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An efficient synthesis of propargylamines *via* C–H activation catalyzed by copper(I) in ionic liquids

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A readily available copper(I) catalyst, in an ionic liquid, can effect three-component coupling of aldehydes, amines and alkynes to generate propargylamines in high yields.

The transition metal-catalyzed multi-component reaction is a powerful synthetic tool to access complex structures from simple precursors by a one-pot procedure. Activation of a terminal alkyne C–H bond by transition metal catalysts[1] is a reaction of fundamental interest in organic synthesis because, for example, the unique properties of acetylenic arrays are of value in non-linear optical devices[2] and natural product synthesis.[3] Propargylic amines are important intermediates for organic synthesis and reliable methods for their synthesis are relatively few. Thus, there is a need for a general and efficient synthetic protocol that would be applicable to a wide range of propargylamines.[4] Recently, Li,[5] Tu,[6] and co-workers reported interesting propargylamine syntheses through three-component coupling of aldehydes, alkynes and amines (A^3 coupling) *via* transition metal (for example gold, silver, ruthenium or copper with microwaves) catalysis in water or organic media. Even though these systems are general, environmentally friendly and applicable to both aliphatic and aromatic aldehydes and amines, there are no reports of the recyclability of the catalyst. It is a considerable drawback that an expensive metal catalyst (silver, gold *etc.*) is often lost at the end of the reaction. Hence, a process for recycling the catalyst system is of importance. Different strategies have been used to separate and reuse homogeneous catalysts, such as aqueous biphasic systems,[7] fluorous biphasic systems,[8] soluble polymer-based ligands[9] and ionic liquids.[10] In continuation of our studies on recyclable catalysts in ionic liquids,[11] we now report an efficient recyclable A^3 coupling reaction *via* C–H activation catalyzed by a copper(I) compound in an ionic liquid.

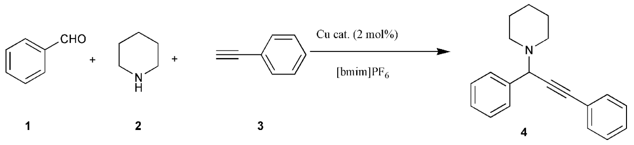
Initially, we examined the A^3 coupling reaction using various palladium catalysts, as we previously found that Sonogashira coupling could be effected using a palladium catalyst in an ionic liquid in the absence of both a copper co-catalyst and extra phosphine ligands. It was found that palladium catalysts (*i.e.*, $PdCl_2$, $PdCl_2(PPh_3)_2$, (cod)$PdCl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$) were not useful to obtain the desired propargylamines, despite the known activity of Pd to catalyze terminal C–H bond activation.[12]

We then turned our attention to the use of copper compounds as catalysts for the A^3 coupling reaction because they are readily available and much cheaper than silver,[5b] gold,[5a] ruthenium,[5c] or other additives[6] in an ionic liquid as the solvent. The catalytic activity of various copper complexes was examined for the A^3 coupling of benzaldehyde, piperidine and phenylacetylene (Table 1).

The coupling process proceeded well in the presence of 2 mol% of copper compounds (CuI, CuBr, CuCl, CuCN, $Cu(OAc)_2$ and Cu powder) to give propargylamines in 60–98% conversion. Whereas about 10% of the corresponding product, *N*-(1,3-diphenyl-2-propynyl) piperidine (**4**), was obtained by using CuBr in water,[5a] the same catalyst, after 2 h, afforded **4** in 95% yield using [bmim]PF_6 as the ionic liquid (Table 1, entry 5). All Cu(I) species (entries 1–6) showed excellent catalytic properties and slightly better than those of Cu(II) or copper powder. Nevertheless hydrated cupric acetate (entry 7) and 800 mesh of copper powder, afforded **4** in 60–77% yield. No reaction occurred in the absence of a copper-containing catalyst (entry 9). The [bmim]PF_6 is a better ionic liquid than, for example, a phosphonium ionic liquid such as trihexyl(tetradecyl) phosphonium hexafluorophosphate for this reaction (entry 10). In addition, no other additive was needed for this system, and the experimental process was quite simple and easy.

Having optimized the reaction conditions, the recyclability of the A^3 coupling reaction with copper(I) catalysts in [bmim]PF_6 was examined (Table 2). Reactions using an aliphatic aldehyde (entry 2), electron-rich (entry 4) or electron-poor (entry 5) styrenes, or a heteroaromatic (entry 6) aldehyde gave the desired products in

Table 1 A^3 Coupling reaction with copper catalysts in [bmim][PF_6][a]



Entry	Cu cat.	Temp. (°C)/ Time (h)	Conversion (%)[b]
1	CuI	100/5	78
2	CuI	120/2	86
3	CuI	120/4	98
4	CuCN	120/2	85
5	CuBr	120/2	95
6	CuCl	120/2	85
7	$Cu(OAc)_2$ monohydrate	120/4	60
8	Copper powder	120/4	77
9	—	120/12	0
10	CuCN	120/2	60[c]

[a] All reactions were carried out using 1 mmol of benzaldehyde, 1.2 eq. of piperidine, 1.5 eq. of phenylacetylene and 2 mL of the ionic liquid. [b] Conversions were determined by ^1H NMR of the crude reaction mixture. [c] Trihexyl(tetradecyl)phosphonium hexafluorophosphate was used as the ionic liquid. Various by-products were observed.

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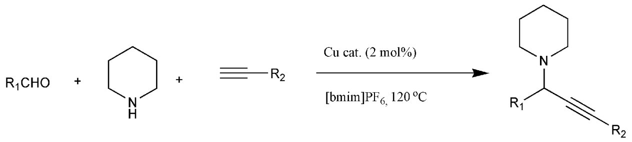
Table 2 Recyclable A^3 coupling reaction with copper catalysts in [bmim][PF$_6$]^a



Entry	R$_1$	R$_2$	Cu cat.	Cycle no. (time, h)^b Corresponding yield (%)				
1	C_6H_5	Ph	CuI	1 (2) 86	2 (2) 84	3 (2) 76	4 (4) 83	5 (4) 77
2	C_7H_{15}	Ph	CuCN	1 (2) 82	2 (2) 80	3 (2) 78	4 (4) 84	5 (4) 78
3	C_6H_5	Ph	CuCN	1 (2) 86	2 (2) 85	3 (2) 84	4 (2) 85	5 (2) 78
				6 (2) 83	7 (2) 77	8 (2) 82	9 (2) 81	10(2) 78
4	4-(MeO)C_6H_5	Ph	CuCN	1 (2) 79	2 (2) 73	3 (2) 73	4 (4) 85	5 (4) 63
5	4-ClC_6H_5	Ph	CuCN	1 (2) 74	2 (2) 87	3 (2) 89	4 (4) 77	5 (4) 75
6	2-Thiophene	Ph	CuCN	1 (2) 83	2 (2) 82	3 (2) 82	4 (4) 78	5 (4) 80
7	C_6H_5	n-C_5H_{11}	CuCN	1 (2) 69	2 (2) 79	3 (2) 83	4 (2) 68	5 (2) 68

[a] All reactions were carried out using 1 mmol of aldehyde, 1.2 eq. of piperidine, 1.5 eq. of the alkyne and 2 mL of [bmim]PF$_6$. [b] Values given for each cycle are based on GC yields (%).

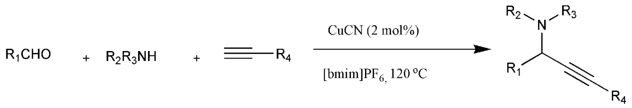
high yields using only 2 mol% of the copper catalyst. CuI (entry 1) and CuCN (entry 3) show similar catalytic activity. It is important to stress that the catalyst was recycled and reused for five or ten runs (entry 3) with only a slight drop in activity.

Having established the recyclability and reusability of this system, we next examined its performance for the coupling reaction of a variety of aldehydes, amines, and alkynes (Table 3). Entries 1–3 and 5–9 of Table 3 indicate that the coupling reactions gave **4** in 74–98% yields.

Furthermore, aliphatic aldehydes having an α-hydrogen (entry 10) also display high reactivity and clean reactions under standard conditions. The reaction is sensitive to steric effects, as 2-methoxybenzaldehyde afforded a trace amount of product (entry 4) while electronic effects are minimal in this reaction (entries 2, 3, 5 and 6).

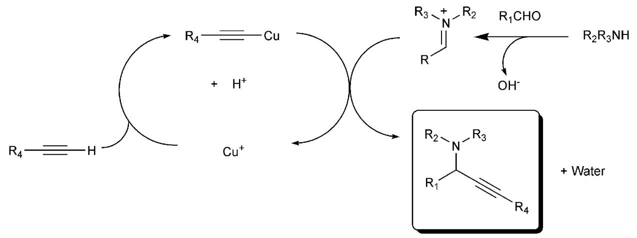
Use of different (aliphatic, aromatic) amines in reaction with phenylacetylene and benzaldehyde (entries 11–16) gave results demonstrating again the sensitivity to steric factors, *e.g.*, using 2-methyl piperidine as the amine gave the propargylamine in 68%

Table 3 A^3 Coupling reaction with copper catalyst in [bmim][PF$_6$]^a



Entry	R$_1$	Amine (R$_2$, R$_3$)	R$_4$	Time (h)	Yield (%)^b
1	C_6H_5	Piperidine	C_6H_5	2	85
2	4-(MeO)C_6H_4	Piperidine	C_6H_5	2	79
3	3-(MeO)C_6H_4	Piperidine	C_6H_5	3	84
4	2-(MeO)C_6H_4	Piperidine	C_6H_5	5	trace
5	4-ClC_6H_4	Piperidine	C_6H_5	2	74
6	4-BrC_6H_4	Piperidine	C_6H_5	2	98
7	4-Biphenyl	Piperidine	C_6H_5	2	95
8	1-Naphthyl	Piperidine	C_6H_5	2	95
9	2-Thiophene	Piperidine	C_6H_5	2	83
10	C_7H_{15}	Piperidine	C_6H_5	2	82
11	C_6H_5	Morpholine	C_6H_5	2	95
12	C_6H_5	$R_2 = R_3 =$ allyl	C_6H_5	2	88
13	C_6H_5	2-Methyl piperidine	C_6H_5	2	68
14	C_6H_5	*cis*-2,6-Dimethyl piperidine	C_6H_5	2	0
15	C_6H_5	$R_2 = R_3 =$ Ph	C_6H_5	2	56
16	C_6H_5	$R_2 =$ Ph, $R_3 =$ H	C_6H_5	3	90
17	C_6H_5	Morpholine	n-C_5H_{11}	2	87
18	C_6H_5	Morpholine	$(EtO)_2CH$	2	79
19	C_6H_5	Morpholine	TIPS	2	54

[a] All reactions were carried out using 1 mmol of aldehyde, 1.2 eq. of amine, 1.5 eq. of acetylene and 2 mL of [bmim]PF$_6$. [b] Isolated yield.



Scheme 1 Tentative mechanism for A^3 coupling reaction.

yield, while no reaction occurred in the case of *cis*-2,6-dimethyl piperidine. Finally, the A^3 coupling reaction proceeded well using alkyl and aryl-substituted acetylenes (entries 17–19).

On the basis of these results, together with several literature publications,[5,6] it is believed that the A^3 coupling reaction proceeds by terminal alkyne C–H bond activation by copper catalysts (Scheme 1). The copper acetylide intermediate thus generated can react with the iminium ion prepared *in situ* from the aldehyde and the amine, to form the corresponding propargylamine. The released Cu(I) species is then able to be recycled. Because [bmim]PF_6 is a hydrophobic room temperature ionic liquid, it is possible to *exclude water which is only by-product formed in these reactions*.

This new method offers the following competitive advantages: (i) recyclability of the catalyst without significant loss of catalytic activity; (ii) use of readily available, cheap copper catalysts without further purification, or without using other additives; (iii) lower catalyst loading (2 mol%); (iv) broad substrate applicability; (v) high yields attained in short reaction times; and (vi) simple and easy operation.

In summary, we have developed an efficient synthesis of propargylamines through three-component coupling of aldehydes, amines and alkynes *via* C–H activation by a copper catalyst in the ionic liquid, [bmim]PF_6. This system can be recycled five times without any significant loss of catalytic activity.

A representative procedure for the coupling reaction follows: a mixture of [bmim][PF_6] (2 mL) and CuCN (2.0 mg, 0.02 mmol) was degassed under reduced pressure at 80 °C for 30 min, and then nitrogen gas was introduced. To the solution was added piperidine (0.12 mL, 1.5 mmol), benzaldehyde (106 mg, 1.0 mmol) and phenylacetylene (0.16 mL, 1.2 mmol), and the resulting mixture was heated at 120 °C for 2 h. The product was extracted from the reaction mixture by addition of diethyl ether and the recovered ionic liquid layer was reused without any pretreatment. The combined organic layer was concentrated and the desired product was isolated by short-path silica gel column chromatography.

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