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Cu_2O Spheres as an Efficient Source of Catalytic Cu(I) Species for Performing Azide-Alkyne Click Reactions

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Abstract

We report herein the high yield synthesis of Cu_2O spheres displaying well-defined shapes and monodisperse sizes that could be employed as the source of highly catalytic active Cu(I) species towards click reactions between several of alkynes and azides to produce a variety of 1,2,3-triazoles under ligand-free and ambient conditions (in an open reactor). The utilization of Cu_2O spheres enabled superior performance as compared to a conventional protocol in which $CuSO_4$ is employed in combination with sodium ascorbate as the catalyst system. In addition, the compounds were obtained in synthetically useful yields, and seven of them have not been previously reported. We believe the results reported herein shed new insights into the optimization of activity and versatility of click reactions towards the synthesis of target molecules in environmentally friendly conditions.

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Introduction

The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) corresponds to one of the best clic examples of click reactions. This transformation enables the connection of two molecular fragments in a facile, selective, and high-yield approach under mild conditions, being not sensitive to aqueous conditions, and with little or no by-product formation.[1–4] Therefore, it represents a transformation of great interest in many fields such as organic synthesis,[5,6] pharmaceuticals,[7,8] polymers,[9,10] and chemical biology[11] due to the possibility of generate relatively complex products under mild conditions.

Conventionally, this click reaction is performed using a water soluble catalyst comprised of Cu(I) salts, Cu(I) complexes, or Cu(II) salts combined with a reducing agent such as sodium ascorbate or hydrazine.[6,12–17] However, the low efficiency of conversion of Cu(II) into Cu(I) species associated with the high toxicity of the reducing agents as well as the demand for improved and greener processes has driven the development of several new catalytic systems towards click transformations.[6,18–21]

In this context, the employment of cuprous oxide (Cu_2O) as the source of highly active Cu(I) species for catalyzing CuAAC reactions represents a promising strategy. This can be performed by two general approaches: by adding pre-synthetized Cu_2O based structures as catalysts in the reaction mixture or by synthetizing them *in-situ* before the substrate addition by using Cu(II) salts combined with reducing agents.[13,22–24] The latter approach, albeit is more widely employed, has several drawbacks that include: *i)* limited amounts of produced Cu(I) based species; *ii*) poor control over their physicochemical properties (size and shape) that usually lead to low substrate conversions and poor yields; and *iii)* formation

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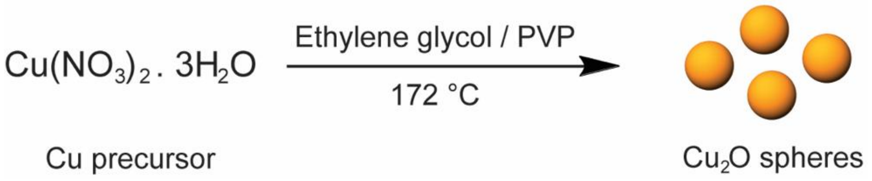
a more complex and toxic reaction mixture, which makes the product purification more troublesome and also decrease environmentally friendliness of the process.[18]

In this paper, we report the high yield synthesis of Cu_2O spheres displaying well-defined shapes and monodisperse sizes by a facile and robust polyol approach. The Cu_2O spheres were then employed as source of highly catalytic active Cu(I) species towards click reactions between a variety of alkynes and azides under ligand-free and mild conditions (in an open reactor). More specifically, the utilization of Cu_2O spheres enabled superior performances as compared to a conventional protocol in which $CuSO_4$ is employed in combination with sodium ascorbate as the catalyst system. In addition, good yields for a variety of click products was achieved, which enabled the synthesis of seven unpublished, novel molecules.

Results and Discussion

Our studies started with the synthesis of Cu_2O spheres by a polyol approach employing $Cu(NO_3)_2{\cdot}3H_2O$ as the precursor, ethylene glycol as the solvent and source of reducing agents, PVP as the stabilizer/reducing agent, and 172 ^{o}C as the reaction temperature (Scheme 1).[25]



Scheme 1. Synthesis of Cu_2O spheres by a polyol approach employing $Cu(NO_3)_2{\cdot}3H_2O$ as the precursor, ethylene glycol as the solvent and source of reducing agents PVP as the stabilizer/reducing agent at 172 ^{o}C.

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As we were interested in the application of Cu_2O spheres as a source of catalytic active Cu(I) species towards click reactions, the development of a synthetic procedure that enabled narrow size distribution in high yields was crucial to achieve reproducible and efficient click protocols, which represents one of the bottlenecks in the field.[26] In fact, SEM images (Figure 1A and B) for the product obtained after only 10 minutes following the addition of $Cu(NO_3)_2\cdot 3H_2O$ to a solution containing ethylene glycol and PVP, revealed the formation of Cu_2O spheres displaying well-defined shapes and monodisperse sizes, having 346 ± 13 nm in diameter (histogram of size distribution is shown in Figure 1C).

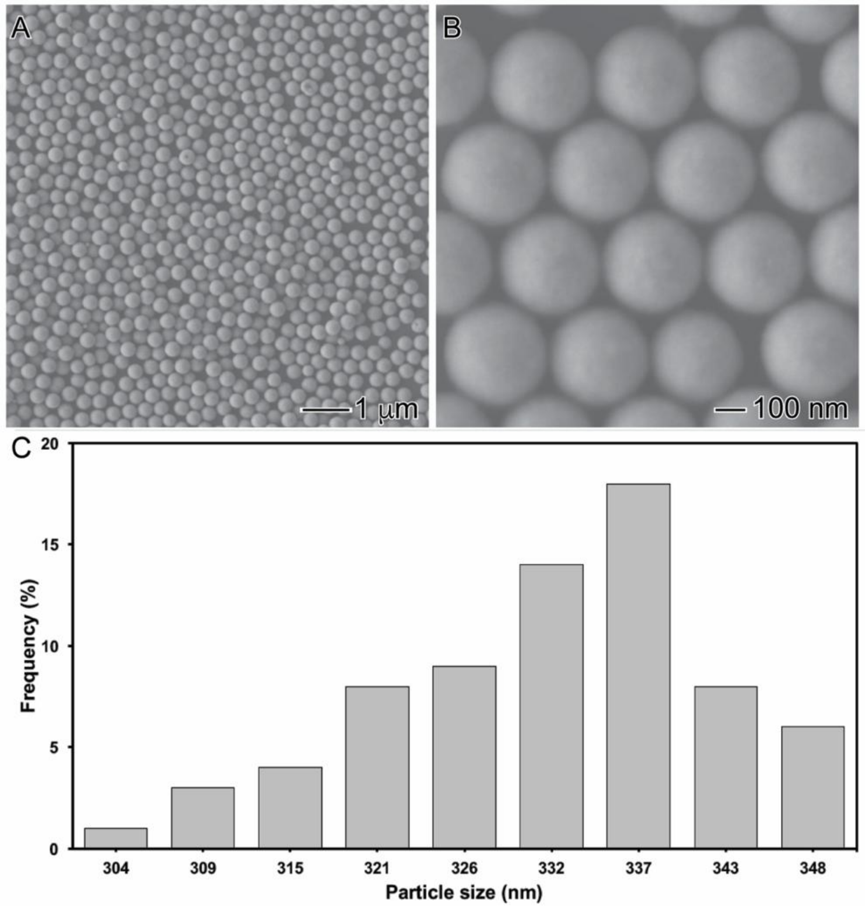

Figure 1. (A-B) SEM images for Cu_2O spheres obtained after only 10 minutes following the addition of $Cu(NO_3)_2.3H_2O$ to a solution containing EG and PVP (C) Histogram showing the particle size distribution for the obtained Cu_2O spheres.

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The formation of Cu_2O spheres was supported by XRD results (Figure 2), in which only the presence of peaks assigned to Cu_2O was detected (cuprite, with lattice constant of 4.26 Å, JCPDS card no. 77-0199) without any crystalline impurities or by-products.[27] The UV-VIS spectrum also supports the formation of Cu_2O (Figure 3). In this case, the UV-vis spectrum for the obtained Cu_2O spheres displayed a broad band centered at ~ 570 nm with a shoulder centered at ~ 650 nm attributed to weak d^{10}-d^{10} interactions in the cuprite structure (*bbc* Cu_2O array), which also explain the origin of the intense yellow color for this material.[28] In addition, the bands centered at ~ 570 and at ~ 650 nm are in agreement with the absorption of Cu_2O structures with particle average size of 300 – 600 nm and their calculated band gap energies corresponded to 2.18 and 1.91 eV, respectively.[29,30] The Cu content from the synthesis, as determined by ICP-OES analyses, corresponded to 0.77 mmol, indicating a yield of 93% for the formation of the spheres under our employed conditions.

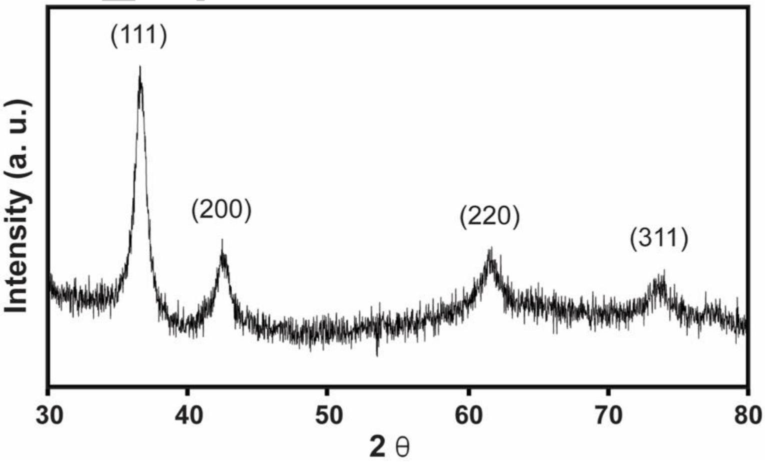

Figure 2. (A) X-ray diffraction pattern recorded from the obtained Cu_2O spheres.

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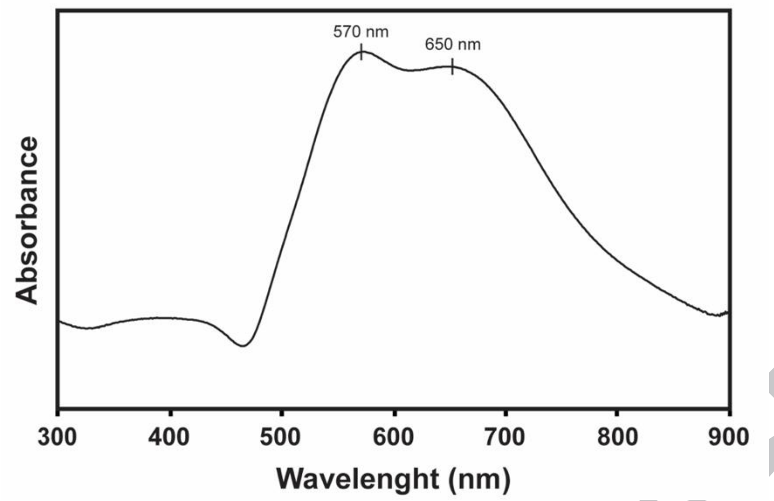

Figure 3. (A) UV–VIS spectra recorded from aqueous suspensions containing the obtained Cu_2O spheres.

After the synthesis of Cu_2O spheres in high yields, having monodisperse sizes, and controlled shapes, we turned our attention to their application as source of highly catalytic active Cu(I) species towards click transformations employing terminal alkynes and benzyl azides as substrates under mild conditions, without additional ligands, and in an open reactor (ambient atmosphere). The alkynes were prepared via standard alkylation procedures of phenols, phtalimide, indan-1,3-dione and cinnamic acid. The synthesis of azides were achieved according previous reports.[31] For the characterization of the compounds, spectroscopic (IR and NMR) and spectrometric (mass spectrometry) techniques were utilized.

Our catalytic investigation started with a control experiment without the utilization of any catalyst (Table 1, entry 1), in which no significant substrate conversion was observed after 10 h of reaction at room temperature, demonstrating the need of Cu(I) species to achieve the target transformation, as demonstrated by previous reports.[1–4] This hypothesis was probed when $CuSO_4$ combined with sodium ascorbate (a traditional catalyst

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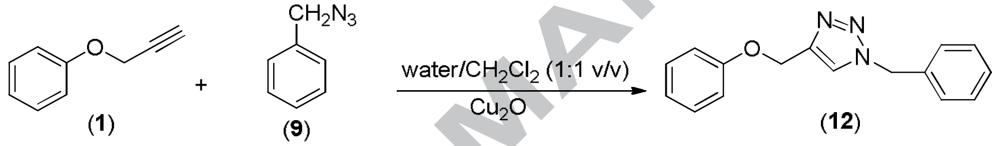
system in click reactions) was added to the system under the same experimental conditions (Table 1, entry 2), in which a yield of (46%) for click product (12) was observed after 10 h at room temperature. However, when Cu_2O spheres were employed as source of Cu(I) species (Table 1, entry 3) a significant increase in yield for the click product was achieved (85%) under the same Cu loading after 10 h, illustrating their superior catalytic activity which can be associated with limited amount of Cu(I) species formed in situ using $CuSO_4$ and sodium ascorbate.

Table 1. Effect of the nature of the catalyst over the click reaction yield [a]



Entry	Source of Cu(I)	Yield (%)[b]
1	-	(-)[c]
2	$CuSO_4$/Sodium ascorbate	46
3	Cu_2O spheres	85

[a] All the reactions were run using 1.0 equivalent of alkyne (1) and 1.2 equivalent of azide (9), 20 mol% of catalyst (Cu basis), at room temperature for 10h.

[b] Isolated yields.

[c] Reaction performed without any catalyst; no product detected.

After demonstrating the superior activity of Cu_2O spheres as catalysts (source of Cu(I) species), we performed a series of experiments in order to optimize the efficiency of

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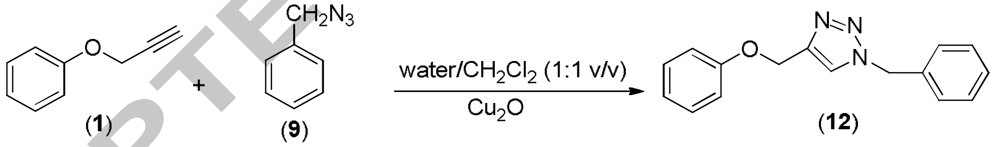
our click process as a function of the temperature (Table 2) using the alkyne 1 and benzylazide 9 as model substrates to afford the triazolic compound 12 as depicted in the first row of Table 2. Herein, when the reaction was performed at room temperature (Table 2, entry 1), a yield of 85 % for compound 12 was obtained after 10 h of reaction. However, when the reaction temperature was increased to 40 ^oC (Table 2, entry 2), almost the same yield (87 %) was achieved after only 2 h of reaction. Finally, at 60 ^oC (Table 2, entry 3), the total conversion of alkyne was observed but a lower yield for the compound 12 (63%) was achieved, indicating a lower selectivity for the click product at this temperature. Thus, 40 ^oC corresponded to lowest temperature in which good yields and maximum selectivity were achieved, and it was chosen as the temperature for our further studies.

Table 2. Optimization of the temperature parameter for the click reaction in the presence of Cu_2O spheres as catalysts[a]



Entry	Temperature	Reaction Time (h)	Yield (%)[b]
1	Room temperature	10	85
2	40 ^oC	2	87
3	60 ^oC	1	63

[a] All the reactions were run using 1.0 equivalent of alkyne (1) and 1.2 equivalent of azide (9), 20 mol% of catalyst (Cu basis, 310 µL of Cu_2O suspension).

[b] Isolated yields.

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Thus, by using the optimized conditions, several alkynes and azides were employed as substrates in the click reactions to afford the corresponding 1,2,3-triazols as shown in Table 3. Herein, we performed several experiments in order evaluate the influence of substrate structures over the click reaction and probe the robustness of our system for the synthesis of 1,2,3-triazols compounds with a large variety of chemical skeleton. Firstly, we employed azides containing electron-donating 10 and electron-withdrawing 11 groups in reactions with alkyne 1 (Table 3, entries 1 and 2, respectively). When the azide contained an electron-donating group (Table 3, entry 1), the triazole product (13) was obtained in 41 % yield after 5 h of reaction. However, when an azide containing an electron-withdrawing group was employed (Table 3, entry 2) a yield of 75 % for the triazole product (14) was observed after 3 h of reaction, indicating a higher reaction rate and selectivity for the click compound in agreement with previous reports.[32,33] Then, we probed the influence of the size of the chain linked to the triazole group over the yield for the respective click product. To this end, we employed as substrates two alkynes derived from eugenol, a natural product found in several aromatic plants and corresponding to the main component of essential oil from cloves. More specifically, we employed alkynes with three (Table 3, entry 3) and five (Table 3, entry 4) carbon atoms in the aliphatic chain. In both cases, high yields were observed after 3 h of reaction. When the eugenol derivative (2) (containing a three carbon atom aliphatic chain) was employed as substrate, 90 % yield for the unpublished, novel click product 15 was observed. On the other hand, the utilization of a substrate with a five carbon aliphatic chain (3) lead to a drop in the yield to 71 % for 16, which is also novel/unpublished. We also performed click reactions employing as substrates alkynes derived from two other natural products, denoted compound 5, which was obtained from

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cinnamic acid, and compound 6, which is derived from vaniline (Table 3, entries 6 and 7). In both cases, the reaction of compounds 5 and 6 with benzyl azide 9 afforded the unpublished click compounds 18 and 19 in synthetically useful yields (61 and 57 %, respectively). This results indicate that the utilization of Cu_2O spheres as source of Cu(I) species under our reported conditions can represent a promising strategy for the synthesis of novel click products derived from natural raw-materials, generating complex molecules with high aggregated-value using natural products as starting material. In order to demonstrate the versatility of our Cu_2O spheres for this target application, satisfactory yields were obtained for a variety of alkynes (4, 7 and 9) as substrates for the reaction with benzilazide 9 (Table 3, entries 5, 8 and 9), which produced three novel, unpublished compounds (17, 20, and 21, respectively).

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Table 3 - Click reactions using different alkynes and azides in the presence of Cu_2O spheres as catalyst[a]

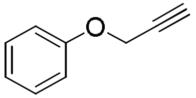
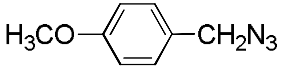
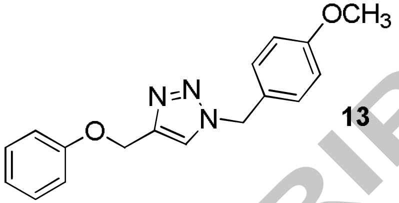
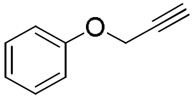
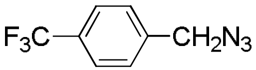
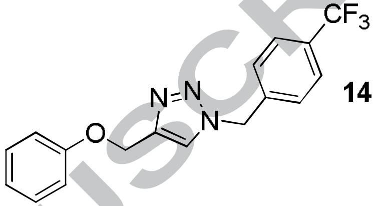
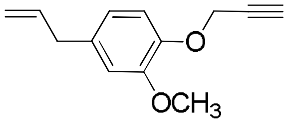
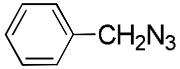
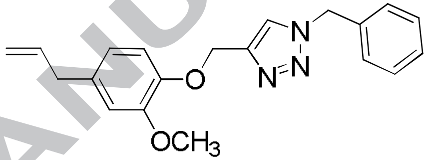
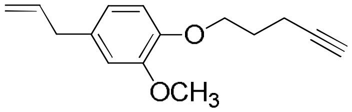
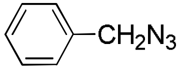
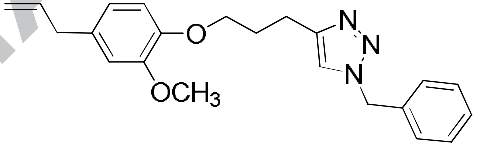
Entry	Alkyne	Azide	Product	Reaction Time (h)	Yield (%)[b]
1	 **1**	 **10**	 **13**	5	41
2	 **1**	 **11**	 **14**	3	75
3	 **2**	 **9**	 **15 (*)**	3	90
4	 **3**	 **9**	 **16 (*)**	3	71

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Table 3 – continued

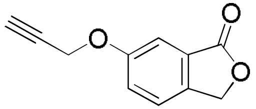
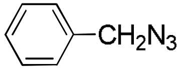
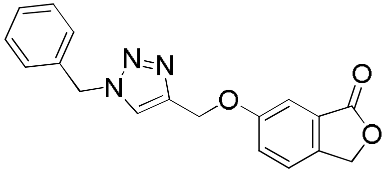
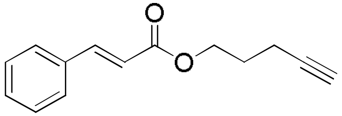
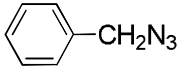
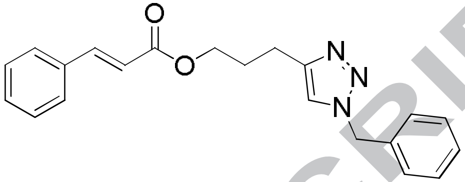
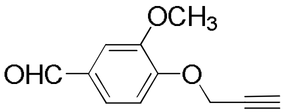
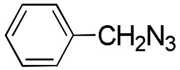
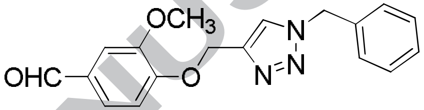
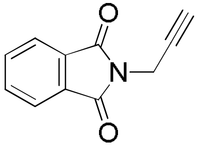
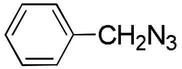
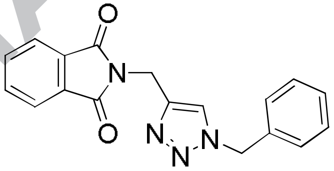
5	 **4**	 **9**	 **17** (*)	2	65
6	 **5**	 **9**	 **18** (*)	2	61
7	 **6**	 **9**	 **19 (*)**	2	57
8	 **7**	 **9**	 **20** (*)	2	76

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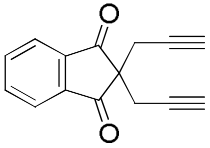
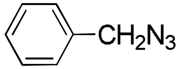
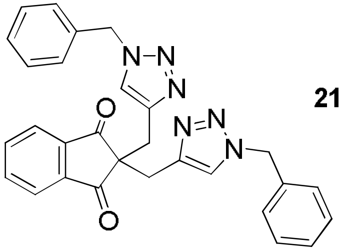
Table 3 – continued

9	 **8** (4)	 **9**	 **21** (*)	17	11

[a] All the reactions were performed using 1.0 equivalent of alkyne (1) and 1.2 equivalent of azide (2), 20 mol% of catalyst (Cu basis, 310 µL of Cu_2O suspension).

[b] Isolated yields.

[*] novel/unpublished molecules

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A general proposed mechanism for the cycloaddition reaction between terminal alkynes and benzyl azides in the presence of Cu_2O spheres as the source of Cu(I) catalytic species is shown in Figure 4.[34] As we employed a suspension containing solid copper(I) species (Cu_2O), it is intuitive that the CuAAC reaction would occur at the particle surface.[35,36] In this context, the proposed reaction mechanism would involve the following steps: *i*) alkyne coordination onto the Cu_2O surface; *ii*) its deprotonation to form the alkynyl-copper(I) intermediate, *iii*) nucleophilic attack from alkynyl-copper(I) intermediate to the azide followed by its coordination onto the Cu_2O surface; (iv) the cycloaddition reaction, (v) protonation of C–Cu bond followed by *iv*) desorption of 1,2,3-triazole product to the reaction medium.

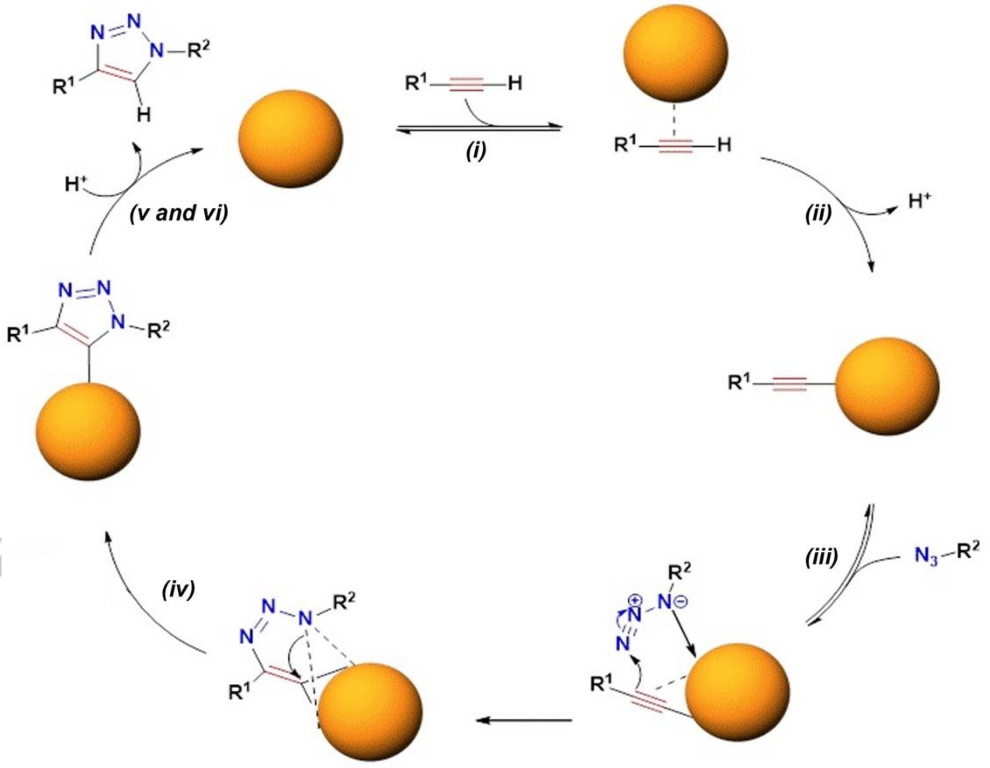

Figure 4. Proposed mechanism for the click reaction in the presence of Cu_2O spheres as catalysts (source of Cu(I) active species).

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Conclusions

We described herein the utilization of monodisperse Cu_2O spheres as an efficient source of Cu(I) catalytic species for the synthesis of 1,2,3-triazoles via the Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction (also known as click reaction) between terminal alkynes and benzyl azides. The Cu_2O spheres were successfully obtained in high yields (93 %) in only 10 minutes by a simple and robust polyol approach using ethyleneglycol as solvent and PVP as stabilizer at 172 ^oC. The utilization of Cu_2O spheres as catalysts (source of Cu(I) species) led superior performance in the click reaction as compared to conventional methods employing $CuSO_4$ and sodium ascorbate as the catalyst system under the same experimental conditions (time, temperature, and Cu loading). Interestingly, using Cu_2O spheres as source of Cu(I) species, satisfactory yields, for a wealth of substrates with different chemical skeletons under mild conditions, ligand-free, and in an open reactor (without inert atmosphere), were obtained demonstrating the promising application of Cu_2O spheres towards click reactions. Moreover, the reported approach enabled the synthesis of seven unpublished/novel molecules including derivate compounds from natural raw-material, showing the applicability of our reported approach for the synthesis of new structures by click chemistry. We believe the results reported herein shed new insights into the optimization of activity and versatility of click reactions towards the synthesis of target molecules in environmentally friendly conditions.

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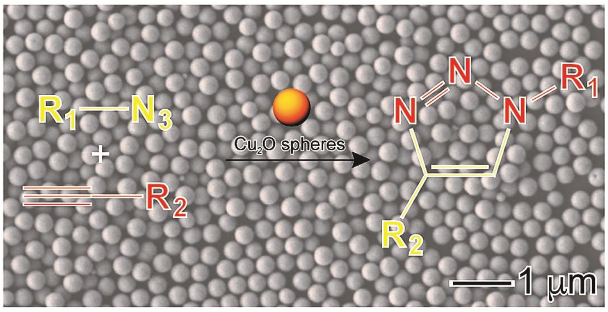
Graphical abstract



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Highlights

- Cu_2O spheres with improved performance towards azide-alkyne click reactions
- High yield synthesis of Cu_2O well-defined spheres displaying monodisperse sizes
- Click reactions under ligand-free and ambient conditions in an open reactor
- Cu_2O spheres enabled superior performance as compared to a conventional protocol
- High yields for click products and seven of them have not been previously reported

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