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# A-21 CuI as a catalyst for Huisgen's reaction: about iodination as a side-reaction



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# ABSTRACT

The polymer-supported catalyst Amberlyst A-21·Cul has found many applications in copper(1)-catalyzed Huisgen's (CuAAC) and other reactions. This catalyst was found to be efficient and reusable for the formation of 1,4-disubstituted 1,2,3-triazoles. It was used with success in several usual procedures, as well as in automated and continuous-flow approaches. However, in a few instances, this heterogeneous catalyst gave a few percentages of the 5-iodotriazole derivative, like it was observed under homogeneous conditions. Since the iodination process was scarcely encountered and that we did not, to the best of our knowledge, observed this side-product before, we became interested in studying the possible causes of this side-reaction. The preparation of the catalyst, and to a lesser extent the purity of the reagents, as well as the substrate and the amount of catalyst used were found to be the cause of iodination up to 12% but kept below 0.5% with the right procedure.

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### Introduction

Copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) is the catalyzed version of Huisgen's reaction (Scheme 1).<sup>1,2</sup> Initially conducted under thermal conditions, the reaction was leading to 1,4 and 1,5 isomers of 1,2,3-triazole, usually under harsh conditions. The CuAAC offers the possibility to conduct the reactions at low temperature, in several solvents and even in biological environment, and is giving exclusively the 1,4-isomer. The reaction can be conducted under homo- and heterogeneous conditions, the latter giving the opportunity of a simple work-up and reuse of the catalytic systems.<sup>3</sup>

In 2006, we published the first polymer-supported copper(I) catalyst for the CuAAC reaction. This catalyst was prepared from dry Amberlyst A-21 after incubation with a copper(I) iodide in acetonitrile: Amberlyst A-21·CuI.<sup>4</sup>

This catalyst has proved its efficiency in regular synthetic procedures, even in solvent-free reactions and automated and continuous flow approaches.<sup>5</sup> The catalyst gives exclusively the pure 1,4isomer of substituted 1,2,3-triazole, usually in high yields, after simple filtration/evaporation procedures, and can be recycled a number of times. The scope of the catalyst is large and it has been used in different reaction types and other metals with success.<sup>6</sup> However, in a few instances, a side-reaction was reported in low percentage: namely iodination at the 5-position of the 1,4-isomer of the formed 1,2,3-triazole.<sup>7–10</sup> Since this iodination was observed in a few cases, and that we did not detect it to the best of our knowledge, we became interested in identifying the origins of this side-reaction. We made the hypotheses that the iodination may be due to different reagents and providers, catalyst preparation, substrate, or reaction conditions. We thus decided to study these factors and their influence on the results on model reactions using the publish procedure for CuAAC in methylene chloride. We report herein our findings.

#### **Results and discussion**

The original procedure was giving indications on the treatment of commercial Amberlyst A-21 and its incubation with cuprous iodide for the preparation of the catalyst (Scheme 2). Shortly, wet commercial Amberlyst A-21 (ca. 50% water) was soaked in methanol (3 times) to remove water and then in purified methylene chloride (distilled from  $P_2O_5$ , 3 times) to remove methanol, before being dried under vacuum in a rotary evaporator (50 °C, 10 mm Hg) and finally overnight under vacuum in a desiccator (10 mm Hg, with  $P_2O_5$ ). The dried polymer was incubated in a Cul solution in acetonitrile overnight before being filtrated and rinsed with acetonitrile, methylene chloride, and finally dried under vacuum (40 °C, 0.01 mm Hg) overnight to give Amberlyst A-21 ·Cul.





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**Scheme 1.** Thermal (regular) and copper(I)-catalyzed (CuAAC) Huisgen's reaction leading to substituted 1,2,3-triazoles.

In order to reproduce some possible mistakes in the procedure, due to lack of details in our published procedure, or reagent origin; we decided first to check out the influence of commercial sources of reagents and some obvious details that were not clearly stated. We thus decided to prepare some versions of the catalyst by the variation of misreading and possibly unclear details (Table 1, Fig. 1).

For entries 1-3, the same source of A-21 (Acr) was selected and magnetic agitation was used during the soaking steps instead of swirling occasionally, while the polymer was in the solvents. Untreated methylene chloride was used for soaking in all cases. In entry 2, the first wash was done using acetonitrile instead of methanol, to simulate a misreading. The same was done for the first drying step in entry 1, in which the polymer was pre-dried in air in an oven. In entries 2 and 3, the polymer was pre-dried in a rotary evaporator under vacuum as written in the procedure. For incubation, the same source of CuI (S.-A.) was used, the solution made using analytic grade CH<sub>3</sub>CN, and the incubation was done in a glass round bottom flask overnight and drying in a Büchi oven, both without protection from light. The catalyst obtained in entry 1 was yellow colored beads with a loading of 1.06 mmol CuI·g<sup>-1</sup>. In entries 2 and 3, the catalysts were isolated dark yellow powders with loadings of 1.30 and as 1.20 mmol Cul $\cdot$ g<sup>-1</sup>, respectively.

In entries 4–7, the preparations were conducted under identical conditions. The different A-21 were soaked with manual agitation using purified methylene chloride this time, pre-dried in an evaporator under vacuum, incubated with two different quality of Cul in analytic grade CH<sub>3</sub>CN, and dried in a Büchi oven, without light protection. In entries 4 and 5, the same A-21 (Acr) was used with two different Cul (S.-A.,  $\geq$  99.5% and A.-C., 98%) giving beige beads with respective loadings of 1.43 and 1.41 mmol Cul·g<sup>-1</sup>. In entries 6 and 7, the A-21 was changed (Ald) and treated with the two Cul (S.-A. and A.-C.). The catalysts were isolated as beige beads and similar loadings (entry 6: 1.36 mmol Cul·g<sup>-1</sup>, entry 7: 1.40 mmol Cul·g<sup>-1</sup>).

In entry 8, A-21 (Acr) and CuI (S.-A.) were used and following the same protocol and using the same solvents as entries 4–7.



Scheme 2. Amberlyst A-21 CuI catalyst preparation.

However, the incubation with the CuI solution and drying of the catalyst were made with light protection (aluminum foil) as we proceeded for the catalyst preparation (unwritten but common while working with iodide derivatives). The catalyst was isolated as white beads with a loading of 1.37 mmol CuI·g<sup>-1</sup>. Finally, entries 9 and 10 followed the same procedure with light protection at the end, with the same CuI (S.-A.) and both A-21 (Acr and Ald), but using HPLC grade CH<sub>3</sub>CN, in one case as such (entry 9) and in the other degassed prior to use (entry 10). Catalysts were isolated with a light green and blue color, with loadings of 1.39 and 1.33 mmol CuI·g<sup>-1</sup>, respectively.

In order to test the different catalysts prepared, we selected our usual model reactions and conducted them in purified methylene chloride at room temperature during 18 h, as previously published (Scheme 3).

The results and conditions for the reactions are indicated in Table 2 and the corresponding <sup>1</sup>H NMR spectra depicted in Figure 2. Percentages of the iodination product 5 were evaluated using the methylene of the N-benzyl substituent, respectively at 5.58 for **4**, and 5.72 ppm for **5**. In order to circumvent any artifacts, the products were analyzed as crude mixtures. Broadening in NMR signals (e.g., in the aromatic proton region and for H-5 around 7.7 ppm) is due to copper(I) presence. In some cases, the excess azide is still present (4.4 ppm). In the case of phenylacetylene (2), the use of A-21 Cul number 1–3 (entries 1–3), for which unpurified CH<sub>2</sub>Cl<sub>2</sub> was used, soaking done with magnetic agitation, mistakes made for one wash (CH<sub>3</sub>CN instead of MeOH) and for predrying (in an oven), preparing the catalyst and doing the reaction without light protection; the 5-iodotriazole 5 was present at 9-12%. Residual azide 1 was also isolated with triazoles 4 and 5 (8-15%). Using catalysts number 4-7 (entries 4-7), prepared this time using purified CH<sub>2</sub>Cl<sub>2</sub> with manual agitation during soaking, two different sources of A-21 and CuI, and without light protection for the catalyst preparation and CuAAC; 1-5% of the iodination product 5 was present, without trace of azide 1. For the catalyst 8 (entries 8 and 9), freshly prepared with all the correct details and protecting from light for the catalyst preparation: when the reaction was conducted with or without light protection, less than 0.5% of iodination took place, once again without azide 1 left. Using the same catalyst, but a one-year old sample (entries 10 and 11), the reactions gave higher contents of 5-iodated derivative **5** being or not protected from light (1.8% and 2.4%, respectively).

Changing from analytic grade  $CH_3CN$  to HPLC one (entries 4–7) for the catalyst preparation while protected from light gave low iodination. Using the solvent as such (entries 12 and 13) gave a slightly higher content of iodotriazole **5** when the reaction was conducted in the presence (1.8%) or the absence (1.1%) of light. When the  $CH_3CN$  was degassed prior to use, iodination levels went down, as for the catalyst in entries 8 and 9, giving only 0.8% of **5** in the presence or the absence of light.

The reaction was also conducted on methyl propiolate (**3**) using what we thought to be the catalysts an average chemist would have prepared while reading our procedure: that is, A-21-Cul numbers 4–7, and conducting the reactions without protection from the light (entries 16–19). In these cases, only the 5-protiotriazole **6** was present, the iodo derivative **7** was never observed. However, in these reactions, some residual azide **1** was present with the cycloaddition product (8–13%). This may be an indication that the iodination reaction can be substrate-dependent.<sup>10</sup>

From the results gathered here, for phenylacetylene (**2**), it seems that mistakes made for the catalysts 1-3 (entries 1-3) have quite deleterious effects on the catalyst's performances. The highest ratios of iodination were observed while using them. Changing the source of A-21 (Catalysts 4 and 5 vs 6 and 7, entries 4-7) does not seem to have a great impact on the iodination levels, neither does the purity of the copper(I) iodide used (Catalysts 4 and 6 vs

Table 1	
Preparation of versions of Amberlyst A-21 CuI by variation of different parameters	

Entry	A-21 source <sup>a</sup>	Washes (agitation) <sup>b</sup>	Drying (50 °C) <sup>c</sup>	CuI source <sup>d</sup>	Incubation (light) <sup>e</sup>	Drying (light) <sup>e</sup>	Loading (mmol CuI·g <sup>-1</sup> )	Aspect
1	Acr	MeOH (MAG)	Oven, air, overnight	SA.	CH <sub>3</sub> CN <sup>h</sup>	Büchi	1.06	Yellow beads
		$CH_2Cl_2^{f}(MAG)$			(+hv)	(+hv)		
2	Acr	$CH_3CN$ (MAG)	Evaporator, 10 mm Hg	SA.	CH <sub>3</sub> CN <sup>h</sup>	Büchi	1.30	Yellow powder
		$CH_2Cl_2^{f}(MAG)$			(+hv)	(+hv)		
3	Acr	MeOH (MAG)	Evaporator, 10 mm Hg	SA.	CH₃CN <sup>h</sup>	Büchi	1.20	Yellow powder
		CH <sub>2</sub> Cl <sub>2</sub> <sup>f</sup> (MAG)			(+hv)	(+hv)		
4	Acr	MeOH (MAN)	Evaporator, 10 mm Hg	SA.	CH₃CN <sup>h</sup>	Büchi	1.43	Beige beads
		$CH_2Cl_2^g$ (MAN)			(+hv)	(+hv)		
5	Acr	MeOH (MAN)	Evaporator, 10 mm Hg	AC.	CH₃CN <sup>h</sup>	Büchi	1.41	Beige beads
		$CH_2Cl_2^g$ (MAN)			(+hv)	(+hv)		
6	Ald	MeOH (MAN)	Evaporator, 10 mm Hg	SA.	CH₃CN <sup>h</sup>	Büchi	1.36	Beige beads
		$CH_2Cl_2^g$ (MAN)			(+hv)	(+hv)		
7	Ald	MeOH (MAN)	Evaporator, 10 mm Hg	AC.	CH₃CN <sup>h</sup>	Büchi	1.40	Beige beads
		$CH_2Cl_2^g$ (MAN)			(+hv)	(+hv)		
8	Acr	MeOH (MAN)	Evaporator, 10 mm Hg	SA.	CH₃CN <sup>h</sup>	Büchi	1.37	White beads
		$CH_2Cl_2^g$ (MAN)			(-hv)	(-hv)		
9	Acr	MeOH (MAN)	Evaporator, 10 mm Hg	SA.	CH₃CN <sup>i</sup>	Büchi	1.39	Light green beads
		$CH_2Cl_2^g$ (MAN)			(-hv)	(-hv)		
10	Ald	MeOH (MAN)	Evaporator, 10 mm Hg	SA.	CH <sub>3</sub> CN <sup>j</sup>	Büchi	1.33	Light blue beads
		$CH_2Cl_2^g$ (MAN)	-		(-hv)	(-hv)		

<sup>a</sup> The source of the polymer does not mean that one is of better quality than the other. Both companies gave the same specifications. Acr: Acros Organics, lot A0270131. Ald: Sigma-Aldrich, older sample, lot MS08728JR.

<sup>b</sup> Type of agitation during the washes: MAN: manual, MAG: magnetic.

<sup>c</sup> Before being dried (10 mm Hg) and kept in a desiccator containing P<sub>2</sub>O<sub>5</sub>.

<sup>d</sup> The source of Cul does not mean that one is of better quality than the other, except for the purity analysis. S.-A.: Sigma-Aldrich, Purum  $\geq$  99.5%, lot SZBB211AV. A.-C.: Aldrich-Chemie, old sample, 98%, lot 4011940.

<sup>e</sup> The light indication is relative to protection from light by aluminum foil (-hv) and non protection (+hv) for incubation and drying in vials (40 °C, 0.01 mm Hg, Büchi oven).

<sup>f</sup> Untreated CH<sub>2</sub>Cl<sub>2</sub>.

<sup>g</sup> CH<sub>2</sub>Cl<sub>2</sub> distilled from P<sub>2</sub>O<sub>5</sub>.

<sup>h</sup> Analytic grade acetonitrile, SDS (France), lot 17119901.

<sup>i</sup> HPLC PLUS Gradient grade acetonitrile Carlo-Erba (France), lot D1 M043141M.

<sup>j</sup> HPLC grade acetonitrile, degassed before use.



Figure 1. Amberlyst A-21 CuI catalysts prepared (Table 1).



**Scheme 3.** Model reactions tested with samples of A-21-Cul for quantification of iodination products.

5 and 7). The iodination levels were in the same range, between 1% and 5%, but maybe somehow lower with a better Cul (entries 4 and 5: 1% and 5%, entries 6 and 7: 2% and 3%). The big difference seems

to be due to light protection during the preparation as seen for the catalysts 4 (entry 4) and 8 (entry 8), where the iodination level drops below 0.5% instead of 1–5%. For the catalyst 8 (entries 8 and 9), protection from light during the reaction does not seem important. However, most of our reactions were conducted in the back of a fume hood during the night. Aging of the catalyst (entries 8 and 9 vs 10 and 11), increases the iodination level from <0.5% to around 2%. Absence of light protection and aging of the catalyst seem to be responsible for more iodination, this may be caused by more iodine presence, or another species, that can give the iodo-triazole. Another factor seems to be the type of CH<sub>3</sub>CN used. Changing from analytic grade (entries 8 and 9) to HPLC (entries 12–15) also increased the iodination from <0.5% to 0.8–1.8%. With HPLC grade CH<sub>3</sub>CN, degassing the solvent seems to help a little since the level was only of 0.8% with the degassed one (entries

Entry	A-21 Cul	Alkyne	hv <sup>b</sup>	5-H <sup>c</sup> (%)	5-I <sup>c</sup> (%)	Entry	A-21 Cul	Alkyne	hv <sup>b</sup>	5-H <sup>c</sup> (%)	5-I <sup>c</sup> (%)
1	1	2	+	<b>4</b> (91) <sup>d</sup>	<b>5</b> (9)	10	8 <sup>e</sup>	2	+	4 (97.6)	<b>5</b> (2.4)
2	2	2	+	<b>4</b> (88) <sup>d</sup>	<b>5</b> (12)	11			-	4 (98.2)	5 (1.8)
3	3	2	+	<b>4</b> (88) <sup>d</sup>	<b>5</b> (12)	12	9	2	+	4 (98.2)	<b>5</b> (1.8)
4	4	2	+	4 (99)	<b>5</b> (1)	13			-	4 (98.9)	<b>5</b> (1.1)
5	5	2	+	4 (95)	<b>5</b> (5)	14	10	2	+	4 (99.2)	5 (0.8)
6	6	2	+	4 (98)	<b>5</b> (2)	15			-	4 (99.2)	5 (0.8)
7	7	2	+	4 (97)	<b>5</b> (3)	16	4	3	+	<b>6</b> (100) <sup>d</sup>	7 (0)
8	8	2	+	4 (>99.5)	<b>5</b> (<0.5)	17	5	3	+	<b>6</b> (100) <sup>d</sup>	7 (0)
9			-	<b>4</b> (>99.5)	<b>5</b> (<0.5)	18	6	3	+	<b>6</b> (100)	7 (0)
						19	7	3	+	<b>6</b> (100) <sup>d</sup>	7 (0)

 Table 2

 Reactions of alkynes 2 and 3 with benzyl azide (1) with samples of A-21 Cul and percentage of 5-iodotriazoles<sup>a</sup>

<sup>a</sup> 0.5 mmol alkyne/0.55 mmol azide/2 mL CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Protected from light (-) or not (+).

<sup>c</sup> By NMR <sup>1</sup>H.

<sup>d</sup> Residual azide (8–15%).

<sup>e</sup> One ween old comple

<sup>e</sup> One year old sample.



**Figure 2.** NMR spectra (300 MHz, CDCl<sub>3</sub>) of protonated triazole **4** (top) and iodotriazole **5** (bottom) and intermediate compositions (Table 2).

14 and 15) versus 1.1–1.8 for the normal one (entries 12 and 13). The main difference between analytical and HPLC grade  $CH_3CN$  is that the latter is filtered. This step can increase the content in oxygen of the solvent, and can explain both the light blue to green color of the catalyst due to copper oxidation. For methyl propiolate (**3**), the reaction seems to be insensitive to lower quality catalysts (entries 16–19) and, as previously said, no 5-iodotriazole **7** was observed, but some azide **1** was present.

We then decided to test the hypothesis of iodine presence onto the outcome of the reaction. In order to do so, we prepared catalysts with iodine added during the copper chelation process in CH<sub>3</sub>CN (Table 3, entries 1–4). Introduction of 1.6–10% iodine based on the copper(I) (entries 1 and 2) does not change the results of the reaction, both catalysts, used at 10 mol % here, giving quantitative yield and iodination at a level between 1.0% and 1.2%. However, when 50% iodine was added (entry 3), the yield dropped to 9% with a similar but a little higher 5-iodotriazole (1.5%). The addition of 100% of iodine (entry 4) completely killed the catalyst, the reaction not even taking place. These results seem to indicate that iodine itself plays a little role in the iodination process but maybe not on this form. The fact that the addition of 100% iodine in respect to the copper is giving an inactive catalyst maybe attributed to the total absence of copper(I) into this catalyst. As a matter of fact, the standard electrochemical potentials for copper ( $E^{\circ}$  Cu<sup>2+</sup>/Cu<sup>+</sup> = 0.15 V) and iodine ( $E^{\circ}$  I<sub>2</sub>/I<sup>-</sup> = 0.62 V) indicate that copper(I) will be oxidized into copper(II) by iodine.<sup>11</sup>

Finally, we studied the influence of the amount of catalyst used onto the iodination process. In order to conduct the reaction under good conditions due to the large amount of catalyst to be added. these reactions had to be conducted in more solvent (5 mL instead of 2) and the results are presented in Table 3, entries 5-11. Under these conditions, the use of 10 mol % of A-21 CuI (entry 5) gave 94% yield with 0.9% of iodotriazole 5. By increasing the amount of catalyst to 25 (entry 6) and 50 mol % (entry 7), yields are still good but the iodination reaches 2% (99/1.8% and 97/2.0%, respectively). When increasing again the amount of catalyst to 75% and to the stoichiometry (100%), the yields are maintained (98% and 99%), but the iodination still increases to 2.3% and 2.9% (entries 8 and 9). The use of 150 mol % (entry 10) gave a good yield of 96% but with the presence of 3.3% of 5-iodotriazole 5. The highest incorporation of iodine onto the triazole was reached with the use of 200 mol % of the catalyst (entry 11), with 4.3% of iodotriazole 5 and a yield of 97%. From these results, it seems obvious that increasing the catalyst far beyond the catalytic level, the iodination process can even become complete.<sup>8</sup>

Even if it is difficult to clearly make a link between hetero- and homogeneous catalysis, iodination as a side-reaction was sometimes observed in solution. By reading the literature, it seems that the iodination while using copper(I) iodide is a multi-factor reaction, as for all chemical reactions we should say. It may be influenced by the solvent nature, the concentration of alkyne and/or azide, the temperature, the length of the reaction, the amount of copper(I) iodide, as well as the amount and nature of the base used.<sup>12</sup> To make a story short, increasing the amount of Cul over the catalytic levels and far beyond stoichiometric amounts, with excess of organic base (amine), and the use of solvent such as acetonitrile, tetrahydrofuran, and organo-aqueous mixtures, usually lead to moderate to complete iodination. By selecting carefully all parameters, it is even possible to make the iodination reaction the main one in order to produce 5-iodo-1,2,3-triazoles.<sup>12,13</sup>

The iodination process is itself unclear. The results extracted from the literature seem in favor an ionic mechanism in which 'I<sup>+</sup>', under the form of iodine or other, could be responsible for the iodination of the transient 5-cuprotriazole.<sup>14</sup> The fact that residual amounts of azide, or even the diyne, are present at the end of the reaction can be indicative of an oxido-reductive mechanism initiating the side-reaction (Glaser coupling). Addition of haloreagents such as NBS and NCS in stoichiometric amounts in CuAAC gave good yields of the iodinated triazole.<sup>15</sup> However, in

Entry	A-21 ·CuI (mol %)	Alkyne	l <sub>2</sub> <sup>b</sup> (%)	Yield (%)	5-I <b>5</b> ° (%)	Entry	A-21 ·Cul (mol %)	Alkyne	I2 <sup>b</sup> (%)	Yield (%)	5-I <b>5</b> ° (%)
1 2	10 10	2 2	1.6 10	99 100	1.2 1.0	6 7	25 <sup>d</sup> 50 <sup>d</sup>	2 2	-	99 97	1.8 2.0
3	10	2	50	9	1.5	8	75 <sup>d</sup>	2	-	98	2.3
4 5	10 10 <sup>d</sup>	2 2	100	0 94	0 0.9	9 10	100 <sup>d</sup> 150 <sup>d</sup>	2 2	_	99 96	2.9 3.3
						11	200 <sup>d</sup>	2	-	97	4.3

Reactions of phenylacetylene (2) with benzyl azide (1) with increasing amounts of added iodine and of A-21 Cul and their influence on the yield in triazole 4 and percentage of 5-iodotriazole 5<sup>a</sup>

<sup>a</sup> 0.5 mmol alkyne/0.55 mmol azide/2 mL CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Iodine added during the catalyst preparation in CH<sub>3</sub>CN.

<sup>c</sup> By NMR <sup>1</sup>H.

Table 3

<sup>d</sup> In 5 mL CH<sub>2</sub>Cl<sub>2</sub>.

this study the addition of iodine was deleterious to the catalyst. When working with organocopper reagents, the chemist is aware of the polymeric nature of those reagents that can occur or be disrupted during the reaction. Polymerization degree and species are ruled by ligand exchanges with the reagents, additives, solvents, and dilutions. According to the suggested mechanisms of the CuAAC,<sup>2,16</sup> we thus cannot rule out the possibility of a mechanism of radical or oxido-reductive nature, passing through suggested dicopper species, polymeric or not, or even copper(III) intermediates, that can ultimately lead to the observed products after reductive elimination and insertion of one of the ligand, especially iodine, like in the case of cuprate derivatives.<sup>17</sup>

For the difference observed between phenylacetylene (**2**) and methyl propiolate (**3**), the iodination reaction also seems to be substrate-dependent. When an activating functional group is present on the alkyne, like a carbonyl group (activated alkyne), the iodination does not take place, while when an unactivated alkyne is used, iodination was observed. This behavior was also reported by others while working in solution. The reactivity difference can be attributed to the availability of charge on the different reaction intermediates.<sup>15</sup>

In this study about the preparation of Amberlyst A-21 CuI, the highest iodination levels were attained when the polymer was air-dried, unpurified methylene chloride used, and light protection not in place. In these cases, we think that amine oxidation onto the polymer, impurities in the solvent, and light influence can produce some iodonium reacting onto the cupriotriazole, or species influencing the fate of the copper intermediates, that can explain the higher levels observed. In the cases where the catalyst was correctly prepared, and since the reaction is using a polymer supported catalyst at defined concentrations of all reagents, the very low iodination seems to be inherent to CuAAC in this system on this scale and using this procedure. Using the catalyst over stoichiometric amounts leads to more iodine incorporation in relation to the amount of A-21 CuI, thus to the amount of amine and copper(I) iodide. At last, important things to point out are that by changing the substrate, the concentrations, the solvent, the amount of catalyst, and the reaction temperature, the iodination levels could be different.

When working using the same procedure and using the clear catalyst preparation procedure that we leave to the readers, the levels of iodination can be kept at a minimum level.<sup>18</sup> We hope that this catalyst will still find useful applications in the future.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.079.

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- 18. Preparation of Amberlyst A-21-Cul: Wet commercial Amberlyst A-21 (250 g, ca. 50% water) was soaked in methanol (250 mL) with occasional swirling during 0.5 h. The process was repeated 2 other times after decantation of the resin. After this cycle, the filtrated polymer was soaked in purified methylene chloride (250 mL, distilled over P<sub>2</sub>O<sub>5</sub> after 1 h reflux) for 0.5 h with manual

agitation from time to time. Two other soakings were done the same way before the A-21 was filtrated on a sintered glass funnel. The resin was the transferred in a round-bottom flask and dried on a rotary evaporator (40 °C, 10 mm Hg, with rotation) until free flowing. The polymer was then placed in a desiccator, over P<sub>2</sub>O<sub>5</sub>, and further dried under vacuum (10 mm Hg) for the night. Dry Amberlyst A-21 was obtained as electrostatic amine-smelling beads (ca. 125 g, depending on the amount of water) and was kept in a closed vial in a desiccator (P<sub>2</sub>O<sub>5</sub>). Specifications from the manufacturer indicated 4.8 mmol amine/g of dry polymer.

Dry Amberlyst A-21 (2.0 g, 9.6 mmol amine) was added to a solution of copper(I) iodide (762 mg, 4.00 mmol) in acetonitrile (15 mL) and gently shaken on an orbital stirrer for 17 h with protection from light (aluminum foil). The solvent was drawn off and the resin washed with CH<sub>3</sub>CN (2 × 30 mL), CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 mL) and dried in vacuum (0.01 mm Hg) at 40 °C (with light protection, aluminum foil). The weight increase was of 0.706 g (3.71 mmol Cul), which gave a loading of 1.37 mmol Cul·g<sup>-1</sup>. The catalyst is kept in dark brown bottles (or protected with aluminum foil) inside a closed cupboard protected from moisture and oxygen.