# Highly active copper-catalysts for azide-alkyne cycloaddition<sup>†</sup>

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Bis-triphenylphosphano complexes of copper(I)-carboxylates serve as efficient catalysts for azide-alkyne cycloaddition. The triazole formation takes place straightforwardly at ambient temperature providing a wide variety of products with good yields in the presence of 0.005–0.05% catalyst.

The copper assisted regioselective 1,3-dipolar cycloaddition of terminal azides and acetylenes has become one of the most popular organic transformations since its discovery.<sup>1</sup> This powerful click method<sup>2</sup> has been applied in drug discovery,<sup>3</sup> polymer chemistry,<sup>4</sup> materials science,<sup>5</sup> bioconjugation<sup>6</sup> and fluorescent imaging.<sup>7</sup> Besides the extension of the applications in the field of chemistry and related sciences, the development of new, highly active copper catalysts is also a target of interest in organic synthesis. Tristriazolylamines,<sup>8</sup> tris(benzimidazolylmethyl)amines,<sup>9</sup> tris(2-dioctadecylaminoethyl)amine<sup>10</sup> and NHC ligands<sup>11</sup> had the largest rate accelerating properties in copper catalyzed azide-alkyne cycloaddition (CuAAC) until recently. Although, the utilization of phosphanes in transition metal catalyzed transformations is common, interestingly, these ligands are not significantly prevalent in click chemistry.<sup>12</sup>

The goal of our research was the development of new, highly efficient catalyst systems for the click reaction using cheap and readily available copper sources and ligands such as phosphanes.

Screening the efficiency of different copper salts, we chose benzyl azide and phenylacetylene as reactants and toluene as solvent. The reactions were carried out at 25 °C in the presence of 1 mol% of catalysts. Not surprisingly, under these conditions, CuI, CuBr, CuCl, and CuCN proved to be not effective at all, supposedly due to the low solubility of the salts in toluene (Table 1. Entries 1–4). In order to increase the solubility of the catalysts, we applied triphenylphosphane as ligand in the reaction. In the presence of the ligand CuI and CuCN showed catalytic activity, and we got 41% and 5% conversion respectively in 3 h (Entries 5 and 6). It is well known that the phosphanes are able to reduce the Cu(II) salts to Cu(I),<sup>13</sup> therefore we tried different copper(II) sources (0.5 mol%) in the presence of PPh<sub>3</sub> (1 mol%) in toluene.

	$\sum_{N_3} = \sqrt{2}$	1mo 2mol 1mo To	ol% "Cu" % Ligand l% Base	N= <sup>N</sup>	
	1a 2a	1	25°C		388
Entry	Cu	Ligand	Base	Time/h	Conv. (%) <sup>b</sup>
1	CuI		_	24	0
2	CuBr		_	24	0
3	CuCl		_	24	0
4	CuCN		_	24	0
5	CuI	PPh <sub>3</sub>	_	3	41
6	CuCN	PPh <sub>3</sub>	_	3	5
7	CuI	PPh <sub>3</sub>	KOAc	3	75
8	CuCN	PPh <sub>3</sub>	KOAc	3	20
9	CuSO <sub>4</sub> *5H <sub>2</sub> O <sup>c</sup>	PPh <sub>3</sub>	_	24	40
10	$Cu(NO_3)_2 * 3H_2O^c$	PPh <sub>3</sub>	_	7	66
11	CuBr <sub>2</sub> <sup>c</sup>	PPh <sub>3</sub>	_	7	83
12	Cu(OAc) <sub>2</sub> *H <sub>2</sub> O	PPh <sub>3</sub>	_	1	100
13	$Cu(OAc)_2 * H_2O^c$	PPh <sub>3</sub>	_	7	99
14	$Cu(OAc)_2 * H_2O^d$	PPh <sub>3</sub>	_	24	100
15	$Cu(OAc)_2 * H_2O$	_	_	30	47
16	CuI	PPh <sub>3</sub>	Na-formate	3	86
17	CuI	PPh <sub>3</sub>	Na-acetate	3	85
18	CuI	PPh <sub>3</sub>	Na-propionate	3	88
19	CuI	PPh <sub>3</sub>	Na-butyrate	3	88
20	CuI	PPh <sub>3</sub>	Na-caprylate	3	94
21	CuOAc		_ ``	3	45
22	CuOAc <sup>d</sup>	PPh <sub>3</sub>	_	1	100
23	CuOAc <sup>e</sup>	PPh <sub>3</sub>	_	3	100

 Table 1
 The copper salt, ligand and base effect on the click reaction<sup>a</sup>

<sup>*a*</sup> Reaction conditions: 0.25 mmol benzyl azide, 0.25 mmol phenylacetylene, 25 °C. <sup>*b*</sup> Conversion was determined by GC. <sup>*c*</sup> 0.5 mol% copper salt and 1 mol% ligand were used. <sup>*d*</sup> 0.1 mol% copper salt and 0.2 mol% ligand were used. <sup>*c*</sup> 0.05 mol% copper salt and 0.1 mol% ligand were used.

 $\label{eq:cusO4*5H2O} CuSO_4*5H_2O gave only 40\% conversion after 24 h (Entry 9), with Cu(NO3)_2*3H_2O the conversion was 66\% after 7 h (Entry 10) and in the presence of CuBr_2 we found 83% conversion (Entry 11). Application of 1 mol% Cu(OAc)_2*H_2O together with 2 mol% PPh_3 in toluene resulted in complete reaction in 1 h at 25 °C (Entry 12). Completion of the reaction was reached in 7 h when 0.5 mol% Cu(OAc)_2*H_2O was used (Entry 13), and 24 h reaction time was necessary when we reduced the amount of the catalyst to 0.1 mol% (Entry 14).$ 

Interestingly, the copper( $\Pi$ )-acetate was able to catalyze the cycloaddition without the addition of any reducing agents (Entry 15).

On the basis of these results, we supposed that the presence of carboxylate anion accelerates the reaction, therefore we intended to examine different type of copper(I)-carboxylates generated *in situ* from Cu(I) salts and different carboxylate additives. In the presence of 1 mol% KOAc, PPh<sub>3</sub> and CuI the reaction rate dramatically increased compared to the base free reaction (75% vs.

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Results of the optimization studies, experimental procedures and the characterization data for the products are available. The identity and purity of the known products was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analysis, and the new products were fully characterized. See DOI: 10.1039/ b920790m

41%, Entry 7). The results of reactions with different bases showed that the cation of the base has not significantly determined the catalytic activity, and increasing the length of the carbon chain of the carboxylate anion showed slightly enhanced reactivity (Entries 16–20).

After finding the importance of the carboxylates, we tested copper(I)-acetate<sup>14</sup> as copper source in CuAAC. Although the click reaction of benzyl-azide and phenylacetylene in toluene, performed with 1 mol% CuOAc without ligand showed better activity than other copper(I) salts (Entry 21),<sup>15</sup> repeating the experiment in the presence of PPh<sub>3</sub> the reaction was complete in 1 h at 25 °C (Entry 22). Reducing the copper catalyst loading to 0.05 mol% and the phosphane to 0.1 mol% the full conversion was reached in 3 h (Entry 23). We suppose that the presence of the ligand not only makes the copper catalyst more soluble in organic media by complexation, but also stabilizes the copper(I) carboxylate, and prevents the catalyst from oxidation.

As an optimal choice,<sup>16</sup> we used triphenylphosphane as ligand for further examination and we prepared three copper phosphane complexes. Catalytic activity of CuNO<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>,<sup>17</sup> CuOAc(PPh<sub>3</sub>)<sub>2</sub><sup>18</sup> and C<sub>3</sub>H<sub>7</sub>COOCu(PPh<sub>3</sub>)<sub>2</sub> were compared in different organic solvents.<sup>19</sup> A general trend in the catalytic activity of the complexes has been found in the cycloaddition with respect to the choice of solvent. In all tested solvents the copper(I)-butyrate complex showed superior activity in the reaction of benzyl azide and phenylacetylene, and dichloromethane proved to be the most suitable solvent for the reaction.

Decreasing the amount of catalyst, we were able to achieve the click reaction with 0.01% C<sub>3</sub>H<sub>7</sub>COOCu(PPh<sub>3</sub>)<sub>2</sub>, but a significant drop in the conversion was detected on lowering the catalyst content (Table 2, Entries 1–5). Under solvent free conditions a further decrease of the catalyst loading was found to be possible. The click reaction of benzyl azide and phenylacetylene in the presence of 50 ppm copper catalyst reached 44% conversion after 6 h at rt. At 50 °C the reaction takes place faster, and we obtained the triazole product with 86% conversion after 6 h. In the presence of 10–30 ppm copper the reaction was found to be very sluggish. In the absence of copper catalyst at 50 °C we have observed only the slow formation of a 1:1 mixture of triazole regioisomers.

After the optimization studies, exploration of the scope of the catalyst system was performed with 0.05–0.15 mol%  $C_3H_7COOCu(PPh_3)_2$  in DCM at room temperature without the exclusion of air with structurally different azides and acetylenes. Cycloaddition of phenylacetylene **2a** with functionalized benzyl azides (**1b–d**) (Table 3, Entries 2–4) also gave the appropriate products (**3ba**, **3ca**, **3da**) with high isolated yields. Reaction of benzyl azide and other aromatic acetylenes, such as tolyl acetylene (**2b**) (Entry 5) and 2-pyridylacetylene (**2c**) (Entry 6) also afforded the triazoles (**3ab**, **3ac**) with high yields.

Besides aromatic terminal acetylenes, the reactivity of aliphatic compounds toward azides was also tested. Although, the reaction of benzyl azide (1a) with 5-cyanopent-1-yne (2d), propargyl acetate (2e) and hex-1-yne (2f) required longer reaction times compared to the aromatic acetylenes, the click product (3ad, 3ae, 3af) was obtained almost quantitatively in all three cases (Entries 7–9).

 Table 2
 Catalyst loading studies<sup>a</sup>



<sup>*a*</sup> Reaction conditions: 0.25 mmol benzyl azide, 0.25 mmol phenylacetylene, 25 °C. <sup>*b*</sup> Conversions were determined by GC. <sup>*c*</sup> Reaction stopped after the indicated time. <sup>*d*</sup> Formation of a negligible amount of 1,5regioisomer was observed. <sup>*e*</sup> Larger amount of 1,5-regioisomer was formed. <sup>*f*</sup> 1:1 mixture of regioisomers was obtained.

For the reaction of azidomethyl phenylsulfide (1e) and phenylacetylene (2a) 0.1 mol% catalyst was used and the reaction was complete in 5 h at 28 °C. The efficiency of the catalyst system was demonstrated with the reaction of bulky 1-azidoadamantane (1f)and phenylacetylene (2a) and the triazol **3fa** was isolated in 92% yield.

Aliphatic azides were also effectively clicked with the terminal acetylenes in the presence of 0.05 mol% bis-triphenylphosphanocopper(I)-butyrate (Entries 12–16). The catalyst also proved to be applicable for the transformation of azido and ethynyl substituted sugar and amino acid derivatives. We were able to prepare straightforwardly different triazoles (**3ke**, **3ig**, **3le**, **3ih**) bearing these important molecular architectures (Entries

#### 17-20).

Summarizing our results, we have demonstrated that copper catalyzed azide-alkyne cycloaddition can be achieved very efficiently with stable phosphane based complexes of copper(1) carboxylates. The presence of phosphane ligands and carboxylate ions makes the copper(1) ion more soluble in organic media, and ensures better accessibility of the transition metal for the reactant. In dichloromethane the cycloaddition takes place in the presence of 0.05 mol% copper catalyst at room temperature in short reaction proceeded in the presence of 50 ppm copper catalyst. The developed conditions proved to be very effective for the azide-alkyne click reaction, and the methodology offers good alternative for the straightforward synthesis of versatile triazole compounds in high yield.

#### **Table 3**The substrate scope<sup>a</sup>

	$R^2N_2 + = R^1 - R^1$	0.05-0.15% <sub>3</sub> H <sub>7</sub> COOCu(PPh <sub>3</sub> ) <sub>2</sub>	N=N	~ _1
	1a-l 2a-l	DCM, 28 °C	R <sup>2</sup> "	<sup>-</sup> R'
Entry	Compound		Time/h	Yield, (%) <sup>b</sup>
1		<b>3</b> aa	3	99
2		3ba	3	85
3		3ca	3	91
4		) 3da	3	87
5		3ab	3	94
6		3ac	3	93
7		3ad CN	5	98
8	N=N	3ae	5	99
9		3af /	8	93
10		3ea	5	96
11	N=N N	3fa	6	92
12		3ga	8	90
13		3ha	8	94
14		- 3ia	8	96
15		3ja	8	91
16		3ie	8	91
17		3ke	12	93

Table	3 (	Contd.
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<sup>*a*</sup> Reaction conditions: 0.5mmol azide, 0.5mmol acetylene, 1M concentration, 28 °C. <sup>*b*</sup> Isolated yields.

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