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Non-Magnetic and Magnetic Supported Copper(I) Chelating Adsorbents as Efficient Heterogeneous Catalysts and Copper Scavengers for Click Chemistry

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Abstract: Novel supported chelating adsorbents bearing diverse multidentate nitrogenated ligands with strong copper(I) affinities are easily prepared in non-magnetic and magnetic variants using silica and silica-coated magnetite nanoparticles as suitable supports and the aza-Michael-type addition of vinyl sulfones as the ligation tool. These adsorbents are versatile materials with applications in the copper-catalyzed alkyne-azide cycloaddition (CuAAC) click chemistry where their complexation abilities enable them to act either as heterogeneous click catalysts when used in their complexed form or as copper(I) scavengers when used in their uncomplexed form. In the first instance, they proved to be robust and efficient heterogeneous catalysts to promote click reactions using extremely low doses and showing negligible copper leaching, particularly in the case of the silica-based non-magnetic adsorbents, allowing a simple operational protocol for their rapid and easy removal by filtration or magnetic decantation and showing good recyclability properties. In their uncomplexed form, the non-magnetic chelating adsorbents are very efficient copper scavengers that are able to remove any traces of metal contamination and that can be applied in tandem with any heterogeneous supported copper(I) catalysts or as standalone copper removing system in any click protocol allowing the isolation of metal-free clicked compounds.

Keywords: chelates; click chemistry; heterogeneous catalysis; magnetic nanoparticles; scavenger

Introduction

The discovery of the catalytic effect of Cu(I) in the 1,3-dipolar cycloaddition reaction of azides with alkynes (CuAAC)[1] was a milestone in the development of the click chemistry concept[2] that has established this process as the most reliable "click" reaction.[3] A prolific research activity in this area during the last decade has led to the development of a plethora of protocols where the use of different Cu(I) sources for homogeneous catalysis constitutes the bulk of the reported applications on many research fields that have benefited from the high reliability of CuAAC reactions. The introduction of new variants to further improve the efficiency of the reaction has determined an outstanding level of development for this ligation methodology. In particular, the use of Cu(I) complexes with nitrogen-based ligands as click catalysts or mediators was revealed[4] shortly after the discovery of the CuAAC coupling[5] and was shown to both enhance the reaction rate and to protect the inherent thermodynamic instability of Cu(I) species from oxidation under aerobic and/or aqueous conditions. In addition, the application of microwave irradiation has demonstrated its utility to increase the reaction rate and to improve yields with a dramatic reduction of reaction times being observed in most protocols.[6]

Despite the pivotal role played by Cu(I) in click cycloaddition reaction of azides and alkynes, the use of this metal is not without drawbacks, especially those related to contamination of clicked products with toxic metal which becomes an issue of utmost importance particularly in bioconjugation and in biomedical and pharmaceutical applications of click chemistry.[7] Nowadays, several approaches have been used to overcome this limitation. In this respect, the development of elegant copper-free click strategies that exploit the ring strain of cyclooctyne reagents is particularly relevant.[8] However, the Cu(I)-catalyzed version is expected to remain one of the most widely applied click reactions due to the straightforward access to clickable building blocks.[9]

The heterogenization of click catalysts constitutes an appealing alternative due to the advantages of easy removal, recovery and reusability that they offer. This heterogenization has been attained by the covalent and non-covalent immobilization of copper species onto a variety of supports such as activated carbon,[10] zeolites,[11] titanium oxide,[12] alumina,[13] aluminium oxyhydroxide fibers,[14] silica,[15] cross-linked poly(ethyleneimine),[16] basic Amberlyst,[17] Tentagel Resin,[18] polystyrene,[15b] ionic polymers,[19] biopolymers[20] and carbon nantotubes.[21] In some of these heterogeneous catalysts, the immobilization of amine-based ligands with a contrasted ability as homogeneous click mediators for the synergetic exploitation of their Cu(I) chelating capabilities and base character has demonstrated to be an efficient approach for the design of such hybrid materials. In particular dimethylaminomethyl,[17] tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA),[18] 3-aminopropyl,[15a] 3-[(2-aminoethyl)amino]propyl,[15a] and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)[15b] have been used as chelating frameworks by their grafting onto a polysterene matrix or silica.

In a related context, magnetic heterogeneous catalysts constitute also an attractive choice. Magnetic nano- and microsized particles[22] have recently emerged as viable and promising supports for immobilization with applications in catalytic transformations as robust, readily available and high-surface-area heterogeneous catalysts. They possess the added advantage of being magnetically recoverable by an external permanent magnet, thereby eliminating the requirement of catalyst filtration after the reaction which circumvents time-consuming and laborious separation steps, and allowing for practical continuous catalysis. Despite the potential inherent stability, the activity of such systems and the attractive operational characteristics that these magnetic materials offer, at the outset of this study only a recent contribution describing the use of copper nitride nanoparticles supported on a mesoporous superparamagnetic silica microspheres as efficient magnetic heterogeneous catalyst in the presence of added tertiary amines had been reported.[23]

Although all the reported heterogeneous click catalysts have proved their high efficiency and practicability, the problem of metal contamination is still a challenge to be overcome due to the leaching of active copper species that is usually detected in these materials. In this respect, the introduction of a subsequent copper-scavenging step has been reported as a feasible improvement in CuAAC reactions performed under continuous flow conditions.[24] Quadrapure™ thiourea resin and activated charcoal (Norite type A) have been successfully applied in this methodology to remove Cu impurities by exploiting the metal scavenging properties of these supports that originate from sulfur complexation and adsorption, respectively. In addition, simple washing with EDTA has also demonstrated its effectiveness due to the strong chelating properties of this complexation agent for Cu species.[24b]

Considering the present state-of-the-art, we hypothesize that further progress in the development of eco-friendly CuAAC protocols where copper contamination is minimized or eliminated is possible by using supported chelating materials with nitrogen-based ligands (**Si-Lm**) with enhanced Cu(I) complex capabilities. These hybrid materials can conceptually be used as dual compounds with the capability to act both as click heterogeneous catalysts when complexed with Cu(I) and also as Cu(I) scavengers when used in their uncomplexed form after a CuAAC reaction (Figure 1). Herein, we report on the preparation of some novel silica-based non-magnetic and magnetic nanoparticles supported Cu(I) chelating adsorbents as well as their application in click chemistry.

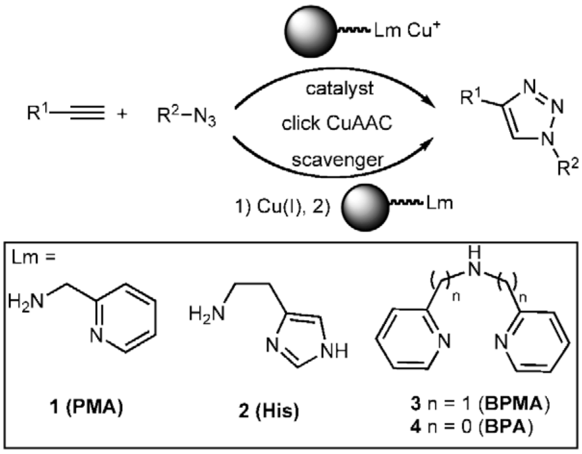
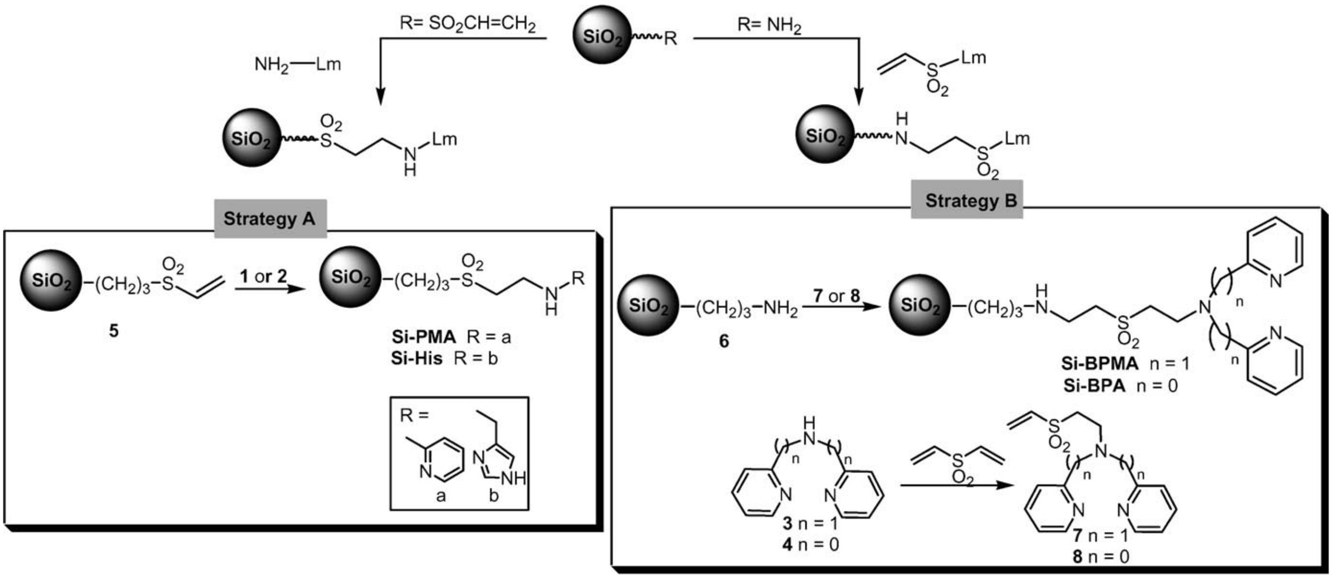


Figure 1. Applications of supported Cu(I) chelating adsorbents in click chemistry.

Results and Discussion

For the preparation of the new supported Cu(I) chelating materials with structural characteristics that facilitate the goal of obtaining copper uncontaminated clicked compounds, we selected two bidentate and two tridentate compounds, namely, 2-pycolylamine (**1**, **PMA**), histamine (**2**, **His**), bispicolylamine (**3**, **BPMA**) and bispyridylamine (**4**, **BPA**) (Figure 1) from the wide range of available nitrogen-based li-



Scheme 1. Strategies for the preparation of **Si-Lm** adsorbents and synthesis of **Si-PMA**, **Si-His**, **Si-BPMA** and **Si-BPA**.

gands on the basis of their well-known high affinities[25] for Cu(I) and Cu(II)and ligand acceleration effect on the kinetics of the CuAAC.[26] In addition, their commercial availability allows a gain in operational simplicity. We further decided to use silica as support for the covalent immobilization of these ligands because of the advantageous properties displayed by this material for the preparation of hybrid materials: excellent chemical and thermal stability, good accessibility due to its high surface area and porosity, and easy derivatization.[27] For anchoring the ligands onto the surface of silica, the aza-Michael-type addition of vinyl sulfones to amines was thought to be an optimal and simple methodology if appropriately functionalized silicas are used. Two plausible strategies are depicted in Scheme 1 starting with vinyl sulfone silica (**5**)[28] and amino functionalized silica (**6**),[29] easily prepared by silanization of activated commercial silica. Reaction of **5** with amino derivatives **1** and **2** afforded the **Si-Lm** adsorbents **Si-PMA** and **Si-His**, respectively, in high yields. Reaction of **6** with vinyl sulfone bipyridyl derivatives **7** and **8**, obtained by reacting divinyl sulfone respectively with **3** and **4**, gave **Si-BPMA** and **Si-BPA** in that order and in good yields.

Considering that the bispicolylamine motif is also present in commercial Dowex M-4195 resin (Figure 2), this polymer-supported chelating adsorbent was also envisaged as a suitable material for our studies. In fact, Dowex M-4195 is a macroporous resin with a polystyrene-divinylbenzene matrix with well-documented chelating capabilities[30] that forms stable complexes with a variety of transition metal cations, including Cu(I) and Cu(II), which has found commercial application for the adsorption of heavy metals.

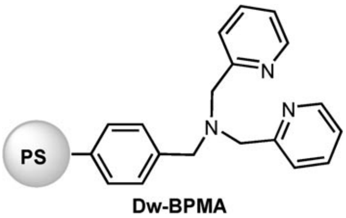


Figure 2. Polymeric Dowex M-4195.

Cu(I) was supported in the silica-based adsorbents **Si-Lm** by simple treatment with a commercial CuCl solution as the metal source in deoxygenated water giving the corresponding **Si-Lm·Cu$^+$** complexes: **Si-PMA·Cu$^+$**, **Si-His·Cu$^+$**, **Si-BPMA·Cu$^+$** and **Si-BPA·Cu$^+$**. In the case of Dowex M-4195 the as-received resin was first conditioned to remove any residual organic and leached materials and then Cu(I) loading was performed by the same treatment as in the case of the silica-based adsorbents giving the corresponding polystyrene-based Cu(I) complex **Dw-BPMA·Cu$^+$**. The metal loadings of the novel Cu(I) supporting materials were evaluated by atomic absorption spectroscopy (AAS) and ranges from 2.4 to 10.4% were found as indicated in the Experimental Section.

To evaluate the catalytic click capabilities of the novel supported Cu(I) materials, a variety of structurally diverse alkynes **9**–**20** and azides **21**–**28** were selected, comprising simple aliphatic and aromatic mono (**9**–**14**, **21**, **22** and **26**) and multi clickable derivatives (**18**–**20**, **27** and **28**) as well as some alkyne and azide functionalized biomolecules such as sugars (**15**, **16** and **23**–**25**) and biotin (**17**) (Figure 3). The reactions were performed under a selection of reaction

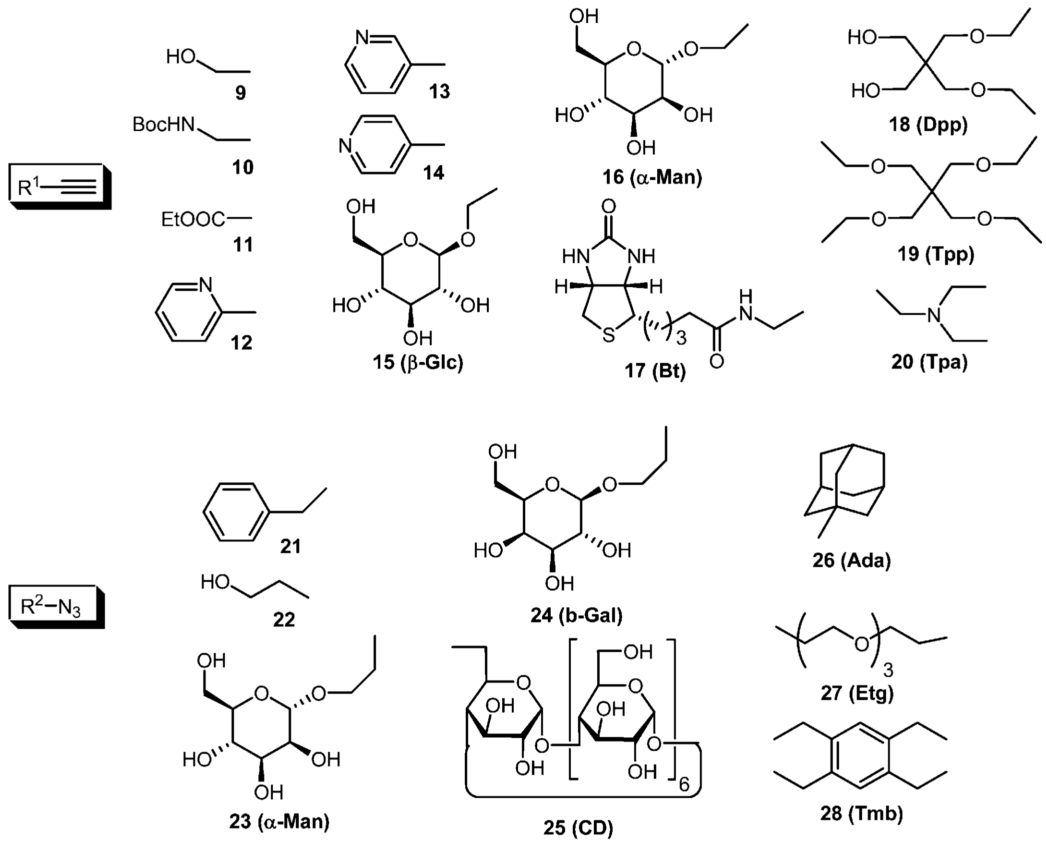
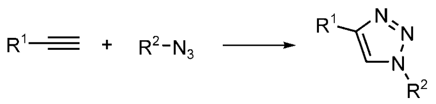


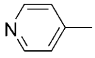
Figure 3. Representative clickable alkynes and azides.

conditions commonly employed in CuAAC, namely, aqueous *t*-BuOH, DMF or water as solvents or by direct mixing of the clickable reagents in the absence of any solvent when this was allowed by the physical characteristics of the reagents. The reactions were performed at room temperature or preferably under microwave (MW) irradiation in order to reduce the reaction time. The results are summarized in Table 1, Table 2 and Table 3.

From these experiments, it can be clearly concluded that all the Cu(I) chelated silicas **Si-Lm·Cu⁺** are very efficient click catalysts since in all cases the 1,4-disubsituted 1,2,3-triazoles were isolated as regiospecific products in excellent yields by using strictly equimo-

Table 1. CuAAC reactions using **Si-PMA·Cu⁺** and **Si-His·Cu⁺** as heterogeneous catalysts.



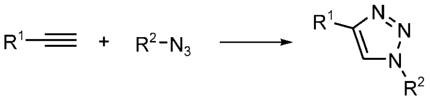
Entry	R¹	R²	Alkyne	Azide	Conditions[a]	Catalyst[b]	Time	Compound[c]
1	CH_2OH	CH_2Ph	**9**	**21**	A	**Si-PMA·Cu⁺** (30)	45 min	**29** (95)
2	CH_2NHBoc	CH_2Ph	**10**	**21**	A	**Si-PMA·Cu⁺** (40)	90 min	**32** (100)
3		CH_2Ph	**14**	**21**	A	**Si-PMA·Cu⁺** (25)	30 min	**40** (85)
4	CH_2OH	CH_2Ph	**9**	**21**	A	**Si-His·Cu⁺** (30)	45 min	**29** (90)
5	COOEt	CH_2CH_2OH	**11**	**22**	A	**Si-His·Cu⁺** (20)	60 min	**36** (94)
6	$N(CH_2)_3$	CH_2Ph	**20**	**21**	B	**Si-His·Cu⁺** (60)	10 min	**50** (87)
7	β-Glc	α-Man	**15**	**23**	C	**Si-His·Cu⁺** (50)	45 min	**42** (100)

[a] *Conditions:* equimolecular amounts of the alkyne (1 mmol) and azide (1 mmol) and **A**: *t*-BuOH:H_2O (10:1, 10 mL), MW; **B**: *t*-BuOH:H_2O (10:1, 0,6 mL), MW; **C**: H_2O (10 mL), MW.

[b] Given as mg catalyst/mmol reagent.

[c] Compound (yield [%]).

Table 2. CuAAC reactions using **Si-BPMA·Cu**$^+$ and **Dw-BPMA·Cu**$^+$ as heterogeneous catalysts.



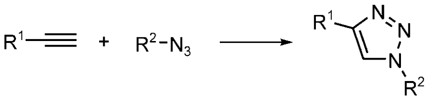
Entry	R^1	R^2	Alkyne	Azide	Conditions[a]	Catalyst[b]	Time	Compound[c]
1	CH_2OH	CH_2Ph	**9**	**21**	A	**Si-BPMA·Cu**$^+$ (10)	3 h	**29** (96)
2	CH_2OH	CH_2Ph	**9**	**21**	B	**Si-BPMA·Cu**$^+$ (20)	20 min	**29** (96)
3	CH_2NHBoc	CH_2Ph	**10**	**21**	B	**Si-BPMA·Cu**$^+$ (20)	40 min	**32** (92)
4	CH_2OH	β-Gal	**9**	**24**	B	**Si-BPMA·Cu**$^+$ (70)	30 min	**31** (99)
5	β-Glc	α-Man	**15**	**23**	C	**Si-BPMA·Cu**$^+$ (150)	90 min	**42** (100)
6	α-Man	Tmb	**16**	**28**	D	**Si-BPMA·Cu**$^+$ (150)	15 min	**45** (90)
7	Bt	Etg	**17**	**27**	D	**Si-BPMA·Cu**$^+$ (150)	15 min	**46** (89)
8	CH_2OH	CH_2Ph	**9**	**21**	A	**Dw-BPMA·Cu**$^+$ (20)	24 h	**29** (80)
9	CH_2OH	CH_2Ph	**9**	**21**	B	**Dw-BPMA·Cu**$^+$ (50)	40 min	**29** (56)
10	CH_2NHBoc	CH_2Ph	**10**	**21**	B	**Dw-BPMA·Cu**$^+$ (50)	40 min	**32** (70)

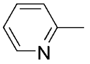
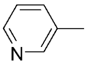
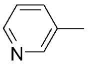
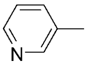
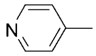
[a] *Conditions:* equimolecular amounts of the alkyne (1 mmol) and azide (1 mmol) and **A**: neat, room temperature; **B**: *t*-BuOH:H_2O (10:1, 10 mL), MW; **C**: H_2O (10 mL), MW; **D**: DMF (10 mL), MW.

[b] Given as mg catalyst/mmol reagent.

[c] Compound (yield [%]).

Table 3. CuAAC reactions using **Si-BPA·Cu**$^+$ as heterogeneous catalyst.



Entry	R^1	R^2	Alkyne	Azide	Conditions[a]	Catalyst[b]	Time	Compound[c]
1	CH_2OH	CH_2Ph	**9**	**21**	A	30	24 h	**29** (88)
2	CH_2OH	CH_2Ph	**9**	**21**	B	30	1 h	**29** (88)
3	CH_2OH	CH_2Ph	**9**	**21**	C	20	15 min	**29** (87)
4	CH_2OH	β-Gal	**9**	**24**	B	70	1 h	**31** (99)
5	COOEt	CH_2CH_2OH	**11**	**22**	B	20	1 h	**36** (100)
6	CH_2NHBoc	CH_2Ph	**10**	**21**	B	55	1 h	**32** (100)
7	CH_2NHBoc	CH_2CH_2OH	**10**	**22**	B	55	1,5 h	**33** (100)
8	CH_2NHBoc	β-Gal	**10**	**24**	D	20	10 min	**34** (98)
9	CH_2NHBoc	Ada	**10**	**26**	E	20	30 min	**35** (100)
10	 N	CH_2Ph	**12**	**21**	B	50	1 h	**37** (100)
11	 N	CH_2CH_2OH	**13**	**22**	B	50	1,5 h	**39** (89)
12	 N	CH_2Ph	**13**	**21**	B	40	1 h	**38**(83)
13	 N	CH_2Ph	**13**	**21**	C	5	15 min	**38** (91)
14	 N	CH_2Ph	**14**	**21**	C	10	15 min	**40** (97)
15	β-Glc	CH_2CH_2OH	**15**	**22**	B	100	2 h	**41** (100)
16	β-Glc	β-Gal	**15**	**24**	F	150	1 h	**43** (85)
17	$C(CH_2O)_4$	α-Man	**19**	**23**	G	30	30 min	**49** (85)

[a] *Conditions:* equimolecular amounts of the alkyne (1 mmol) and azide (1 mmol) and **A**: *t*.BuOH:H_2O (10:1, 10 mL), room temperature; **B**: *t*-BuOH:H_2O (10:1, 10 mL), MW; **C**: neat, MW; **D**: *t*-BuOH:H_2O (10:1, 1.90 mL), MW; **E**: *t*-BuOH:H_2O (10:1, 0.6 mL), MW; **F**: H_2O, MW; **G**: DMF, MW.

[b] Given as mg catalyst/mmol reagent.

[c] Compound (yield [%]).

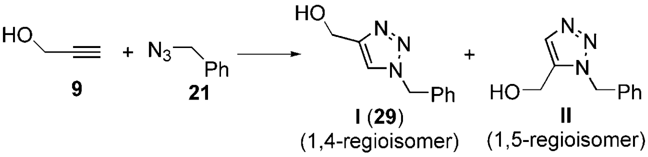
lecular amounts of the clickable reagents without the use of any additives such as reducing agents or nitrogenated bases. The catalytic ability was independent of the chemical nature of the chelating ligand, as all the Cu(I) supported silicas have a similar behaviour and gave similar results when the reactions were performed using the same reagents and reaction conditions. This is clearly illustrated in the coupling of the model propargyl alcohol (**9**) and benzyl azide (**21**), where the corresponding 1,2,3-triazole **29** was obtained in yields ranging from 88 to 96% when the reactions were carried out in aqueous *t*-BuOH under MW irradiation (see Table 1, entries 1 and 4, Table 2, entry 2 and Table 3, entry 2).

The catalytic efficiency of the **Si-Lm·Cu$^+$** materials was the same in all tested solvents. Particularly relevant is the fact that the click reactions can be efficiently performed under aerobic conditions using water as solvent when the reagents are hydrosoluble. Moreover, the use of these catalytic systems allows a considerably solvent economy, as exemplified in the case of catalyst **Si-His·Cu$^+$** (Table 1, entry 6) and **Si-BPA·Cu$^+$** (Table 3, entries 8 and 9). The reactions can even be executed in the absence of a solvent either at room temperature or under MW irradiation when the reagents can be mixed together homogenously (Table 2, entry 1, Table 3 entries 3, 13 and 14). Although these silica-based CuAAC reactions can be carried out at room temperature, as expected MW assistance reduces considerably the reaction times required.

An additional advantage offered by the use of these hybrid materials as catalysts is the simplicity of the operational procedure since in all cases the triazoles are obtained by direct filtration and evaporation of the solvent without the need of further chromatographic purification. This permits the easy recovery of the catalysts facilitating their reuse. In fact, the recyclability of the silica-based catalyst was tested for the model reaction of alkyne **9** and azide **21** catalyzed by **Si-BPMA·Cu$^+$** (see Experimental Section). This heterogeneous catalyst could be reused at least four times in new cycloaddition experiments without any critical loss of activity or yield (97%, 96%, 97% and 94% for the successive runs).

Further experiments also corroborated the robustness of the silica-supported Cu(I) adsorbents as click catalysts. Thus, they exhibited an excellent efficiency when sterically demanding clickable substrates were used as denoted by the quantitative yield obtained in the reaction of the alkyne **10** with the azide adamantane derivative **26** (Table 3, entry 9). Moreover, the preparation of multivalent structures by the concomitant formation of multiple 1,2,3-triazole rings was easily attained by the reaction of clickable derivatives bearing multiple copies of either the alkyne or the azide function as illustrated by the reactions performed with compounds **19**, **20**, **27** and **28** (Table 1, entry 6; Table 2, entries 6 and 7; Table 3, entry 17). On the other hand, a series of experiments were also carried out to study the minimum loadings required to maintain the catalytic activity of our supported systems (Table 4). In this regard, progressively reduced amounts of catalyst were used in the model click reaction between alkyne **9** and azide **21** either in solution or under neat conditions. The results obtained showed that catalysis occurs with doses as low as 2.5 and 1.0 mg of **Si-BPA·Cu$^+$** and **Si-His·Cu$^+$** per mmol of reagent, respectively, (entries 4 and 6) when the reactions were performed in solution. These minimal loadings should be slightly higher when the reactions were performed under neat conditions either at room temperature or with MW irradiation (entries 7, 12 and 13). Below this minimal dose, either no reaction (entry 5) or formation of the thermal 1,5-regioisomer is observed (entries 8–10). Finally, it should be noted that the **Si-Lm·Cu$^+$** catalysts are air-stable compounds since their catalytic activity remains intact after long-term air exposure on storage.

Table 4. Optimization of the **Si-Lm·Cu$^+$** catalyst loadings.



Entry	Conditions[a]	Catalyst[b]	mol% Cu	I:II[c]
1	A	**Si-BPA·Cu$^+$**(30)	1.53	1:0 (96)
2	A	**Si-BPA·Cu$^+$**(10)	0.51	1:0 (92)
3	A	**Si-BPA·Cu$^+$**(5)	0.25	1:0 (99)
4	A	**Si-BPA·Cu$^+$**(2.5)	0.13	1:0 (97)
5	A	**Si-BPA·Cu$^+$**(1.0)	0.05	n.r.
6	A	**Si-His·Cu$^+$**(1.0)	0.16	1:0 (93)
7	B	**Si-BPA·Cu$^+$**(20)	1.02	1:0 (87)
8	B	**Si-BPA·Cu$^+$**(10)	0.51	6.8:1 (86)
9	B	**Si-His·Cu$^+$**(10)	1.64	4:1 (89)
10	B	**Si-BPA·Cu$^+$**(5)	0.25	2.5:1 (94)
11	B	none	–	1.3:1 (83)
12	C	**Si-BPA·Cu$^+$**(10)	0.51	1:0 (97)
13	C	**Si-His·Cu$^+$**(5)	0.82	1:0 (85)
14	C	none	–	n.r.

[a] *Conditions:* equimolecular amounts of the alkyne and azide and **A**: *t*-BuOH:H_2O (10:1), MW, 80 min, 60 °C; **B**: neat, MW, 15 min, 60 °C; **C**: neat, room temperature, 3 h.

[b] mg catalyst/mmol reagent.

[c] (Yield [%]).

Once the feasibility of the silica-based supported Cu(I) adsorbents as click catalysts was clearly established, the capabilities of the polystyrene-supported **Dw-BPMA·Cu$^+$** were next investigated in order to determine possible benefits in the use of this hybrid material. This copper-containing matrix was assayed

Table 5. Leaching values of CuAAC reactions catalyzed by supported Cu(I) chelating adsorbents.

Entry	Alkyne	Azide	Conditions[a]	Catalyst[b]	Leaching ppm Cu in product	Leaching % Cu released from initial Cu	Table.Entry
1	**9**	**21**	A	**Si-BPMA** (10)	36	1.9	2.1
2	**9**	**21**	B	**Si-BPMA** (20)	17	0.4	2.2
3	**15**	**24**	C	**Si-BPA** (150)	62	0.5	3.16
4	**9**	**21**	A	**Dw-BPMA** (20)	1500	15	2.8
5	**10**	**21**	B	**Dw-BPMA** (50)	3200	18	2.10
6	**9**	**22**	C	**Fe_3O_4@Si-BPA·Cu** (10)	690	7.4	7.1
7	**15**	**22**	C	**Fe_3O_4@Si-BPA·Cu** (10)	260	8.9	7.4

[a] *Conditions:* equimolecular amounts of the alkyne (1 mmol) and azide (1 mmol) and **A**: neat, room temperature; **B**: *t*-BuOH:H_2O (10:1, 10 mL), MW; **C**: H_2O (10 mL), MW.

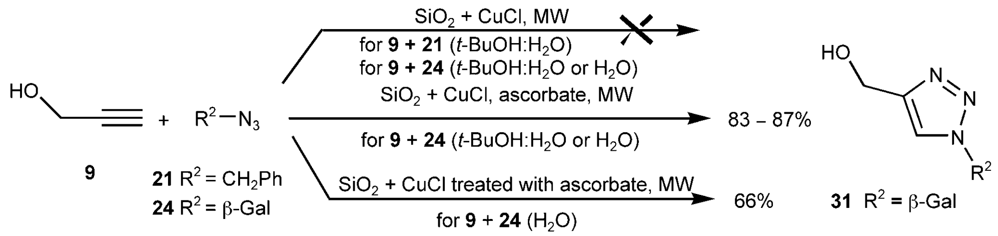
[b] mg catalyst/mmol reagent.

to click the model alkynes **9** and **10** with benzyl azide **21** where it was demonstrated to have a click catalytic profile either in solution or under neat conditions (Table 2, entries 8–10). A comparison of the reaction outcomes (yield and time) of these assays with those of similar experiments using the homologous **Si-BPMA·Cu$^+$** catalyst containing the same BPMA chelating agent (Table 2, entries 1–3) reveals a lower performance of the polymer-based catalyst since decreased yields are obtained with increased reaction times and higher catalyst loadings.

Moreover, coloured green reaction crudes are obtained in spite of the conditioning protocol to which the commercial resin was subjected prior to the Cu(I) immobilization, and chromatographic purification was needed to obtain clear clicked compounds. This different behaviour of both catalytic systems can be tentatively ascribed to the higher particle size for **Dw-BPMA·Cu$^+$** with respect to **Si-BPMA·Cu$^+$** that determines a lower surface for the former heterogeneous catalyst. From these results, it can be stated that the use of silica-based adsorbents is more advantageous for click catalysis purposes.

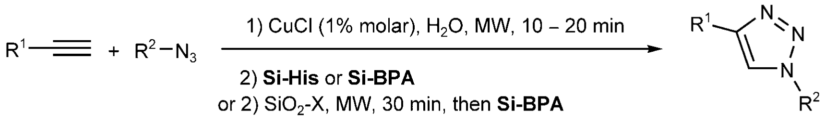
In the next phase, the leaching of active copper species from the catalysts to the reaction media was evaluated as this is a key issue in our CuAAC study in the search of protocols that allow the isolation of copper-free clicked compounds (Table 5). The leaching from the silica-based **Si-Lm·Cu$^+$** catalysts showed to be negligible when quantified directly in the reaction crudes. Thus, in the reactions of **9** with **21** and of **15** with **24** the levels of residual copper detected by AAS were very low ranging between 0.4% and 1.9% of the initial amount of copper present in the catalysts employed (Table 5, entries 1–3). However, in the case of the reactions catalyzed by the polystyrene-based **Dw-BPMA·Cu$^+$** catalyst the leaching values and contamination of the clicked compounds are surprisingly higher (Table 5, entries 4 and 5). The residual presence of copper in the reaction media in the case of the silica-based catalyst is in accordance with our expectations based on the strong copper affinity of the chelating ligands incorporated to the adsorbents when they were conceptually designed allowing not only for the stabilization of Cu(I) but also for the readsorption of the migrated metal onto the support after the catalytic cycle is complete. The better performance of the **Si-Lm·Cu$^+$** catalysts over the **Dw-BPMA·Cu$^+$** counterpart on that concerning the leaching of the supported metal is also indicative of an active role for the silica matrix in the adsorption of the copper species which is in agreement with previous observations reported in the literature.[31]

At this point, a series of assays were designed to prove that the catalytic activity of the supported Cu(I) chelating adsorbents **Si-Lm·Cu$^+$** is associated to the stabilization of Cu(I) attained by its heterogenization through complexation with the nitrogenated li-



Scheme 2. Assays to probe the influence of the Cu(I) stabilization by **Si-Lm** adsorbents in their catalytic activity.

Table 6. Use of **Si-Lm** adsorbents as stand-alone scavenger or in combination with alkyne and azide scavengers.

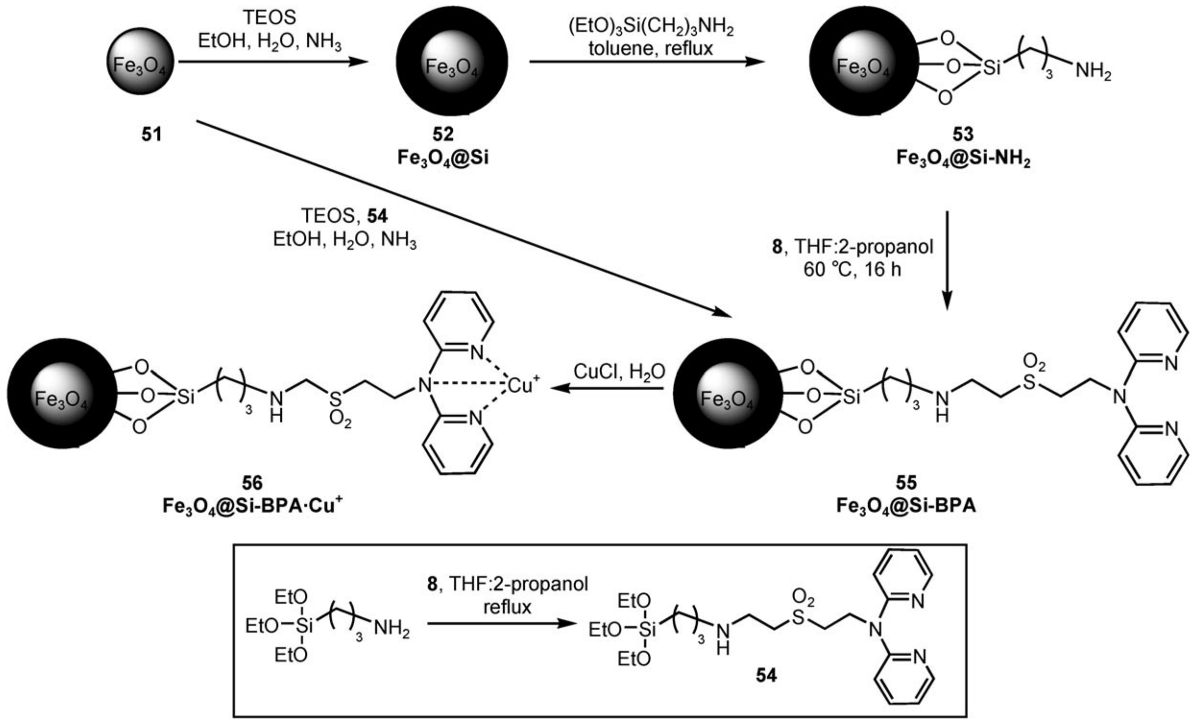


Entry	R^1	R^2	Alkyne	Azide	Alkyne/Azide	SiO$_2$–X	Compound (yield [%])
1	CH_2OH	CH_2CH_2OH	**9**	**22**	1.0/1.0	–	**30** (86)
2	β-Glc	CH_2CH_2OH	**15**	**22**	1.0/1.0	–	**41** (100)
3	Dpp	CH_2CH_2OH	**18**	**22**	1.0/2.0	–	**47** (100)
4	Dpp	α-Man	**18**	**23**	1.0/2.4	SiO_2–C≡CH	**48** (99)
5	β-Glc	CD	**15**	**25**	2.0/1.0	SiO_2–N_3	**44** (100)

gands **Lm** (Scheme 2 and Supporting Information). First, activated silica previously treated with a CuCl solution was added to a mixture of the alkyne **9** with the azides **21** or **24** as indicated in Scheme 2. In these cases, no cycloaddition products were observed in the assayed solvents (*t*-BuOH-H_2O or H_2O). These results suggest a complete oxidation of the Cu(I) to Cu(II) during copper adsorption over the activated silica or under the reaction conditions used for the attempted click reactions. To verify this point, ascorbate was simultaneously added to the activated silica treated with CuCl to act as a reducing agent in the reaction of **9** and **24**. The clicked 1,2,3-triazole **31** was obtained in this way in the MW assisted reaction with an acceptable outcome in relation to that obtained in the case of **Si-BPMA·Cu$^+$** although the leaching levels are higher in this case (28% of the initial amount of copper). Finally, the activated silica containing adsorbed copper was first treated with ascorbate and, after filtration, was directly used in the reaction of **9** with **24** to afford triazole **31** in a reduced yield after a longer reaction time. Overall, these results clearly indicated the catalytic benefits obtained by immobilizing Cu(I) on supported chelating adsorbents that prevents its oxidation to Cu(II).

The excellent complexation attributes of the ligand incorporated to the supported chelating adsorbents also point to the potential of their uncomplexed form to act as copper scavengers. The inherent scavenging capabilities of both **Si-Lm** and **Dw-BPMA** were initially verified by treating a commercial CuCl solution with these materials where we observed a complete removal of the metal present by **Si-BPA** and **Si-His** adsorbents and an almost quantitative elimination by **Dw-BPMA** (see Supporting Information, Table 1S). To demonstrate the scavenging abilities in click reactions, the **Si-Lm** adsorbents were first used in tandem with their complexed forms **Si-Lm·Cu$^+$**. The crudes obtained after filtration in the reactions of **9** with **21** and of **15** with **24** when catalyzed respectively by **Si-BPMA·Cu$^+$** and **Si-BPA·Cu$^+$** (Table 2, entry 2, and Table 3, entry 16) were simply mixed with the uncomplexed form of the catalyst, **Si-BPMA** and **Si-BPA.** Complete removal of the already insignificant metal traces was evident after a new filtration. In this way, the isolation of uncontaminated materials was attained in a facile manner (see Experimental Section).

To explore the scope of the **Si-Lm** supported copper chelating adsorbents as scavengers in CuAAC reactions and further expand their utility as stand-alone copper removing systems, additional assays were carried out (Table 6). First, the scavenging abilities were tested in click reactions performed using a homogeneous click catalyst. Thus, stoichiometric amounts of the alkynes **9**, **15** and **18** with azide **22** were reacted using CuCl[32] as a source of Cu(I) (Table 6, entries 1–3). After the reaction was completed, the scavenging treatment of the crudes with **Si-BPA** or **Si-His** gave the clicked derivatives **30**, **41** and **47**, respectively, free of any detectable copper contamination. It should be also mentioned that a similar scavenger performance was observed for **Dw-BPMA** in the reaction of **15** with **22** (see Supporting Information, Table 2S). Secondly, bearing in mind that Cu-catalyzed triazole formations are in many cases accomplished using an excess of one of the clickable reagents, particularly, a surplus of the azido building block to avoid C–C coupling reactions of two alkyne moieties, and also the plausible implementation of the **Si-Lm** adsorbents in click reactions under continuous flow conditions,[24] the dialkynyl derivative **18** and the monoazide derivative of β-cyclodextrin **25** were reacted with an excess of the complementary α-Man azide (**23**) and the β-Glc alkynyl (**15**) derivatives, respectively, using CuCl as catalyst (Table 6, entries 4 and 5). The extra amounts of the unreacted clickable reagents were first removed by using alkyne or azido functionalized silicas[33] as "click chemistry scavengers" followed by subsequent treatment with **Si-BPA** to eliminate copper species. The use of comparable polystyrene-based functionalized alkyne and azide resins as azide and alkyne scavengers has been previously reported in the literature.[34] Excellent results were obtained as pure uncontaminated triazoles **48** and **44** were respectively obtained in almost quantitative yields in a expeditious manner due to the simulta-



Scheme 3. Preparation of magnetic nanoparticles-supported Cu(I) **Fe_3O_4@Si-BPA·Cu$^+$**.

neous use of MW irradiation that not only assists the click reaction but also speeds up the scavenging process of the clickable reagents. In addition, chromatographic purification is not necessary in this protocol.

Having established the feasibility of the silica-supported copper chelating adsorbents in their complexed and uncomplexed forms as both efficient and robust heterogeneous click catalysts and Cu(I) scavengers, we decided to extrapolate these satisfactory results to the preparation of a magnetic version of those adsorbents for the synergetic exploitation of the inherent properties offered by magnetic heterogeneous catalysts (magnetic recovery and recyclability) with the enhanced Cu(I) complex capabilities of the chelating ligands.

From the various magnetic materials available, magnetite (Fe_3O_4) is one of the iron oxides most commonly used for the preparation of magnetic nanoparticles. For these particles, increasing attention has been paid to develop protection strategies that ensure their chemical stability against agglomeration or precipitation as well as oxidation in air. In particular, coating Fe_3O_4 with a thin layer of silica is an attractive alternative with additional advantages such as the stability under aqueous conditions, the easy surface modification and the facile control of interparticle interactions of the resulting core-shell structures. Taken into account these facts, silica-based magnetite composites were thought to be ideal candidates for the preparation of magnetic supported-Cu(I) catalysts **Fe_3O_4@Si-Lm·Cu$^+$** through the immobilization on their surface of chelating ligands Lm that in the present study we restricted to the bispyridylamine ligand (**4**, **BPA**).

To attain the covalent linkage of **BPA** onto the surface of magnetite nanoparticles, the two main strategies commonly used to incorporate functionalies onto the surface of silica nanoparticles were envisaged: a) post-synthesis functionalization (*grafting*) and direct synthesis (*co-condensation*) (Scheme 3). For both strategies monodisperse ferrite nanoparticles (**51**) were first easily prepared using a variation of the solvothermal reduction methodology reported by Li et al.[35] which constitutes a simple, general and inexpensive one-step procedure for the preparation of such materials.

For the grafting strategy, the magnetic ferrite nanoparticles **51** were initially coated with a silica shell using tetraethyloxysilane (TEOS) according to a standard sol-gel literature method[36] and the resulting core/shell **Fe_3O_4@Si** particles (**52**) were next treated with excess of aminopropyltriethoxysilane (APTS) as the surface modification reagent in refluxing toluene to yield the amino functionalized particles **Fe_3O_4@Si-NH_2** (**53**). In fact, amino groups are one of the most widely used functional groups on magnetic nanoparticles to allow further modifications.[37] In our case, the immobilization of the copper chelating ligand **BPA** was attained by means of the aza-Michael-type addition of the **BPA** vinyl sulfone derivative **8**, in a similar maner to that used in the preparation of the silica based adsorbents **Si-Lm**, giving an easy access to the

Fe_3O_4@Si-BPA composite (**55**). Alternatively, this functionalized hybrid material was prepared with an identical outcome by the co-condensation strategy by reaction of the magnetic nanoparticles **51** with a mixture of TEOS and the BPA-containing silane **54**, previously prepared by the Michael addition of the vinyl sulfone **8** and aminopropyltriethyloxysilane.

Cu(I) was then supported on the **Fe_3O_4@Si-BPA** nanoparticles (**55**) by simple treatment with commercial CuCl solution in deoxygenated water giving the corresponding complex **Fe_3O_4@Si-BPA·Cu^+** (**56**) that showed metal loadings of 8.3% and 7% for the particles obtained by the grafting and the co-condensation strategies, respectively, according to the quantification performed by atomic absorption spectroscopy (AAS). It should be noted that either strategy involves a multistep transformation of the magnetite silica-coated particles **51** into the new magnetic nanoparticle-supported Cu(I) **56** that can be performed in a one-pot simplified procedure by taking advantage of the magnetic decantation properties of those composites. A TEM micrograph (Figure 4) confirmed the formation of the expected core/shell structure of the **Fe_3O_4@Si-BPA** nanoparticles showing a thin silica shell (25 nm) and iron oxide cores possessing diameters of about 250 nm. The analysis of the magnetization curves (see Supporting Information) reveals that silica cover influences the magnetic properties and that the Fe_3O_4@Si particles show only 80% of magnetic saturation value of the ferrite nanoparticles

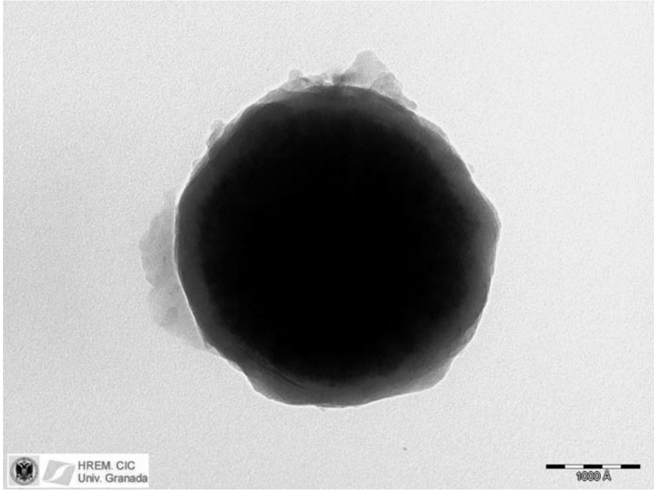


Figure 4. TEM image of core/shell magnetite silica composite-supported Cu(I) click catalyst **56**.

The catalytic capabilities of the copper containing magnetic nanoparticles **Fe_3O_4@Si-BPA·Cu^+** in click reactions were then examined in a representative set of click reactions using similar conditions as in the case of the reactions catalyzed by their non-magnetic counterparts **Si-Lm·Cu^+**. The results summarized in Table 7 (entries 1–6) show that these magnetic supported-Cu(I) nanoparticles **56** have also an excellent catalytic profile identical to that of the **Si-Lm·Cu^+** catalysts. Thus, the 1,4-disubstituted 1,2,3-triazoles were isolated in almost quantitative yields using precise equivalent amounts of the clickable reagents and low catalyst loading (10 mg per mmol of clickable reagent) in very short reaction times when the click ligation was assisted by MW irradiation or in acceptable periods when the reaction is performed at room temperature. The suitability of this magnetic-supported Cu(I) catalyst in click reactions is further reinforced by its extremely easy manipulation and recovery, which can be efficiently performed by magnetic decantation in accordance with the pursued goal of gaining in simplicity and recyclability. In fact, the recycling efficiency was investigated in the case of the reaction of alkyne **10** with azide **21** (Table 7, entry 3) where no discernible loss of catalytic activity was detected after three cycles, the resulting triazole **32** being isolated in almost quantitative yields after each run (see Experimental Section). In addition, the use

Table 7. CuAAC reactions using magnetic composite **Fe_3O_4@Si-BPA·Cu** (**56**) as heterogeneous catalysts (entries 1–6) and blank assays using **Fe_3O_4@Si-BPA** (**55**) (entries 7 and 8).

Entry	R^1	R^2	Alkyne	Azide	Composite	Conditions[a]	Time	Compound[b]
1	CH_2OH	CH_2CH_2OH	**9**	**22**	**56**	A (10)	10 min	**30** (99)
2	CH_2OH	CH_2Ph	**9**	**21**	**56**	B (10)	15 h	**29** (99)
3	CH_2NHBoc	CH_2Ph	**10**	**21**	**56**	C (20)	15 min	**32** (99)
4	β-Glc	CH_2CH_2OH	**15**	**22**	56	A (10)	10 min	**41** (96)
5	β-Glc	α-Man	**15**	**23**	56	A (10)	15 min	**42** (98)
6	$N(CH_2)_3$	CH_2Ph	**20**	**21**	**56**	C (10)	10 min	**50** (100)
7	CH_2OH	CH_2Ph	**9**	**21**	**55**	B (10)	24 h	n.r.[c]
8	CH_2NHBoc	CH_2Ph	**10**	**21**	**55**	C (20)	2 h	(10)[d]

[a] *Conditions:* equivalent amounts of alkyne and azide and **A**: H_2O (10 mL), MW, 60 °C; **B**: neat, room temperature; **C** *t*-BuOH:H_2O (10:1, 1 mL), MW, 60 °C; In parenthesis mg catalyst/mequiv reagent.

[b] Compound (yield [%]).

[c] No reaction.

[d] A mixture of the 1,4-regiosiomer (**32**) and the corresponding 1,5-regioisomer was isolated in this case.

of **Fe_3O_4@Si-BPA·Cu^+** as heterogeneous catalyst allows the use of minimal amounts of an aqueous alcohol or even water when the reagents are hydrosoluble. Moreover, the reactions can be executed in the absence of any solvent when the reagents can be mixed together reducing the use of organic solvent to very small amounts for allowing the magnetic decantation and recovery of the catalyst. On that concerning the leaching of active copper species from the catalyst to the reaction media, the copper content of the crudes obtained in the reaction of alkynes **9** and **15** with azide **22** was evaluated by AAS showing disappointing values of 7.4 and 8.9% of the initial metal present in the catalyst (Table 5, entries 6 and 7). This observation reinforces additionally the hypothesis pointed out above about the synergistic role played by the silica matrix in the non-magnetic **Si-Lm** adsorbents on the decreasing of the leaching.

In a similar fashion as in the case of the non-magnetic **Si-Lm·Cu^+** catalysts, additional experiments were carried out to demonstrate that the catalytic activity is exclusively related to complexed Cu(I) present in the magnetic catalyst **56**. Two blank experiments were performed using uncomplexed **Fe_3O_4@Si-Lm** particles (**55**) in the clicking of alkynes **9** and **10** with azide **21**. As expected, no cycloaddition reaction was detected when the reaction was performed under neat conditions and long reaction times (Table 7, entry 7) and a mixture of the 1,4- and 1,5-regioisomers was isolated in very low yield when MW irradiation was used (Table 7, entry 8) proving that thermal cycloaddition is operative in the last case.

Conclusions

In summary, supported chelating adsorbents containing multidentate nitrogenated ligands with strong copper(I) affinities are easily accessible in both non-magnetic and magnetic forms and are shown to be versatile materials in click chemistry for the implementation of eco-friendly protocols that allow the isolation of metal-free clicked compounds. These adsorbents were prepared from silica or silica-coated magnetite nanoparticles by the incorporation of the chelating ligands through a variety of efficient strategies based on the aza-Michael-type addition of vinyl sulfone to amines. The copper complexation abilities of these materials enable them to play a dual role as heterogeneous click catalytic systems when used in their complexed form and also as efficient copper scavengers in their uncomplexed form. In the first instance, the novel non-magnetic and magnetic Cu(I)-supported hybrid materials proved to be robust and efficient heterogeneous catalysts that are able to both promote click reactions by using extremely low doses with negligible copper leaching, particularly in the case of the silica-based non-magnetic adsorbents, and exploit the attractive characteristics inherent to catalytic heterogenization: rapid and easy removal by filtration or magnetic decantation together with recyclability properties. This excellent catalytic profile is due to the stabilization of Cu(I) mediated by its complexation. In the second case, the non-magnetic uncomplexed copper chelating adsorbents are efficient scavengers that can operate in tandem with the Cu(I) complexed materials or as stand-alone copper removing system to eliminate the copper contamination from any CuAAC reaction media. These materials open new opportunities for the preparation of greener clicked compounds. Further work is in progress for the implementation of these supported-Cu(I) chelating adsorbents in CuAAC reactions using flow conditions.

Experimental Section

General

Unless otherwise noted, commercially available reagents [TEOS, (3-aminopropyl)trimethoxysilane, compounds **1**–**4**, **9**, **11**–**14**, **20**, **26** and Cu(I)Cl solution (*ca.* 14%)], and solvents were used as purchased without further purification. The Dowex M-4195 resin was purchased from Supelco and subjected to a conditioning treatment. The vinyl sulfone propyl silica gel **5**,[28] the aminopropyl silica gel **6**,[29] the alkynes **10**,[38] **15**,[39] **16**,[40] **17**,[41] **18**[42] and **19**,[43] the azides **21**,[44] **22**,[45] **23**,[46] **24**,[47] **25**,[48] **27**,[49] and **28**[50] and the alkyne and azido functionalized silicas[33] used as click scavengers were prepared according to reported procedures in literature. TLCs were performed on Merck Silica Gel 60 F_{254} aluminium sheets. Reagents used for developing plates include ceric sulfate (1% w/v) and ammonium sulfate (2.5% w/v) in 10% (v/v) aqueous sulfuric acid, iodine, ethanolic sulfuric acid (10% v/v) and by UV light when applicable. Microwave assisted reactions were performed in a Milestone Star Microwave Labstation at 500 W until thin layer chromatography and IR spectra showed complete disappearance of the starting materials. Flash column chromatography was performed on Merck silica gel (230–400 mesh, ASTM). Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Satellite Mattson FTIR. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker (300–400–500 MHz) spectrometer. *J* values are given in Hz. MALDI-TOF and NALDI-TOF mass spectra were recorded on an Autoflex Brucker spectrometer using HCCA and NaI, respectively, as matrix. Electrospray ionization (ESI) mass spectra were recorded on an LCT Premier Spectrometer. Cu content was determined by atomic absorption spectroscopy (AAS) using a spectrophotometer Perkin–Elmer AAnalyst100. XRD diffraction pattern was collected on a PW101710/00 Philips diffractometer with CuKα radiation ($\lambda = 1.5418$ Å) and analyzed with XPOWDER®.

Preparation of Silica-Supported Chelating Adsorbent Si-PMA

Vinyl sulfone silica **5**[28] (1.0 g) was suspended in THF-2-propanol (1:1, 25 mL). 2-Picolylamine (**1**) (108 mg, 1.0 mmol) was then added. The reaction mixture was heated at 60 °C for 16 h. Filtration and successive washing with dichloromethane (500 mL) and ether (500 mL) furnished the corresponding functionalized silica **Si-PMA** that was dried under vacuum (1 mm Hg) at 50 °C for 16 h; yield: 0.98 g.

Preparation of the Silica-Supported Chelating Adsorbent Si-His

Vinyl sulfone silica **5**[28] (1.0 g) was suspended in a solution of THF-2-propanol (1:1, 25 mL) containing histamine·2 HCl (184 mg, 1.0 mmol) and Et_3N (420 μL, 3.0 mmol). The reaction mixture was heated at 60 °C for 16 h. Filtration and successive washing with dichloromethane (500 mL) and ether (500 mL) furnished the corresponding functionalized silica **Si-His** that was dried under vacuum (1 mm Hg) at 50 °C for16 h; yield: 0.98 g.

Preparation of the Silica-Supported Chelating Adsorbents Si-BPMA and Si-BPA

Amino propyl silica gel 6[29] (1 g) was suspended in THF-2-propanol (1:1, 50 mL). The corresponding vinyl sulfone ligand derivative **7** or **8** (1.0 mmol) was added. The reaction mixture was heated at 60 °C for 16 h. Filtration and successively washing with dichloromethane (500 mL) and ether (500 mL) furnished the corresponding functionalized silicas that were dried under vacuum (1 mm Hg) at 50 °C for16 h; yields: 1.12 g for Si-BPA and 1.11 g for Si-BPMA.

Preparation of the Cu-Supported Silica Catalysts Si-Lm·Cu$^+$

De-ionized water (30 mL) was first deoxygenated with argon and functionalized silicas **Si-PMA**, **Si-His**, **Si-BPMA** or **Si-BPA** (1.0 g) and commercial copper(I) chloride solution (1.7 mL) were added. The resulting suspension was magnetically stirred at room temperature for 7 h. Filtration and extensively washing with water and ether yields the corresponding Cu-supported silica catalysts **Si-PMA·Cu$^+$**, **Si-His·Cu$^+$**, **Si-BPMA·Cu$^+$** and **Si-BPA·Cu$^+$** that were dried under vacuum (1 mm Hg) at 50 °C for 16 h; yields: 1.10 g for **Si-PMA·Cu$^+$**, 1.11 g for **Si-His·Cu$^+$**, 1.14 g for **Si-BPMA·Cu$^+$** and 1.09 g for **Si-BPA·Cu$^+$**. The Cu contents were evaluated by AAS: 5.28% for **Si-PMA·Cu$^+$**, 10.42% for **Si-His·Cu$^+$**, 2.44% for **Si-BPMA·Cu$^+$** and 3.24% for **Si-BPA·Cu$^+$**.

Preparation of the Cu-Supported Dowex M4195 Catalysts Dw-BPMA·Cu$^+$

The as-received resin Dowex M-4195 (5.0 g) was first conditioned by washing successively with DMF (2×50 mL) and water (2×50 mL) under MW irradiation (15 min 80 °C). After filtration, the resin (1.0 g) was suspended in de-ionized water (30 mL) deoxygenated with Argon and then commercial copper(I) chloride solution (1.7 mL) was added. The suspension was magnetically stirred at room temperature for 7 h. Filtration and extensive washing with water and ether yields the **Dw-BPMA·Cu$^+$** catalyst. The Cu content was evaluated by AAS: 7.08%.

General Procedure for the Synthesis of 1,2,3-Triazoles Catalyzed by Cu-Supported Silica Catalysts Si-Lm·Cu$^+$ or Dw-BPMA·Cu$^+$

A neat mixture or a solution in *t*-BuOH-H_2O (10:1 or 2:1) or H_2O of equivalent amounts of the corresponding alkyne **9**–**20** (1 mmol) and azido derivatives **21**–**28** (1 mmol) was reacted at room temperature or by MW irradiation at 60 °C after the addition of the Cu-supported catalyst **Si-PMA·Cu$^+$**, **Si-His·Cu$^+$**, **Si-BPMA·Cu$^+$**, **Si-BPA·Cu$^+$** or **Dw-BPMA·Cu$^+$** (the amounts of solvent and catalyst are indicated in Table 1, Table 2, and Table 3). The reactions were followed by TLC until complete disappearance of the starting materials (reaction times are indicated in the tables). Filtration of the catalyst was then directly performed in the case of the reactions in solution or after the addition of CH_2Cl_2 (10 mL) in the case of the neat reactions. Evaporation of the solvent under vacuum afforded the pure 1,2,3-triazoles in the yields indicated in the tables.

Assay to Prove the Recyclability of the Si-Lm·Cu$^+$ Catalysts

Alkyne **9** (1.0 mmol) and azide **21** (1.0 mmol) in *t*-BuOH-H_2O (10:1, 10 mL) were reacted by MW irradiation at 60 °C for 20 min after the addition of **Si-BPMA·Cu$^+$** (30 mg) as catalyst. After centrifugation and separation of supernatant solution, the **Si-BPMA·Cu$^+$** catalyst was washed with the reaction solvent and reused in a second cycle of an identical solution of the clickable reagents. The procedure was repeated until a fifth cycle. Evaporation of the corresponding crude solutions obtaining in each cycle gave the triazole **29** in yields 97, 96, 97 and 94%.

Procedure for Copper Removal Using Si-BPMA or Si-BPA as Scavenger in Reactions Catalyzed by Si-BPMA·Cu$^+$ or Si-BPA·Cu$^+$

The solution obtained after filtration in the reactions of alkyne **9** or **15** with azide **21** or **24**, using **Si-BPMA·Cu$^+$** or **Si-BPA·Cu$^+$**, respectively (Table 2, entry 2 and Table 3, entry 16) that contains the triazole **29** or **43** and 0.4 ppm of Cu as detected by AAS, corresponding to leaching from the heterogeneous catalyst, was treated in batch for 6 h with **Si-BPMA** or **Si-BPA** (25 mg), respectively. The solution was then filtrated and the copper contamination was evaluated by AAS giving a negative result in both cases. Evaporation of the solution gave copper-free **29** and **43** in similar yields that those obtained in the reactions where the scavenging treatment was not performed.

Procedure for Copper Removal using Si-His or Si-BPA as Scavenger in Reactions Catalyzed by CuCl

A water solution (10 mL) of equivalent amounts of alkynes **9**, **15** or **18** (0.7 mmol) with azide **22** (0.7 mmol for the reaction with **9** and **15**, and 0.14 mmol for the reaction with **18**) (Table 6, entries 1–3) was reacted using a commercial solution of CuCl (1% mol, 5 μL for the reaction with **9** and **15**, and 10 μL for the reaction with **18**) under MW irradiation for 10 min. Copper content was evaluated by AAS (45 ppm for the reaction with **9** and **15**, and 90 ppm for the reaction with **18**). The reaction mixture was then filtered through a short column containing **Si-BPA** or **Si-His** (0.25 g for the reaction with **9** and **15**, and 0.5 g for the reaction with **18**). New evaluation of the copper contamination by AAS gave negative results. Evaporation of the solvent under vacuum yield the copper-free 1,2,3-triazoles **30**, **41** and **47** respectively, in the yields indicated in Table 6.

Procedure for the Use of Si-BPA as Copper Scavenger in Combination with Azide and Alkyne Functionalized Silica as Click Chemistry Scavengers

A water solution (10 mL) of alkyne **18** (0.7 mmol) or **15** (1.4 mmol) and azide **23** (1.68 mmol) or **25** (0.7 mmol) was respectively reacted using a commercial solution of CuCl (1% mol, 10 μL or 5 μL) under MW irradiation for 10–20 min (Table 6, entries 4 and 5). Alkyne silica (0.93 g) or azide silica (0.2 g)[33] was respectively added to the crude of each reaction and reacted under MW irradiation for 30 min to remove excess of the complementary clickable reagent. Copper content was then evaluated by AAS (90 ppm and 45 ppm, respectively). The reaction mixture was then filtered through a short column containing **Si-BPA** (0.5 g and 0.25 g, respectively). New evaluation of the copper contamination by AAS gave negative results. Evaporation of the solvent under vacuum yield the copper-free 1,2,3-triazole **44** and **48**, respectively, in the yields indicated in Table 6.

Preparation of Magnetite (Fe_3O_4) Nanoparticles (51)

The magnetite nanoparticles were prepared by a modification of the procedure described by Li et al.:[35] $FeCl_3$ (815 mg, 5 mmol) was dissolved in ethylene glycol (40 mL) to form a clear solution. After the addition of NaOAc (3.6 g) the reaction mixture was vigorously stirred for 30 min and then heated at 200 °C by means of an oil bath for 8 h. After cooling, ethanol (30 mL) was added and the resulting magnetite nanoparticles were collected using a magnet. The particles were washed successively with EtOH (4×30 mL), water (4×30 mL) and absolute EtOH (30 mL), and dried under vacuum (1 mm Hg) at 50 °C for 16 h giving **51**; yield: 0.446 g.

Preparation of Silica-Coated Magnetite Nanoparticles Fe_3O_4@Si-BPA (55)

Grafting method: Magnetite nanoparticles **51** (0.1 g) were coated with silica by the Stöber method by suspending them in a mixture of EtOH (300 mL), water (80 mL) and ammonia (10 mL) and subsequent addition of TEOS (1.0 mL). The mixture was stirred under orbital stirring for 24 h at room temperature. The resulting silica-coated particles were collected using a magnet, washed successively with EtOH:H_2O 1:1 (6×50 mL) and EtOH (50 mL), and dried under vacuum (1 mm Hg) at 50 °C for 16 h giving **52**; yield: 0.125 g. These nanoparticles were suspended in dried toluene (25 mL) and then (3-aminopropyl)triethoxysilane (APTS) (0.120 mL) was added. The reaction mixture was heated under reflux for 3 h. The resulting functionalized silica-coated magnetite particles **53** (**Fe_3O_4@Si-NH_2**) were collected by using a magnet and washed with EtOH:H_2O 1:1 (3×30 mL) and EtOH (30 mL) and used directly for the next step by suspension in THF-2-propanol (2:1, 10 mL). The vinyl sulfone ligand derivative **8** (30 mg, 0.1 mmol) was added to this suspension and the reaction mixture heated at 60 °C for 16 h. Magnetic separation of the new particles using a magnet and successively washing with THF-2-propanol (2:1, 2×30 mL), dichloromethane (2×30 mL), EtOH (2×30 mL) and water (30 mL), furnishing the magnetic chelating nanoparticles **55** (**Fe_3O_4@Si-BPA**); yield: 0.125 g.

Co-condensation method: Magnetite nanoparticles **51** (0.1 g) were suspendend in a mixture of EtOH (300 mL), water (80 mL) and ammonia (10 mL). After addition of TEOS (1.0 mL) and **54** (53 mg) the reaction mixture was stirred under orbital stirring for 24 h at room temperature. The resulting silica-coated particles were collected using a magnet, washed successively with EtOH:H_2O 1:1 (6×50 mL) and EtOH (50 mL), and dried under vacuum (1 mm Hg) at 50 °C for 16 h giving the magnetic chelating nanoparticles **55** (**Fe_3O_4@Si-BPA**); yield: 0.115 g.

Preparation of Magnetic Cu(I)-Supported Catalyst Fe_3O_4@Si-BPA·Cu^+ Nanoparticles (56)

Silica-coated magnetite nanoparticles **Fe_3O_4@Si-BPA** (**55**) were suspended in de-ionized water (3 mL) previously deoxygenated with argon. Commercial copper (I) chloride solution (0.3 mL) was added and the resulting mixture stirred under orbital stirring at room temperature for 16 h. Magnetic separation of the particles using a magnet and successive washing with water (10×30 mL), EtOH (2×30 mL) gave the corresponding magnetic nanoparticles supported-Cu(I) **56** (**Fe_3O_4@Si-BPA·Cu^+**) that were dried under vacuum (1 mm Hg) at 50 °C for 16 h.

General Procedure for the Synthesis of 1,2,3-Triazoles Catalyzed by Magnetic Cu(I)-Supported Catalyst Fe_3O_4@Si-BPA·Cu^+

A neat mixture or a solution in *t*-BuOH-H_2O (10:1) or H_2O of equivalent amounts of the corresponding alkynes (**10**, **15** and **20**) and azido derivatives (**21–23**) (Table 7) was reacted at room temperature or by MW irradiation at 60 °C after the addition of the **Fe_3O_4@Si-BPA·Cu^+** catalyst **56** (the amounts of solvent and catalyst are indicated in Table 7, entries 1–6). The reactions were followed by TLC until complete disappearance of the starting materials (reaction times are indicated in Table 7, entries 1–6). The catalyst was collected using a magnet directly in the case of the reactions in solution or after the addition of CH_2Cl_2 (10 mL) in the case of the neat reactions. After washing the catalyst with the reaction solvent (10 mL), evaporation of the assembled solutions under vacuum yielded the pure 1,2,3-triazoles **29**, **30**, **32**, **41**, **42** and **50** in the yields indicated in Table 7 (entries 1–6) without any chromatographic purification.

Assay to Prove the Recyclability of the Fe_3O_4@Si-BPA·Cu^+ Catalyst

Alkyne **10** (1 mmol) and azide **21** (1 mmol) were reacted as described above (Table 7, entry 3) using **Fe_3O_4@Si-BPA·Cu^+** (20 mg) as catalyst. After collecting the catalyst with a magnet the reaction crude was decanted, the catalyst was washed with the reaction solvent and reused in a second cycle of an identical solution of the clickable reagents. The procedure was repeated for a third cycle. Evaporation of the corresponding collected solutions obtaining in each cycle gave the triazole **32** in yields 99%, 100% and 97%, respectively.

Supporting Information

Syntheses of **7**, **8** and **53**, assays with supported Cu(I) silica $\mathbf{SiO_2+CuCl}$, assays to probe the inherent scavenging capabilities of **Si-His**, **Si-BPA** and **Dw-BPMA**, assays to probe the scavenging capabilities of **Dw-BPMA** in CuAAC reactions, XRD pattern of ferrite nanoparticles , magnetization curves of ferrite nanoparticles and silica coated ferrite nanoparticles, assay with uncomplexed magnetic nanoparticles $\mathbf{Fe_3O_4}$**@Si-BPA** (**55**), analytical and spectroscopic data of 1,2,3-triazoles **29**–**50**, and ^{1}H- and ^{13}C NMR spectra for new compounds are available in the Supporting Information.

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