Copper(I)–Phosphinite Complexes in Click Cycloadditions: Three-Component Reactions and Preparation of 5-Iodotriazoles

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Abstract: The remarkable activity displayed by copper(I)-phosphinite complexes of general formula [CuBr(L)] in two challenging cycloadditions is reported: a) the one pot azidonation/cycloaddition from boronic acids, NaN₃ and terminal alkynes; b) the cycloaddition of azides and iodoalkynes. These air-stable catalysts led to very good results in both cases and the expected triazoles could be isolated pure under ‘Click-suited’ conditions.

Introduction

Huisgen 1,3-dipolar cycloadditions represent a powerful methodology for the preparation of a wide range of five-membered ring cyclic compounds.1–2 These reactions have recently made a strong comeback due to the huge interest attracted by the copper(I)-catalyzed [3+2] cycloaddition of organic azides and alkynes, unarguably the best Click reaction to date. This transformation leads to the extremely efficient formation of 1,4-disubstituted [1,2,3]-triazoles as a sole regiosomer.3 Barely ten years after the original groundbreaking reports by Sharpless and Meldal,4 a myriad of ligandless as well as ligated copper systems have been reported in the literature and found applications in diverse fields.5

Unsurprisingly, phosphorous ligands, and PPh₃ in particular, were among the first ligands applied to the cycloaddition of azides and alkynes.6,7 We recently reported the excellent activity in CuAAC reactions of novel copper(I) complexes bearing phosphinite or phosphonite ligands.8 These complexes of general formula [CuBr(L)] are stable and can be handled with no particular precautions to exclude moisture or air. Furthermore, we showed that they outperformed related complexes with one phosphinite or phosphonite ligand.9

Organic azides are generally stable towards water and oxygen, and safe to use,10 except those of low molecular weight,11 which historically caused a tangible azidophobia in the chemical community.12 As a result, several approaches have been explored in order to avoid the handling and isolation of organic azides in [3+2] cycloadditions. These reactions are straightforward for aliphatic azides since these can be easily accessed from the corresponding halides or amines via a simple nucleophilic substitution with NaN₃11 or TfN₃12 respectively. However, reactions involving aryl azides are significantly more limited. Anilines can be reacted with tert-butyl nitrite and TMSN₃ to generate in situ the corresponding aryl azides, however the scope of this reaction is limited.13 Alternatively, a proline/copper(I) system has been reported to mediate the one-pot azidonation/cycloaddition reactions from aryl halides (iodide or bromide).14,15

We turned our attention to the in situ preparation of aryl azides from the corresponding boronic acids due to their low toxicity, and wide availability supported by the popularity of Suzuki-Miyaura cross-coupling reactions. To the best of our knowledge, no homogeneous, ligated copper(I) system has been reported in this context. To date, reports on this three-component copper-mediated transformation have focused on heterogeneous systems requiring high metal loadings (10 mol% [Cu]), and often, a large excess of NaN₃.16,17

On the other hand, the preparation of 5-iodotriazoles from the corresponding organic azides and iodoalkynes remains a challenging transformation as only a handful of efficient catalysts has been described in the literature so far.18,19 Despite the obvious similarities, important differences in the reactions of terminal and iodo-alkynes have been reported. Whereas the ligand-less combination CuSO₄·Na ascorbate is very popular for the cycloaddition of terminal alkynes, the presence of coordinating ligands is crucial for any iodotriazole to be formed. In addition to ancillary ligands, most reported systems also require an N-additive such as triethyl amine or lutidine. These facts are aligned with an increasing evidence of different mechanistic pathways in both reactions. Fokin first suggested that cleavage of the carbon–iodine bond is not required for the
Results and Discussion

The three component reaction: In a first step, we explored the three-component reaction between boronic acids, NaN₃ and terminal alkynes for the one pot preparation of 1,4-disubstituted triazoles. Both steps of this transformation (azidation and cycloaddition reactions) are copper(I)-mediated, and therefore we chose [CuBr(PPh₃)₂(Ph₂−OMe)] A for the initial screening, as it had previously shown the highest activity in CuAAC reactions. [⁸] With para-methoxyphenyl boronic acid and phenylacetylene as model starting materials, different solvents were screened (Table 1). Reactions in acetonitrile or acetonitrile only led to mixtures with various unknown by-products. Reactions were cleaner in toluene but only 28% of the expected triazole was observed as the starting boronic acid and its corresponding boroxine derivative were the major products in the crude mixture. Satisfyingly, very clean reactions were obtained in a mixture of water/MeOH 1:1. When water or MeOH were used separately the overall conversion drastically dropped due to the presence of intermediate azide and boroxine. It is important to note that if all materials, phenylacetylene included, were added simultaneously, only 15% conversion into the expected triazole was observed under otherwise identical reaction conditions.

Table 1. Solvent screening in the three-component reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ar–B(OH)₂ [%]</th>
<th>Boroxine [%]</th>
<th>Azide [%]</th>
<th>Triazole [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>37%</td>
<td>35%</td>
<td>-</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>MeOH/Water</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>-</td>
<td>18%</td>
<td>27%</td>
<td>54%</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>-</td>
<td>22%</td>
<td>25%</td>
<td>53%</td>
</tr>
</tbody>
</table>

[a] ¹H NMR conversions are the average of at least two independent experiments.

The trimerisation of aryboronic acids to their anhydride trimers (boroxines) is well established in the literature (Scheme 2), [⁹] and it is broadly acknowledged that commercial boronic acids may contain different percentages of the corresponding boroxines. The control of this equilibrium has proven essential in several cases, either because only the boronic acids underwent the desired reaction, [¹⁰] or because the boroxine trimer was more reactive than its monomer. [¹¹] Either way, we did not expect the dehydration of the boronic acid to be problematic as we ran all reactions in air and in technical solvent, or even on water.

Scheme 2. Boronic acid/boroxine equilibrium.

A mild and efficient alternative to thermal dehydration of boronic acids is the use of Lewis bases for the ligand facilitated trimerisation of aryboronic acids. [¹²] Decoordination of the phosphinite ligand would generate a Lewis base in the reaction, however, we found no evidence of such behavior by ¹H or ³¹P NMR. Since only the boronic acid, and not its trimer reacted efficiently under our reaction conditions, we recrystallized and dried the starting boronic acids employed in this study whenever boroxines were observed in the starting boronic acids by ¹H NMR spectroscopy. [¹³]

We next screened different phosphinite and phosphonite complexes in the model reaction (Scheme 3). With most of the catalysts tested, significant amounts of boronic acid and/or boroxine were recovered in the crude products, whereas the intermediate azide, 2a, was only evidenced with catalyst C. In general, phosphinite complexes performed better than the corresponding phosphonite ones, with the exception of complexes A and B. Even if high conversions were obtained with phosphonite complexes B and G, A still outperformed all other complexes in the series.

Scheme 3. Catalyst screening in the three components reaction. ¹H NMR conversions are the average of at least two independent experiments.
When the loading of A was halved, 40% of the starting boronic acid was recovered, but still no azide was observed. This clearly shows that it is the azidonation, and not the cycloaddition step, that requires a higher metal loading. With an optimized catalytic system in hand, we next explored the scope of the reaction (Scheme 4). After hydrolysis and extraction with ethyl acetate, the crude solid products were washed with water, ether and pentane to isolate the expected triazoles analytically pure with no need of further purification. Different aryl boronic acids could be efficiently used in this preparation of triazoles 3, including heteroaromatic ones. On the other hand, both functionalized alkynes as well as simple aliphatic ones were successfully used under these reaction conditions.

Scheme 4. Scope of the three component reaction. Isolated yields are the average of at least two independent experiments. \(^{1}^1^\)H NMR conversion.

Cycloaddition of azides and iodoalkynes: We started screening different phosphinite and phosphonite complexes with benzyl azide and iodoethylbenzene as the model substrates. Reactions were carried out neat at room temperature (Scheme 5). No reactivity trends could be drawn from the obtained results. Average conversions were observed with complexes B and C, whereas complexes with no functionalized ligands gave even poorer results. No reaction was observed in different solvents including MeCN, EtOH, toluene and water, and only 12% conversion in THF.

Several reports in the literature feature the importance of nitrogen additives in this reaction, including our own work with related [CuI(PPh\(_3\)\(_2\))]\(^{10b}\).

Scheme 5. Catalyst screening in the preparation of 5-iodotriazoles. \(^{1}^1^\)H NMR conversions are the average of at least two independent experiments.

No improvement, however, was observed with 5 mol \% of N,N-diisopropylethylamine, 2,6-lutidine, or triethylamine. In the presence of 1,10-phenanthroline the reaction conversion dropped to 25\%. Nevertheless, during the catalyst screening we noticed that complexes B and C remained active over several days\(^{10c}\) and by simply raising the reaction temperature to 40\(^\circ\)C, full conversion into triazoles 6a was obtained overnight with C. By contrast, only 20% conversion into 6a was observed with B, which indicates that this complex is significantly more heat sensitive.

The optimized reaction conditions were next applied to different pairs of azides and iodoalkynes (Scheme 6). In all cases, either high or complete conversions into 5-iodotriazoles were obtained. Interestingly, whereas dehalogenated triazoles were sometimes observed in the reactions with [CuI(PPh\(_3\)\(_3\))]\(^{10e}\) this was never the case with phosphinite catalyst C. This allowed us to use iodoalkynes with \(R' = \) cyclopropyl, dimethylaminomethyl and butyl, which with our previous phosphine system produced inseparable products. In all cases, either full conversion into triazoles 6 could be easily isolated after a simple extraction and washing with pentane. Catalyst C was also efficient with aryl azides, even sterically hindered ones such as mesityl azide (Table 2, entry 3). Another important advantage of this catalytic system is that it shows a wider functional group tolerance. C–C unsaturations, and pyridines did not prevent the reaction from taking place and the respective iodoaromatics could be easily isolated, whereas no reaction whatsoever had previously been observed with the phosphine catalyst (Table 2, entries 4–6). Such an unequivocal change in reactivity is striking and evidence a key role of the phosphinite ligand in the outcome of the reactions.
Scheme 6. Scope of the azido-iodoalkyne cycloaddition. Isolated yields are the average of at least two independent experiments. 1H NMR conversion are shown in brackets for reactions that did not reach completion \(^{[a]}\). Reaction time = 48 h

### Conclusions

The utility of phosphinite–copper(I) complexes in cycloaddition reactions has been explored. In particular, we have developed two competent catalytic systems for the 1,3-dipolar cycloaddition of terminal alkynes with aryl azides generated in situ from the corresponding boronic acids as well as azides and iodoalkynes. These rely on robust air-stable copper complexes which can be handled in air with no particular precautions. Importantly, both the reaction conditions as well as the isolation of the desired product are ‘Click-friendly’.

Phosphinite–copper complex A represents the first homogenous copper(I) complex for the one pot azidonation/cycloaddition of boronic acids and allows the clean formation of the desired 5-H-triazoles with a lower metal loadings than reported heterogeneous alternatives. On the other hand, our results in the synthesis of 5-iodotriazoles clearly show that phosphinite–copper complex C is not a mere analogue of \([\text{Cu}(\text{PPh}_3)_2]\), with somewhat improved reactivity. Even if slightly higher metal loadings (5 instead of 1 mol %) and mild heating are required, the use of a phosphinite ligand has a profound impact on the scope of the catalytic system, both in terms of steric hindrance and functional group tolerance.

Compared to ubiquitous phosphine ligands, phosphinites (or phosphonite) ligands have only been used in a handful of copper-catalyzed transformations\(^{[27]}\). Moreover, to the best of our knowledge, no other pre-formed copper complexes with these ligands have been found application in catalysis to date.

However, the remarkable improvement in reactivity and applicability make of these system attractive candidates for other copper-mediated processes. Efforts in this direction are currently ongoing in our laboratory and will be reported in due course.

### Experimental Section

Catalytic reactions were carried out in air and using technical solvents without any particular precautions to exclude moisture or oxygen. The reported isolated yields for the catalytic studies are an average of two independent reactions.

**CAUTION:** Although we did not experience any problems, the cycloaddition of azides and (iodo)alkynes is highly exothermic and, as a consequence, adequate cooling should always be available when performing these reactions in the absence of solvent.

#### A. Three component reaction (boronic acid, \(\text{NaN}_3\), alkyne):

In a vial fitted with a screw cap, \([\text{CuBr(PPh}_{2}(\text{OPh}-2-\text{OMe}))]\) A (11 mg, 5 mol %), a boronic acid (0.5 mmol), sodium azide (0.5 mmol), water (1.5 mL) and MeOH (1.5 mL) were added and stirred for 18 h. Then, a terminal alkyne
(0.5 mmol) was added and the solution was stirred for 18 h. The precipitate was extracted with ethyl acetate, stirred vigorously in aqueous saturated ammonium chloride solution (10 mL) for 3 h. After separation, the organic layer was concentrated under reduced pressure and the resulting solid residue was washed with water and pentane, then dried under reduced pressure. In all examples, the crude products were estimated to be >95% pure by 1H NMR.

(B). [3+2] Cycloaddition of Azides and Iodoalkynes: In a vial fitted with a screw cap, (OuB(O)(O)-(4-OMe)) C (11 mg, 5 mol %), azide (0.5 mmol) and iodoalkyne (0.5 mmol) were loaded. The reaction was allowed to proceed at 40°C for 18 h. Then, saturated aqueous ammonium chloride solution (10 mL) was added and the resulting mixture was stirred vigorously for 3 h. The resulting precipitate was filtered and washed with water and pentane, then dried under reduced pressure. In all examples, the crude products were estimated to be >95% pure by 1H NMR.

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Keywords: azide • cycloaddition • copper • Click chemistry • P ligands
Copper(I)-phosphinite complexes have been applied to a) the one pot azidonation/cycloaddition from boronic acids, NaN₃ and terminal alkynes; b) the cycloaddition of azides and iodoalkynes. These air-stable catalysts displayed remarkable activities in these challenging reactions and the expected products could be isolated pure under ‘Click-suitable’ conditions.

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