CHEMISTRY AN ASIAN JOURNAL

www.chemasianj.org

Accepted Article

Title: A study of graphene-based Cu-catalysts. Cu(I) nanoplatelets for batch and continuous-flow applications

Authors: Sonia De Angelis, Mario Franco, Alessandra Triminì, Ana Gonzalez de Prádena, Raquel Sainz, Leonardo Degennaro, Giuseppe Romanazzi, Claudia Carlucci, Valentina Petrelli, Alejandro de la Esperanza, Asier Goñi, Rafael Ferritto, José Luis Aceña, Renzo Luisi, and Belén Cid

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Asian J. 10.1002/asia.201900781

Link to VoR: http://dx.doi.org/10.1002/asia.201900781

A Journal of

A sister journal of Angewandte Chemie and Chemistry – A European Journal



WILEY-VCH

A study of graphene-based Cu-catalysts. Cu(I) nanoplatelets for batch and continuous-flow applications

Sonia De Angelis,^[a] Mario Franco,^[b] Alessandra Triminì,^[a,b] Ana González,^[b] Raquel Sainz,^[c,d] Leonardo Degennaro,^[a] Giuseppe Romanazzi,^[e] Claudia Carlucci,^[a] Valentina Petrelli,^[a,b] Alejandro de la Esperanza,^[b] Asier Goñi,^[c] Rafael Ferritto,^[c] José Luis Aceña,^{*[f]} Renzo Luisi,^{*[a]} and M. Belén Cid^{*[b,g]}

Abstract: The use of graphene derivatives as supports improves the properties of heterogeneous catalysts, being graphene oxide (GO) the most frequently employed. In order to explore greener possibilities as well as to get some insights into the role of the different graphenic supports (GO, rGO, carbon black, and graphite nanoplatelets), we prepared, under the same standard conditions, a variety of heterogeneous Cu-catalysts and systematically evaluated their composition and catalytic activity in azide-alkyne cycloadditions as a model reaction. The use of sustainable graphite nanoplatelets (GNPs) afforded a Cu(I) stable catalyst with good recyclability properties, compatible with flow conditions, and able to catalyse other reactions such as the regio- and stereoselective sulfonylation of alkynes (addition reaction) and the Meerwein arylation (SET process).

Introduction

[a]	S. De Angelis, A. Triminì, Dr. L. Degennaro, Dr. C. Carlucci, V.
	Petrelli, Dr. R. Luisi
	Department of Pharmacy – Drug Sciences
	University of Bari "A. Moro"
	FLAME-Lab – Flow Chemistry and Microreactor Technology
	Via E. Orabona 4, I-70125 Bari (Italy)
	E-mail: renzo.luisi@uniba.it
[b]	M. Franco, A. Triminì, A. González, V. Petrelli, A. de la Esperanza,
	Dr. M. B. Cid
	Department of Organic Chemistry
	Universidad Autónoma de Madrid
	Cantoblanco, 28049 Madrid (Spain)
	E-mail: belen.cid@uam.es
[c]	Dr. R. Sainz, Dr. A. Goñi, Dr. R. Ferritto
	NanoInnova Technologies SL.
	Avenida de las Naciones 11, Illescas, 45200 Toledo (Spain)
[d]	Dr. R. Sainz
1.1	Current address: Instituto de Catálisis y Petroleoguímica. CSIC
	C/ Marie Curie 2, 28049 Madrid (Spain)
[e]	Dr. G. Romanazzi
[-]	DICATECh Politecnico di Bari
	Via E. Orabona 4. Bari 70125 (Italy)
[f]	Dr. I.I. Aceña
1.1	Departament of Organic and Inorganic Chemistry, Chemical
	Research Institute "Andrés M. del Río" (IOAR)
	Liniversidad de Alcalá, IRVCIS
	Alcalá de Henaros, 28871 Madrid (Spain)
	E mail: ioso acona@uab.os
[a]	
[9]	DI. W. B. Clu
	Institute for Advanced Research in Chemical Sciences (IAdChem)
	Universidad Autonoma de Madrid
	Cantobianco, 28049 Madrid (Spain)
	Supporting information for this article is given via a link at the end of
	the document

Environmental compliance is a critical concern in modern industrial settings, and when developing new chemical processes. Thus, sustainable methods in organic synthesis are nowadays increasingly needed, with a special focus on the recyclability of materials and the reduction of waste. In this context, heterogeneous catalysis may offer several advantages when compared to homogeneous protocols, namely the ease in handling the catalysts and the possibility of recovering and recycling them after use.^[11] Moreover, supported catalysts allow easy access to the benefits of flow chemistry: faster and safer reactions, cleaner products, quick reaction optimization, easy scaling-up, and post-synthesis integration steps such as work-up, and analysis.^[2]

Other limitations associated to homogeneous methods (the relatively high cost and potential toxicity of transition metal catalysts, as well as the need of organic ligands) are easily circumvented when the catalysts are anchored onto a solid support, and hence new heterogeneous metal-based catalytic systems are nowadays in great demand. In addition to mesoporous materials, lately carbon-based materials^[3] and especially some graphene derivatives constitute a very interesting alternative.^[4] This is due to the exclusive properties of graphene, which include a highly active surface area, outstanding electronic and mechanical properties and thermal stability that contribute to the overall catalytic activity.^[5] Nevertheless, the vast diversity of graphene-supported metal catalysts, the variety of methods for preparing them as well as the different reactions employed to test the catalytic activity, hamper a rational design to choose the best support in terms of sustainability, accessibility, efficiency in catalysis and recyclability for a given process.[6]

The Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC), a well-known example of click chemistry, is also one of the most useful transformations in the arsenal of a synthetic organic chemist and allows accessing 1,2,3-triazole scaffolds in a straightforward manner.^[7] The CuAAC reaction has been frequently adapted to heterogeneous conditions^[8] and is usually employed as a model reaction to prove the efficiency of new catalysts. Quite expectedly, a seminal example of а heterogeneous copper-in-charcoal catalyst was tested in this reaction.^[9] Despite the excellent performance of the catalyst, some aspects that exemplified the difficulties to understand composition and reaction mechanisms for this type of materials, deserve to be mentioned. First, the preparation of the material required long times of sonication, which is not a straightforward technique for all laboratories. Moreover, CuO or Cu₂O were initially proposed as the active catalyst, although nine years later a different species (Cu₂(OH)₃NO₃) was identified as the real

FULL PAPER

precatalyst, which is reduced under the reaction conditions to a copper(I) acetylide intermediate that is able to catalyse the reaction.^[10] In addition, an impurity identified as Cu₂(PO₄)OH that inactivate the CuAAC reaction was also found.

Graphene oxide (GO) as well as reduced graphene oxide (rGO) surfaces have also been recently used as supports of Cu nanoparticles (Cu NPs)^[11] to catalyse click reactions^[12] as well as several other processes.^[13] However, it is worth mentioning that the preparation of GO implies oxidation of graphite under harsh and hazardous conditions posing problems for scalability. Furthermore, different conditions were employed in each case for anchoring the Cu NPs on the graphenic surface, and the resulting materials displayed a variety of properties regarding composition, distribution on the surface and oxidation state of copper. The conditions in the click reaction were also guite different, which hampers the comparison between materials in terms of catalytic activity (See SI for a more detailed information). Graphene itself. prepared by exfoliation of graphite using surfactants and ultrasound, has also been used as support to provide an efficient Cu(II)-material.[14]

It is thus manifest that a good understanding of the effect of each support, as well as the consequences of all the abovementioned parameters, is essential in the development of catalytic processes in terms of activity, leaching and reuse. According to the existing information, it is difficult to predict the necessary conditions in the formation of the material to control factors such as the oxidation state of the metal after using a certain deposition method. Therefore, systematic comparative studies would be required to rationally choose a type of support as well as the preparation conditions that allow a rationally designed graphene metal/metal oxide material with tailor-made properties and optimal catalytic activity.^[6] Moreover, when using graphene derivatives as solid supports, it would be desirable to avoid materials such as GO or rGO and address the research towards the development of more sustainable, general, scalable and economical heterocatalysts.

In this context, graphite nanoplatelets (GNPs) might represent a practical solution, since they are usually obtained from sources other than GO, and therefore they constitute a greener and cheaper alternative for the deposition and growth of metal nanoparticles.^[15]

Based on our previous experience on graphene-supported organocatalysts^[16] and flow chemistry,^[17] we present herein the preparation of different heterogeneous graphene-based Cucatalysts under the simplest standard reaction conditions, as well as a systematic comparison in terms of composition, catalytic activity and recyclability by using a classical click process as a test reaction. We found that the material based on graphite nanoplatelets presented interesting properties such as a surprising stability for Cu(I) species and recyclability and we also analysed the scope and limitations of this catalyst under batch and continuous flow conditions.^{[18],[19]} Moreover, we have validated its utility as catalyst in some other valuable reactions scarcely explored in a heterogeneous version such as the sulfonylation of alkynes and the Meerwein arylation.

Results and Discussion

We started our study focusing on the development of graphenederived surfaces avoiding the use of GO or rGO as supports. In this sense, we used graphenit-OX, which is a scarcely oxidized (ca. 2% oxygen content) low dimensional graphite nanoplatelet with ca. 2-3 microns size and a few layers thickness.^[20] Graphenit-OX is produced by means of an environmentally friendly protocol, using a mechanochemical procedure in the absent of any solvent and displays several advantages compared to other graphenederived materials in terms of chemical stability, dispersibility, Brunauer-Emmett-Teller (BET) surface area (101 m²/g), and bulk density (0.2 g/mL).^[20] With the aim of preparing a homogeneously dispersed material, we adapted typical conditions found in the literature for preparing Cu NPs, entailing the use of a Cu(II) salt and a reducing agent^[21] to graphenit-OX. After testing several combinations of Cu(II) salts and reducing agents under different concentrations and temperatures, the optimal conditions used CuCl₂ and NaBH₄ at 0 °C (Scheme 1). Such a prepared new material, graphenit-Cu(I) (A), displayed good catalytic activity (see infra).



Scheme 1. Synthesis of graphenit-Cu(I) A.

Characterization of graphenit-Cu(I) (**A**) was performed using different analytical techniques detailed in the Supporting Information. For instance, the scanning electron microscopy (SEM) analysis showed that the Cu particles were homogeneously dispersed, and not significantly concentrated on small surface areas (Figure 1a).



Figure 1. SEM and XRD of material A.

Graphenit-Cu(I) shows similar structural characteristics compared to the starting graphenit-OX. The X-ray diffraction (XRD) pattern showed characteristic peaks for Cu₂O (36.5° and 42.3°)^[22] and graphene nanoplatelets (26.2°, 43.8°, 54.6°, 77.6°). The crystallite size (Lc) estimated from the peak width of the (111) Bragg reflection using the Scherrer's equation was 20 nm (Figure

FULL PAPER

1b). We should point out that the crystallite size measured here is not the particle size, as our catalyst is polycrystalline. Energy-



dispersed X-ray spectroscopy (EDX) analysis and IR spectrum confirmed the presence of Cu (see the Supporting Information). The Cu content in graphenit-Cu(I) was examined by inductively coupled plasma mass spectrometry (ICP-MS) giving a 7 wt% of Cu.

Then, we turned our attention to the preparation of the different materials **B-F** following the same protocol employed for material **A**, starting from copper salts and different supports such as GO, rGO and carbon black (Scheme 2). We also studied the different properties (% Cu, oxidation state, SEM and crystallite size) observing that all of them were very dependent on the support (Table 1). Material **B** was prepared from GO and displayed a higher content of copper compared to material **A** (entry 1), but consisted of a mixture of Cu(I) and Cu(0) particles (entry 2). In contrast, material **C** was obtained using hydrazine as reducing agent, which caused a full reduction of copper to Cu(0) (entry 3). Two more materials were prepared from rGO (material **D**) and carbon black (material **E**) (entries 4 and 5). Cu nanoparticles (**F**) were also prepared in the absence of support.

Similarly to graphenit-Cu(I), SEM images of material **B** also showed a good and homogeneous distribution of copper (Figure 2). However, in materials **C-E**, areas with accumulation of particles and areas with little copper were observed. Material **C** seems the less homogeneous material, probably due to the use of hydrazine as reducing agent.

The catalytic activity of each material (**A-F**) in the CuAAC reaction was analysed under several reaction conditions (Table 1). We performed all the click reactions between azide **1a** and phenylacetylene **2a** using equimolecular amounts of the reagents in THF as solvent at 80°C. It is worth mentioning that some problems of reproducibility arose when using different sources of the azide. A recent report indicated the presence of long-chain alkyl amines as impurities that may affect the catalytic behaviour of Cu NPs.^[23] Therefore, the catalytic activity of the materials in Table 1 was assessed employing azide **1a** previously purified by column chromatography.









Figure 2. SEM images of: a) material $\bm{B};$ b) material $\bm{C};$ c) material $\bm{D};$ d) material $\bm{E}.$

FULL PAPER

After some experimentation using material **A**, we established that 0.8-1.0 mol % was the optimal catalyst loading (see the Supporting Information). In a preliminary assessment of the catalytic activity of all materials, we employed the same weight of material regardless of their Cu ratio, by using a 0.4 M solution and by analysing conversions after 6 h. Thus, the reaction catalysed by materials **A** and **B** proceeded in high yields (entries 1-2), but rather disappointing catalytic performances were observed instead in the click reaction with the rest of materials **C-E** (entries 3-5) or the non-supported Cu NPs (**F**) (entry 6). When we readjusted the amount of catalyst according to the Cu amount of each material (0.8 mol %), we found that material **A** provided higher conversions than **B**

Table 1. Properties	and	comparison	of	catalytic	activity	of	graphenic	Cu
materials A-F.								



Entry	Material, copper oxidation states ^[a]	% Cu ^[b]	3a (%), 0.4 M, 6 h ^[c,d]		3a (%), 0.8 M, 3 h (1 h) ^[d,e,f]
			3 mg	0.8 mol % Cu ^[e]	
1	Graphenit-Cu(I)(A) Cu (I)	7	84	84	100 (64)
2	GO-Cu (B) Cu(I), Cu(0)	10.2	93-100	54-100	17 (traces)
3	GO-Cu (C), Cu(0)	10.8	21	- /	24 (traces)
4	rGO-Cu (D) Cu(I), Cu(0)	6.6	41	- ^	28 (6)
5	CB-Cu (E) Cu(I)	7.2	46	-	37 (9)
6	Cu NPs (F) Cu(I), Cu(0)	-	25	-	26 (traces)
7	-	-	_	-	Traces (-)
8	Cu ₂ O	-	-	-	11 (–)
9	Graphenit-OX	- 🦰	-	-	Traces (–)
10	Graphenit-OX	-	-		Traces (-)

[a] Established by XRD. [b] Established by TXRF. [c] The reaction was performed at a 0.43 mmol scale of azide 0.43 M using 3 mg of each catalyst.
 [d] Conversion calculated by ¹H NMR analysis. [e] Using 0.8 mol% of catalyst calculated according to the amount of Cu of each material. [f] The reaction was performed at a 0.86 mmol scale of azide 0.86 M.

The effectiveness of material **A** increased with the concentration. Interestingly, we observed the opposite effect for

material B (entries 1 and 2, last columns). Nevertheless, after some more experiments we observed that this surprising result was a consequence of an erratic behavior of material B. We speculated that it could be due to the irregular distribution of both Cu(I) (more active) and Cu(0) (less active) on different samples taken for each experiment. This unreliable performance did not occur with material A as only Cu(I) was present. The conversion for the rest of materials was slightly affected (entries 3 and 6, last columns). We also determined that the reaction did not work in the absence of catalysts, neither using Cu₂O nor graphenit-OX separately (Table 1, entries 7-9) or together (entry 10) pointing out the synergistic effect between Cu₂O and the support. These results agree with the theory that graphene derivatives are more than innocent supports and that the electronic interactions between the conducting surface and the metal increase the efficiency of a given catalytic process.[24]

Therefore, following the same preparation method, only graphenit-Cu(I) (A) keeps Cu(I) as a stable and sole oxidation state, showing a homogeneous copper distribution and results. Moreover, it is prepared starting from a green and cheaper material.

Using 1 mol % catalyst loading, and 2-methyltetrahydrofuran (2-MeTHF) as a greener solvent because of its environmental compliance,^[25] the scope of the CuAAC reaction was explored, employing different azides and alkynes. Thus, substituted triazoles **3a-g** were obtained in good to excellent yields (Scheme 3).



Scheme 3. Synthesis of triazoles **3** from azides **1** and alkynes **2**.

The recyclability of the catalyst was also considered. For practical reasons, and to reduce the loss of catalyst between different cycles, a 2 mol % loading was employed. As reported in Table 2, the catalyst was tested for up to 5 cycles, evaluating complete NMR conversion. For each catalytic cycle, the catalyst was recovered by centrifugation, rinsed with solvent, and further re-suspended for a new catalytic cycle. As dispersion methods, both ultrasounds (US) and vortex were used and compared. As can be seen in Table 2, yields were high and comparable in both cases, but the final amount of Cu was found slightly higher with

FULL PAPER

the use of vortex. According to SEM analysis, neither structural changes nor change in oxidation state were observed in material \bf{A} after recycling.

After assessing the performance of the catalyst under batch conditions and its excellent recyclability, the possibility to use this material for performing reactions under continuous flow conditions was considered. Because of the beneficial features of flow chemistry, the use of flow processing in synthetic chemistry is becoming a paradigm when developing a sustainable process.^[25b]

Table 2. Recyclability study in the formation of triazole 3a using US and vortex.

Ph 1a (1 equiv	Ph 2a (1 equiv)	gra (TH	aphenit-Cu(2 mol %) F, 90 °C, 6ł	ו) 	$\xrightarrow{Ph}_{N_{N_{N_{Ph}}}}$			
Cycle	1	2	3	4	5	%wt Cu ^[c]		
US ^[a] (% yield) ^[b]	99	99	97	96	96	5.94±0.18		
Vortex ^[a] (% yield) ^[b]	99	97	97	95	95	6.40±0.14		

[a] The sample was dispersed for 2 minutes using sonication, and 5 minutes using vortex. [b] Determined by ¹H NMR using mesitylene as internal standard. [c] Cu content after 5 runs. Measurements are referred to four independent samples and were determined by graphite furnace atomic absorption spectroscopy (GFAAS) after all samples were dissolved in an aqueous mixture of HNO₃/HCI (1/3 ratio) using microwave irradiation.

In order to perform the CuAAC reaction under continuous flow conditions, an Omnifit® cartridge of 700 μ L volume was filled with homogenous powder made of 100 mg of graphenit-Cu(I) (A) blended with celite or silica. The best conditions were found when a 2-MeTHF solution of azide **1a** and alkyne **2a** was introduced into the cartridge by a syringe pump using 233 μ L/min as flow rate (Scheme 4). Under these conditions, steady-state and full conversion were observed after 20 min as ascertained by ¹H NMR monitoring. Interestingly, the flow set up could be run up to 5 h without observing any decrease of yield.

The optimized conditions were further applied for the continuous flow synthesis of several substituted triazoles **3a**, **3c**, **3e**,**f** as reported in Scheme 3. Nicely, the catalytic continuous flow system performs well in producing triazoles in modest to excellent yields.

WILEY-VCH



Scheme 4. Flow conditions for CuAAC reaction.

Once demonstrated the higher overall performance compared to the other supports, and the recyclability of graphenit-Cu(I) in the CuAAC reactions under batch and continuous flow conditions, we were keen to test the material in other types of reactions implying different mechanistic pathways. First, given the synthetic versatility of sulfones and our interest in their chemistry, including that of vinyl sulfones,^[26] we decided to apply this material to the synthesis of 2-substituted vinyl sulfones. With this aim, we adapted the protocol developed by Taniguchi for the regio- and stereoselective copper-catalysed sulfonylation of alkynes using sodium sulfinates under acidic conditions.^[27] The heterogeneous version of this transformation required optimal conditions achieved after performing a systematic study to analyze the effect of solvent, temperature, nature of the acid and reaction time (Table 3, see also the Supporting Information).

Starting from phenyl acetylene 2a and sodium phenylsulfinate 4a as model reagents, we evaluated several mixtures of solvents, to eventually find that ultrasound dispersion of graphenit-Cu(I) in a 1:1 DMSO/AcOH mixture effectively promoted the reaction to produce the *E*-vinyl sulfone **5a**, although a conspicuous leaching of the metal catalyst was observed (entry 1). This inconvenience was overcome by using Amberlyst-15 as solid acid (200 mg/mmol) with just a slight decrease of yield (entry 2). We also studied other mixtures of solvents. For instance, adding a small amount of water allowed us to reduce the reaction time without much detriment in yield (entry 3). Next, dispersion for 3 min in a vortex mixer and increasing the temperature to 100 °C was also tested (entries 4-5), but the highest yield was achieved by using an 80:20 mixture of DMSO and EtOH as solvent, without observing catalyst leaching. Thus, after 4 h the E-vinyl sulfone 5a was obtained in a reasonable 62% yield minimizing the formation of the undesired ketosulfone 6a (entry 6). Longer reaction times were not effective (entry 7), and control experiments in the absence of the Cu catalyst or in the absence of the acid (entry 8) indicated that the process did not occur.

FULL PAPER

WILEY-VCH

Table 3. Optimization study in the formation of sulfone 5a. graphenit-Cu(I) (5 mol %) Ph-SO₂Na ŏ2 ŏ2 ö solvent / acid 2a 4a temperature (1 equiv) (1 equiv) 5a 6a Entry Solvent Acid Temp Time Suspension Yield (%)^[b] method^[a] (° C) (h) 5a 6a DMSO 80 US AcOH 24 53 1 2 DMSO Amberlyst 80 24 US 45 5 15 DMSO/ 2 US 3 Amberlvst 80 32 8 H₂O^[c] 15 DMSO/ 4 Amberlyst 100 41 trac 2 vortex H₂O^[c] 15 es DMSO/ 5 Amberlyst 100 4 vortex 45 4.5 $H_2O^{[c]}$ 15 DMSO/ Amberlyst 6 100 62 2.5 4 vortex EtOH^[c] 15 DMSO/ 4.5 7 Amberlyst 100 24 vortex 45 EtOH[c 15 DMSO/ 8 none 100 2 vortex traces EtOH^{[c}

[a] The sample was dispersed for 3 min using either sonication or vortex. [b] Determined by ¹H NMR using mesitylene as internal standard. [c] 80:20 ratio.

Under optimized conditions (Table 3, entry 4), an array of representative 2-aryl vinyl sulfones **5** was prepared in moderate to good yields, varying the substitution at both the sulfinate and alkyne moieties (Scheme 5). In all cases a single regioisomer was detected, and the products were isolated as pure *E* geometrical isomers. The substitution pattern at the aryl ring of alkynes **2a-d** included electron-donating or withdrawing groups without substantial variation in the chemical yield.



Graphenit-Cu(I)

Scheme 5. Scope of graphenit-Cu(I)-catalysed regio- and stereoselective sulfonylation of alkynes.

Finally, we selected the Meerwein arylation as a model of a three-component reaction.^[28] In this transformation, an aryl group and a halogen atom are coupled to an alkene, through the intermediacy of aryl radicals formed from an *in situ* generated arenediazonium salt. To the best of our knowledge, a single example of heterogeneous Meerwein arylation on benzoquinone has been reported, entailing aniline activation and graphite-supported copper oxide nanoparticles as catalyst.^[29] In our case, we accomplished a representative example that involved coupling aniline and methyl acrylate in the presence of NaNO₂ and HBr to render α -bromoester **7** in a reasonable 50% yield, thus demonstrating the ability of graphenit-Cu(I) to participate in SET processes (Scheme 6).



Scheme 6. Meerwein arylation reaction catalysed by graphenit Cu(I).

Conclusions

The lack of systematic studies that help understanding the role of different graphene supports on the properties and catalytic performances of these materials pushed us to prepare, under the same deposition conditions, a variety of Cu-based catalysts using GO, rGO, carbon black, and graphite nanoplatelets. We analysed

FULL PAPER

the oxidation state, crystal size, dispersion and catalytic behaviour using the CuAAC reaction as a model. All materials except graphenit-Cu(I) were obtained as a mixture of Cu(I) and Cu(0) species. We found that GO-Cu and graphenit-Cu(I) were homogeneously dispersed and catalysed click processes in an efficient manner. Nevertheless, only graphenit-Cu(I), which can be easily prepared from a more sustainable and economical starting material, provided reproducible results, maintaining Cu(I) as unique oxidation state, even after being employed as catalyst in air several times. 2-MeTHF can be used as a greener alternative to traditional solvents, the reaction even works in a 1 mol % catalyst loading under batch conditions, and the catalyst can be recycled at least 5 times. Moreover, it could be employed under continuous flow conditions and a cartridge-based packed bed reactor has been developed and tested for continuous flow synthesis. The flow reactor could be run up to 5 hours without clogging, assuring a productivity of >300 mg/h of triazole 3a. The use of graphenit-Cu(I) has also been successfully expanded to other types of transformations involving both carbon-carbon and carbon-heteroatom bond forming processes, namely the sulfonylation of aryl alkynes, and the Meerwein arylation of methyl acrvlate. Further uses of this catalyst are underway in our laboratories and will be reported in due course.

Experimental Section

Preparation of graphenit-Cu(I) (A): A suspension of 1.75 g of graphenit-OX in deionized H₂O (175 mL) was sonicated for 1 h. Then, CuCl₂ (381 mg, 2.83 mmol) was added and the mixture was vigorously stirred at room temperature for 16 h. After that, the mixture was cooled down to 0 °C and a solution of NaBH₄ (227 mg, 6.00 mmol) in deionized H₂O (175 mL) was added dropwise over 30 min. After stirring at room temperature for 24 h, the material was filtered, washed with deionized water (4 x 50 mL) and acetone (3 x 50 mL), and dried under vacuum for 4 h to afford 1.98 g of graphenit-Cu(I).

Characterization of graphenit-Cu(I) (A): Graphenit-Cu(I) (A) was characterized using different analytical techniques. First the scanning electron microscopy (SEM) of graphenit-Cu(I) showed that the Cu particles were homogeneously dispersed, and not significantly concentrated on small surface areas. Figure S1 shows structural characteristics of graphenit-Cu(I) compared to the starting graphenit-OX. The energy-dispersed X-ray spectroscopy (EDX) analysis also confirmed the presence of Cu (Figure S2). The IR spectrum seems to reveal the presence of Cu (Figure S2). The IR spectrum seems to reveal the presence of Cu (I) because it is possible to see two new peaks at 550 and 583 cm⁻¹ that can be matched with the Cu-O vibration. Moreover, the 1576 and 1473 cm⁻¹ peaks can indicate the displacement of the C=C bond due to the interaction with Cu₂O (Figure S3). The Cu content in graphenit-Cu(I) was examined by inductively coupled plasma mass spectrometry (ICP-MS) giving a concentration of 7 wt% of Cu.

General batch optimized procedure for 1,2,3-triazole synthesis: In a capped vial, 3 mg (1 mol %) of graphenit-Cu (I) was dispersed in 1 mL of 2-MeTHF and suspended by using vortex for 5 minutes. Then, azide (0.43 mmol) and acetylene (0.43 mmol) were added to the catalyst solution and refluxed for 6 h. The crude of the reaction was filtered with an HPLC filter (0.45 μ m), washed with EtOAc and concentrated at reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc, 6:4) to afford the corresponding 1,2,3-triazole.

WILEY-VCH

10.1002/asia.201900781

Flow procedure for 1,2,3-triazole synthesis: 100 mg of graphenit-Cu (I) was blended with silica powder to load a 700 μ L volume Omnifit cartridge. The solution of azide and acetylene 0.1 M in 2-MeTHF was pumped through the cartridge by a syringe pump, with 233 μ L/min as flow rate: full NMR conversion was observed after 20 min. The cartridge was housed on a Syrris FRX Volcano at 90 °C. When the steady state conditions were reached (after 20 min), the solution dispensed had the maximum NMR conversion. The residue was purified by flash column chromatography (hexane:EtOAc, 6:4) to afford the corresponding 1,2,3-triazole.

General reaction procedure for the preparation of vinyl sulfones: In a vial the sulfonate 4 (1.5 equiv), Amberlyst 15 (140 mg) and graphenit-Cu (I) (5%) were dissolved in DMSO:EtOH 1:1. The vial was sealed and suspended in a Vortex system for 3 min at room temperature. The alkyne 2 (1 equiv) was added and the reaction was kept under continuous stirring at 100 °C. After 24 h the reaction crude was filtered through HPLC filters. The organic phase was dried over Na₂SO₄, and the solvent was removed under reduced pressure yielding the desired products **5a-5q**.

Meerwein arylation procedure: A sealed vial equipped with a magnet was charged with graphenit-Cu (I) (12.3 mg, 4.4 mol %), 0.8 mL of acetone and 0.3 mL of MeOH and the mixture was sonicated for 3 min. In a second vial, aniline (1.15 mmol, 105 µL) and HBr (0.3 mL of a 47% solution) were mixed with 0.6 mL of MeOH and 0.8 mL of acetone and cooled below 5 °C. Then, a solution of NaNO2 (18.8 mg / 0.6 mL) was added and the mixture was stirred for 30 min, whereupon methyl acrylate (2.3 mmol, 195 µL) was added dropwise. The mixture was heated to 37 °C and the dispersion containing the catalyst, previously sonicated, was added to the reaction mixture which was stirred vigorously for 90 min. The catalyst was removed by filtration, washed with EtOAc and the filtrates were concentrated under reduced pressure. The crude was redissolved in EtOAc, and sequentially washed with NaOH, dilute HCI and a sat. NaCl solution. Finally, it was dried over anhydrous MgSO4 and the solvent was evaporated. The crude reaction was further purified by column chromatography (20:1 cyclohexane: EtOAc) to afford 140 mg of 7 (50% yield).

Acknowledgements

We acknowledge Fondo di Sviluppo e Coesione 2007-2013 – APQ Ricerca Regione Puglia "Programma regionale a sostegno della specializzazione intelligente e della sostenibilità sociale ed ambientale - FutureInResearch" (TBFPTF6_CC) and the Spanish Government (CTQ-2012-35957, CTQ2016-78779-R) for financial support. We also thanks Dr. Angel Lozano for suggesting the use of vortex.

Keywords: graphene • copper • nanoparticles • heterogeneous catalysis • click chemistry

- a) C. Descorme, P. Gallezot, C. Geantet, C George, *ChemCatChem* 2012, 4, 1897–1906; b) S. Hübner, J. G. de Vries, V. Farina, *Adv. Synth. Catal.* 2016, 358, 3–25.
- a) Microreactors in Organic Synthesis and Catalysis, 2nd Edition (Ed.: T. Wirth), Wiley-VCH, Weinheim, Germany, 2008; b) D. Zhao, K. Ding, ACS Catal. 2013, 3, 928–944; c) Microreactors in Preparative Chemistry: Practical Aspects in Bioprocessing, Nanotechnology, Catalysis and more (Ed.: W. Reschetilowski), Wiley-VCH, Weinheim, Germany, 2013; d) R. Munirathinam, J. Huskens, W. Verboom, Adv. Synth. Catal. 2015, 357, 1093–1123.

FULL PAPER

- [3] E. Pérez-Mayoral, V. Calvino-Casilda, E. Soriano, *Catal. Sci. Technol.* 2016, 6, 1265–1291.
- [4] a) X. Fan, G. Zhang, F. Zhang, *Chem. Soc. Rev.* 2015, *44*, 3023–3035;
 b) V. Georgakilas, J. N. Tiwari, K. C. Kemp, J. A. Perman, A. B. Bourlinos, K. S. Kim, R. Zboril, *Chem. Rev.* 2016, *116*, 5464–5519; c) D. Deng, K. S. Novoselov, Q. Fu, N. Zheng, Z. Tian, X. Bao, *Nature Nanotechnol.* 2016, *11*, 218–230.
- a) S. Navalón, A. Dhakshinamoorthy, M. Álvaro, H. García, *Chem. Rev.* 2014, *114*, 6179–6212; b) C. K. Chua, M. Pumera, *Chem. Eur. J.* 2015, *21*, 12550–12562; c) N. M. Julkapli, S. Bagheri, *Int. J. Hydrogen Energy* 2015, *40*, 948–979.
- [6] Y. Cheng, Y. Fan, Y. Pei, M. Qiao, *Catal. Sci. Technol.* 2015, *5*, 3903– 3916.
- a) E. Haldón, M. C. Nicasio, P. J. Pérez, Org. Biomol. Chem. 2015, 13, 9528–9550; b) C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard, D. Astruc, Coord. Chem. Rev. 2016, 316, 1–20.
- [8] a) S. Chassaing, V. Bénéteau, P. Pale, *Catal. Sci. Technol.* 2016, 6, 923– 957; b) F. Alonso, Y. Moglie, G. Radivoy, *Acc. Chem. Res.* 2015, *48*, 2516–2528.
- [9] B. H. Lipshutz, B. R. Taft, Angew. Chem. Int. Ed. 2006, 48, 8235–8238.
- [10] B. R. Buckley, R. Butterworth, S. E. Dann, H. Heaney, E. C. Stubbs, ACS Catal. 2015, 5, 793–796.
- [11] a) M. B. Gawande, A. Goswami, F.-X. Felpin, T. Asefa, X. Huang, R. Silva, X. Zou, R. Zboril, R. S. Varma, *Chem. Rev.* 2016, *116*, 3722–3811;
 b) S. Navalón, A. Dhakshinamoorthy, M. Álvaro, H. García, *Coord. Chem. Rev.* 2016, *312*, 99–148.
- [12] a) A. S. Nia, S. Rana, D. Döhler, X. Noirfalise, A. Belfiore, W. H. Binder, *Chem. Commun.* **2014**, *50*, 15374–15377; b) X. Xiong, H. Chen, Z. Tang, Y. Jiang, *RSC Adv.* **2014**, *4*, 9830–9837; c) I. Roy, A. Bhattacharyya, G. Sarkar, N. R. Saha, D. Rana, P. P. Ghosh, M. Palit, A. R. Das, D. Chattopadhyay, *RSC Adv.* **2014**, *4*, 52044–52052; d) V. H. Reddy, Y. V. R. Reddy, B. Sridhar, B. V. S. Reddy, *Adv. Synth. Catal.* **2016**, *358*, 1088–1092
- a) X. Guo, C. Hao, G. Jin, H. Zhu, X. Guo, *Angew. Chem. Int. Ed.* 2014, 53, 1973–1977; b) N. Hussain, P. Gogoi, M. V. K. Azhaganand, M. V. Shelke, M. R. Das, *Catal. Sci. Technol.* 2015, *5*, 1251–1260; c) M. Nasrollahzadeh, Z. Issaabadi, M. M. Tohidi, S. M. Sajadi, *Chem. Rec.* 2018, *18*, 165–229.
- [14] T. Vats, R. Gogoi, P. Gaur, A. Sharma, S. Ghosh, P. F. Siril, ACS Sustainable Chem. Eng. 2017, 5, 7632–7641.
- [15] a) R. Imran Jafri, N. Rajalakshmi, S. Ramaprabhu, *J. Mater. Chem.* 2010, 20, 7114–7117; b) Q. Wan, Y. Liu, Z. Wang, W. Wei, B. Li, J. Zou, N. Yang, *Electrochem. Commun.* 2013, 29, 29–32.
- a) E. Rodrigo, B. García Alcubilla, R. Sainz, J. L. García Fierro, R. Ferritto, M. B. Cid, Chem. Commun. 2014, 50, 6270–6273; b) R. Ramírez-

Jiménez, M. Franco, E. Rodrigo, R. Sainz, R. Ferritto, A. M. Lamsabhi, J. L. Aceña, M. B. Cid, *J. Mat. Chem.* A **2018**, *6*, 12637–12646.

- [17] a) L. Carroccia, B. Musio, L. Degennaro, G. Romanazzi, R. Luisi, *J. Flow Chem.* 2013, *4*, 29–33; b) A. Giovine, B. Musio, L. Degennaro, A. Falcicchio, A. Nagaki, J. Yoshida, R. Luisi, *Chem. Eur. J.* 2013, *19*, 1872–1876; c) L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synt. Cat.* 2015, 357, 21–27.
- [18] M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe, Adv. Synth. Catal. 2010, 352, 323–328.
- [19] a) S. Zhang, X. Shen, Z. Zheng, Y. Ma, Y. Qu, *J. Mater. Chem. A* 2015, 3, 10504–10511; b) K. W. Brinkley, M. Burkholder, A. R. Siamaki, K. Belecki, B. F. Gupton, *Green Proc. Synth.* 2015, *4*, 241–246.
- [20] Graphenit-OX has been previously employed as a support of copper, in the context of the development of new additives to improve the flammability and thermal properties of epoxy composites, see: Y. Liu, H. V. Babu, J. Zhao, A. Goñi-Urtiaga, R. Sainz, R. Ferritto, M. Pita, D.-Y. Wang, *Composites Part B* 2016, *89*, 108–116. However, the resulting material (graphenit-Cu) was obtained as a mixture of Cu(I), (II) and (0) particles with relatively large particle size, and with very poor catalytic activity.
- [21] K. Zhang, Appl. Surface Sci. 2012, 258, 7327–7329.
- [22] D. E. Diaz-Droguett, R. Espinoza, V. M. Fuenzalida, *Appl. Surface Sci.* 2011, 257, 4597–4602.
- [23] M. Rodríguez-Rodríguez, P. Llanes, C. Pradel, M. A. Pericàs, M. Gómez, *Chem. Eur. J.* 2016, *22*, 18247–18253.
- Y. Yang, A. C. Reber, S. E. Gilliland III, C. E. Castano, B. F. Gupton, S. N. Khanna, *J. Catal.* 2018, 360, 20–26.
- [25] a) D. F. Aycock, Org. Process Res. Dev. 2007, 11, 156–159; b) F. Fanelli,
 G. Parisi, L. Degennaro, R. Luisi, *Beilstein J. Org. Chem.* 2017, 13, 520–542.
- [26] a) G. Parisi, L. Degennaro, C. Carlucci, M. de Candia, P. Mastrorilli, A. Roller, W. Holzer, C. D. Altomare, V. Pace, R. Luisi, *Org. Biomol. Chem.* 2017, *15*, 5000–5015; b) E. Rodrigo, I. Alonso, J. L. García Ruano, M. B. Cid, *J. Org. Chem.* 2016, *81*, 10887–10899; c) E. Rodrigo, I. Alonso, M. B. Cid, *Org. Lett.* 2018, *20*, 5789–5793.
- [27] a) N. Taniguchi, Synlett 2012, 23, 1245–1249; b) N. Taniguchi, Tetrahedron 2014, 70, 1984–1990.
- [28] a) M. R. Heinrich, Chem. Eur. J. 2009, 15, 820–833; b) C. S. Rondestvedt, Org. React. 1976, 24, 225–259.
- [29] A. Honraedt, F. Le Callonnec, E. Le Grognec, V. Fernandez, F.-X. Felpin, J. Org. Chem. 2013, 78, 4604–4609.

FULL PAPER

Entry for the Table of Contents

FULL PAPER



An efficient and green recyclable heterogeneous graphene-based Cu-catalyst has been applied in batch and continuous-flow click reactions, sulfonylations and Meerwein arylation Sonia De Angelis, Mario Franco, Alessandra Triminì, Ana González, Raquel Sainz, Leonardo Degennaro, Giuseppe Romanazzi, Claudia Carlucci, Valentina Petrelli, Alejandro de la Esperanza, Asier Goñi, Rafael Ferritto, José Luis Aceña, * Renzo Luisi* and M. Belén Cid*

Page No. – Page No.

A study of graphene-based Cucatalysts. Cu(I) nanoplatelets for batch and continuous-flow applications