that the catalyst developed is maintaining its catalytic activity under reuse circumstances.

Mechanistic pathway for click cyclization between organic azide and terminal alkyne mediated by $[Cu(Im^{12})_2]CuCl_2$ is depicted in Figure 2.

The priority of this method to some of the previously reported ones is shown by the comparison of the obtainedresults in Table 3.

CONCLOSION

We have introduced a new, homogeneous, green and reusable catalyst for regiospecific synthesis of 1,4-disubstituted-1H-1,2,3-triazoles via Huisgen 1,3-dipolar cycloadditionreaction between terminal alkynes and organic azides in various solvents. The introduced ionic liquid containing copper (I), ($[Cu(Im^{12})_2]CuCl_2$), is the first ionic liquid which can promote and catalyze click cyclization. The main advantages of this catalyst over previously reported catalysts are its applicability for a wide range of solvents, high ability to promote CuAAC reactions, simple recovery and reusability procedure. Moreover, the mild reaction conditions, high yield of the products, ease of work-up and the ecologically clean procedure will make the present catalyst a useful and superior candidate for the synthesis of 1,4-disubstituted-1H-1,2,3-triazoles.

EXPERIMENTAL

All of the triazole derivatives were prepared by our procedure. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker Advanced DPX 500 and 400 MHz instrument spectrometers using TMS as internal standard. IR spectra were recorded on a BOMEMMB-Series 1998 FT-IR spectrometer. The spectroscopic and physical data of all known compounds were compared with those of authentic samples.[24,25]

Preparation Of $[Cu(Im^{12})_2]Cucl_2$

To a Schlenk flask filled with CuCl (1.21 g, 12.22 mmol) a solution of 1-dodecylimidazole (3.06 g, 12.95 mmol) in CH_3CN (5 mL) was added. It was placed in an ultrasonic bath at ambient temperature for about 30 min. The solvent was removed in vacuo and the precipitate was washed with ether and dried under vacuum to give $[Cu(Im^{12})_2]CuCl_2$ as a fine crystalline colorless solid.[23]

General Procedure For Synthesis Of 1,4-Disubstituted-1H-1,2,3-Triazoles Using $[Cu(Im^{12})_2]Cucl_2$ As Catalyst

$[Cu(Im^{12})_2]CuCl_2$ (0.1mmol) was added to a round-bottomed flask containing $[bmim]BF_4$ (4 mL), α-azido ketone (1 mmol), terminal alkyne (1 mmol). The reaction mixture was stirred at room temperature for appropriate time (table 2).After completion of the reaction (10-15 min) as monitored by TLC (EtOAc/n-hexan; 4:1 v/v),organic phase was extracted with ethyl acetate (2×8 ml)and concentrated in vacuo. Ionic liquids mixture was kept for the similar next runs. The solid residual was recrystallized froma mixture of ethanol/water(3:1 v/v) to give pure product crystals. Isolated product was dried in vacuum over night.

Spectroscopic Data

- *1-phenyl-2-(4-phenyl-1H-1,2,3-triazole-1-yl)-1-ethanon*(table 2, entry 1b): IR ($\square_{max}$ in cm^{-1}, KBr): 1702(CO);^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 6.28 (s, 2H, $COCH_2$), 7.34-7.38 (m, 1H), 7.47 (t, *J*= 7.7 Hz, 2H), 7.63 (t, *J*= 7.7 Hz, 2H), 7.78-7.74 (m, 1H), 7.88 (d, *J*= 8.15 Hz, 2H), 8.11 (d, *J*= 8.15 Hz, 2H), 8.53 (s, 1 H, CH Triazole);^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 56.5, 13.5, 125.6, 128.4, 128.7, 129.4, 129.5, 131.2, 134.6, 134.8, 146.8, 195.0 (CO).HRMS-FAB: m/z [M + H]$^+$calcd for $C_{16}H_{13}N_3O$: 263.3; found: 263.3.Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.92; H, 4.94; N, 15.95. Found: C, 73.00; H, 4.86; N, 16.03.

- *Ethyl 2-(4-phenyl-1H-1,2,3-triazole-1-yl)acetate* (table 2, entry 6b): IR ($\square_{max}$ in cm^{-1}, KBr): 1198, 1215, 1755(CO); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J*= 7.12 Hz, 3H), 4.36 (q,*J*= 7.12 Hz, 2H), 5.23 (s, 2H), 7.38 (t, *J*= 7.38 Hz, 1H), 7.46 (t, *J*= 7.46 Hz, 2H), 7.89-7.87 (m, 2H), 7.96 (s, 1H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.49, 51.38, 62.87, 121.42, 126.24, 128.69, 129.27, 130.82, 148.66, 166.72.HRMS-FAB: m/z [M + H]$^+$calcd for $C_{12}H_{13}N_3O_2$: 231.3; found: 231.3. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.67; H, 5.30; N, 18.06.

- *1-(4-bromophenyl)-2-[(4-(1-hydroxyethyl)-1H-1,2,3-triazole-1-yl)]-1-ethanone*(table 2, entry 7b):IR ($\square_{max}$ in cm^{-1}, KBr): 1250, 1497, 1599, 1704 (CO), 3417 (OH); ^{1}H NMR (400 MHz, DMSO-d$_6$): 1.54 (d, *J*= 5.20 Hz, 3H), 4.19-4.16 (m, 1H), 4.95 (s, 1H), 5.96 (s, 2H), 7.79 (d, *J*= 8.60 Hz, 2H), 7.95 (d, 2H, *J*= 8.6 Hz), 8.37 (s, 1H, CH Triazole);^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.13, 45.97, 52.37, 121.47, 130.48, 130.86, 132.67, 148.81, 153.86, 189.82,. HRMS-FAB: m/z [M + H]$^+$calcd for $C_{12}H_{12}BrN_3O_2$:

310.2; found: 310.2. Anal. Calcd for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.90; N, 13.55; Found: C, 46.34; H, 3.91; N, 13.34.

- *2-[4-(1-hydroxyethyl)-1H-1,2,3-triazole-1-yl)]-1-(4-methoxyphenyl)-1-ethanone*(table 2, entry 8b): IR (□$_{max}$ in cm^{-1}, KBr): 1170,1232, 1597, 1694 (CO), 3503 (OH); ^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (d, *J*= 8.75 Hz, 3H),3.89 (s, 3H), 4.89-4.86 (m, 1H), 5.28 (s, 1H), 6.07 (s, 2H), 7.13 (d, *J*= 8.75 Hz, 2H), 7.87 (s, 1H, CH Triazole), 8.06 (d, *J*= 8.75 Hz, 2H);^{13}C NMR (125 MHz, $CDCl_3$): δ =28.13, 45.97, 52.37, 121.47, 130.48, 130.86, 132.67, 148.81, 153.86, 189.82. HRMS-FAB: m/z $[M + H]^+$calcd for $C_{13}H_{15}N_3O_3$: 261.3; found: 260.3. Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 60.11; H, 5.65; N, 16.25.
- *2-(4-{4-[1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)]phenyl}-1H-1,2,3-triazol-1-yl)-1-phenyl-1-ethanone* (table 2, entry 11b): IR (□$_{max}$ in cm^{-1}, KBr): 686, 1226, 1696 (CO);^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.30 (s, 4H, $COCH_2$), 7.58 (t, *J*= 5.17 Hz, 1H), 7.64 (t, *J*= 5.17 Hz, 4H), 7.76 (t, *J*= 4.95 Hz, 2H), 7.87 (q, *J*= 2.33 Hz, 2H), 8.12-8.13 (m, 4H), 8.44 (s, 1H), 8.64 (s, 2H, CH triazole);^{13}C NMR (125 MHz, DMSO-d_6): δ = 56.91, 122.70, 125.51, 129.11, 129.90, 130.56, 132.29, 135.01, 135.17, 146.97, 193.06. Anal. Calcd for $C_{28}H_{20}N_6O_2$: C, 69.63; H, 4.49; N, 18.74. Found: C, 69.22; H, 5.56; N, 18.81.

See the Supplementary Material, available online, for complete spectral details.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Research Council of ShahidChamran University for financial support.

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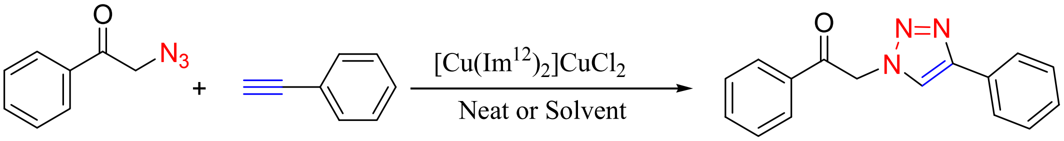
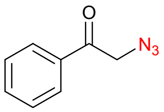
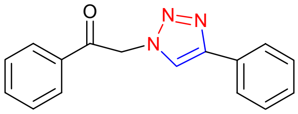
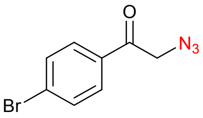
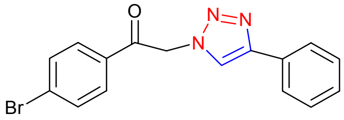
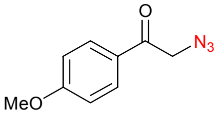
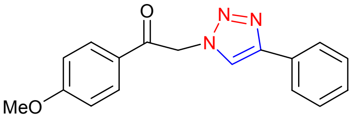
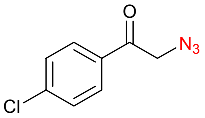
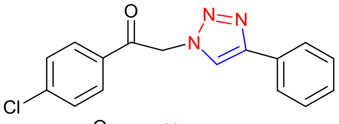
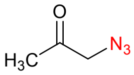
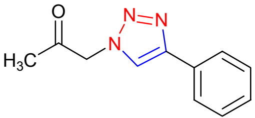
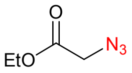
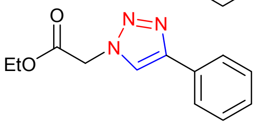
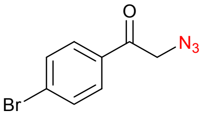
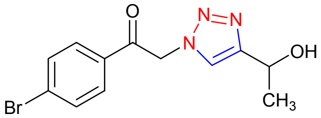
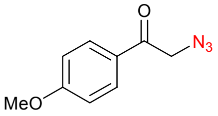
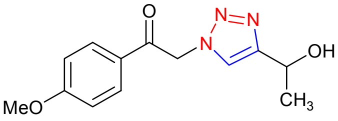
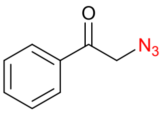
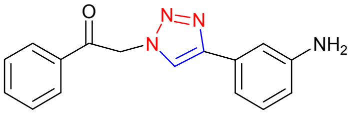
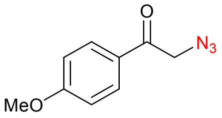
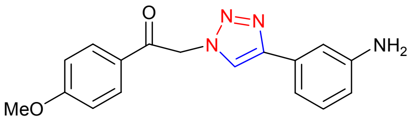
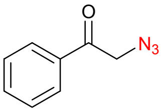
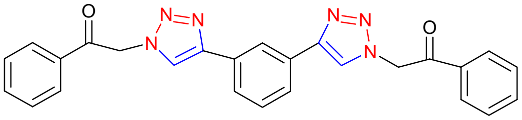
Table 1 Evaluation of copper containing ionic liquid catalyst efficiency for CuAAC reaction in various solvents



Entry	Solvent	Temperature(°C)	Time(min)	Yield(%)[a]
1	neat	60	25	75
2	[bmim]BF_4	25	10	90
3	Dioxane/H_2O (1:1 v/v)	25	20	75
4	THF/H_2O (1:1 v/v)	25	20	78
5	[bmim]BF_4/H_2O (1:1 v/v)	25	15	80
6	CH_2Cl_2	25	20	79
7	H_2O/DMF (1:1 v/v)	25	20	75
8	H_2O	50	25	80

[a] Yield refer to **isolated** and pure products

Table 2 [Cu(Im^{12})$_2$]CuCl$_2$/[bmim]BF$_4$mediumpromotes click cyclization between α-azido ketones and terminal alkynes

Entery	α-azido ketone(a)	Product(b)	Time (min)	Melting point(°C)	Yield (%)^c
1			10	146[24]	90
2			10	145[24]	86
3			10	142[24]	87
4			10	152[25]	84
5			10	138[25]	84
6			10	112	88
7			15	108	83
8			15	118	85
9			10	146[24]	82
10			10	163[24]	85
11			15	More than 300	85

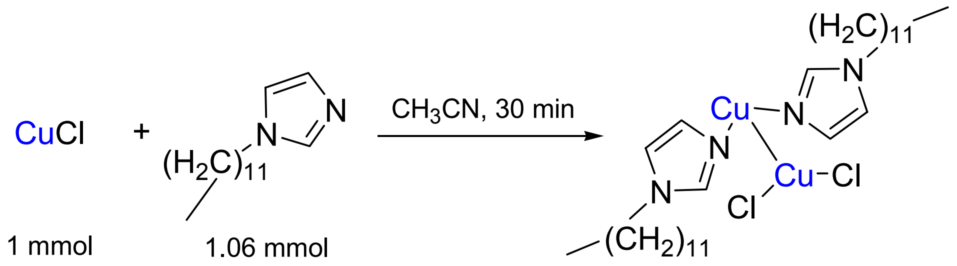
^{c}Yields refer to isolated and pure products

Table 3 Comparison of the results obtained by the present method with some of the previous methods

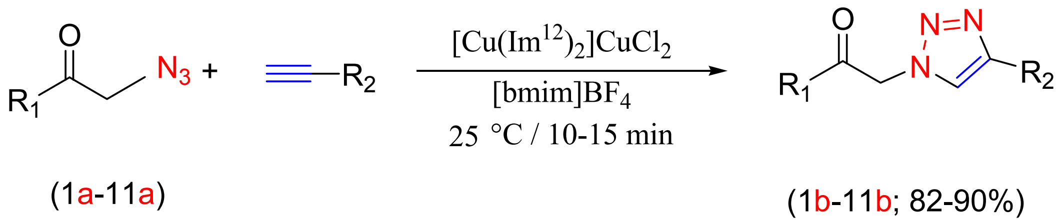
No.	Solvent	Catalyst	T (°C)	t (min)	Yield (%)[a]
1	[bmim]BF_4	[Cu(Im^{12})$_2$]$CuCl_2$	25	10-15	82-90 [This work]
2	[C_8dabco][N(CN)$_2$]	CuI/ i-Pr_2EtN(additive)	25	960	95 [21]
3	[bmim]BF_4	CuI/ i-Pr_2EtN(additive)	25	960	68 [21]
4	n-Hexan	Cu/ AlO(OH)	25	180-1440	82-97 [26]
5	t-BuOH (80%)	PS[NEt_3][OAc](CuI)	25	150-1440	82-99 [27]

[a] Yields refer to isolated and products

Scheme 1 Preparation of [Cu(Im^{12})$_2$]$CuCl_2$



Scheme 2 Click cyclization between various α-azido ketones and terminal alkynes using ionic liquids as solvent and catalyst



Scheme 3 Synthesis of symmetrical bis-triazoles using task specific ionic liquids

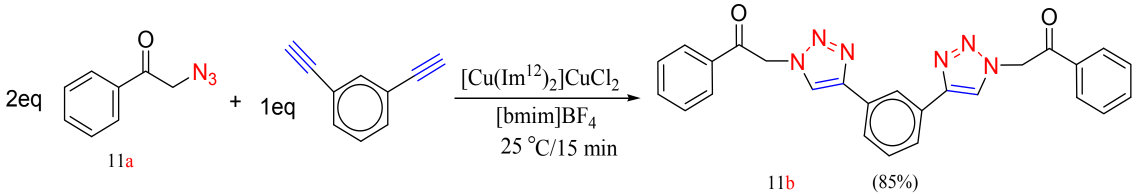
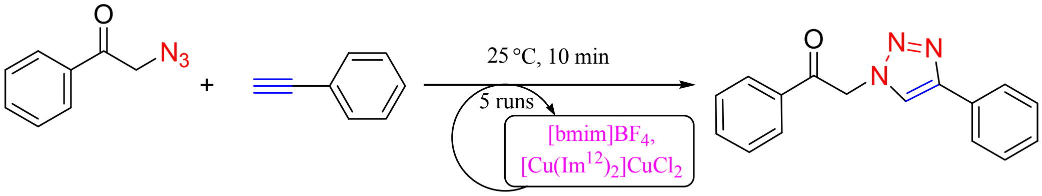


Figure 1. Reusability study of $[Cu(Im^{12})_2]CuCl_2/[bmim]BF_4$ in azide-alkyne cycloaddition



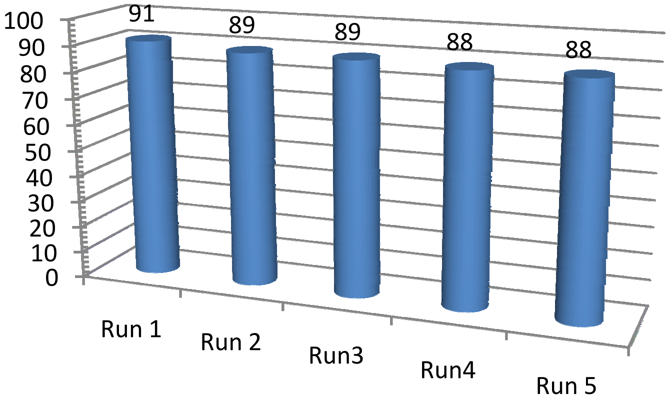


Figure 2. Proposed mechanistic pathway for $[Cu(Im^{12})_2]CuCl_2$ catalyzed azide-alkyne cycloaddition