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Nanoparticle-catalysed 1,3-dipolar cycloadditions

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Author Comments:	Due to the fact that the present minireview represent the first attempt to cover the whole field of inorganic nanocatalysts applied to 1,3-dipolar cycloadditions with emphasis to the various metals involved, their structure, characterisation and recyclability, we think that it would be particularly well suited for the Rolf Huisgen's commemorative issue.
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Please provide us with information about the history of your manuscript, including previous submissions, transfers, or prior versions:	To the best of our knowledge, this is the first attempt to cover the whole field of inorganic nanocatalysts applied to 1,3-dipolar cycloadditions with emphasis to the various metals involved, their structure, characterisation and recyclability and, when interesting, their preparation. Although intended for an audience of organic chemists, it was avoided to produce a mere list of hundreds of cycloadducts that would result rather tedious. Whenever possible, emphasis has been given to improvements with respect to cycloadditions performed with the usual (non-nano) catalysts. For the sake of simplicity, the results were summarised according to the 1,3-dipole type (azomethine ylides, azomethine imines, nitrone, nitrilimine and azide cycloadditions) and, in the case of the azide-alkyne cycloaddition, further subdivision was made according to the nature of the metal-based catalyst, namely its unsupported or supported nature. The present minireview consist of 17 pages of the Wiley template (about 12000 words), 29 Schemes, 4 Tables and about 120 references, and follows our interest in the field documented by several research works published in the period 2006-2020. There are no previous submissions, transfers or prior versions of the present manuscript.
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Nanoparticle-catalysed 1,3-dipolar cycloadditions

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NANOCATALYSTS

100 nm

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Abstract: The 1,3-dipolar cycloadditions of azomethine-ylides and -imines, nitrones, nitrilimines and azides catalysed by inorganic nanoparticles are described. Emphasis is given to the nanometric catalysts involved, their structure, characterisation, and recyclability and, when remarkable, their preparation. Whenever possible, the improvements with respect to cycloadditions performed with the usual (non-nano) catalysts are discussed.

1. Introduction

In the last twenty years there has been a growing interest in nanosystems both in industry and academia.[1] Scientists have been particularly concerned in the synthesis of nanoconjugates, which could possibly be used in the biomedical field or as innovative materials.[2] Metallic nanoparticles derived from gold or other precious metals have been intensively studied as catalysts due to the fact that these nanomaterials exhibit novel and better activity when they turn into their nanometric dimension.[3] On the other hand, nanocrystalline metal oxides derived from non-precious metals, *e.g.* magnetite-supported nanocatalysts, have attracted attention in organic synthesis[4] due to their easy and efficient removal with external magnets.[5] As a consequence, the preparation of nanoparticles with well-defined composition, shape, size, and structure was accomplished.[6] Then, the immobilisation of metal nanoparticles was exploited on inorganic supports with high surface area;[7] the high stability and dispersion of these supported nanoparticles leads to active and well-recyclable catalysts, which often display negligible metal leaching.[8] Finally, the use of water or aqueous media as solvents in the reactions catalysed by metal nanoparticles represents an effort to minimise the environmental impact of chemistry, according to the golden rules of green chemistry.[9] In all these context, copper or copper-supported nanoparticles are particularly attractive because of copper's natural abundance in Earth's crust (68 ppm)[10] and the various methodologies devoted to the preparation of copper-based nanomaterials.[11]

1,3-Dipolar cycloadditions constitute a well-established topic in organic chemistry.[12] Since the discovery of the "click" azide-alkyne cycloaddition,[13] the whole field of 1,3-dipolar cycloaddition chemistry has experienced a rebirth.[14] A number of reports has appeared concerning the recent developments of 1,3-dipolar cycloadditions including their synthetic versatility,[15] the use of non-conventional solvents like ionic liquids[16], water[17] or aqueous media[18] and, of course, the application of inorganic nanocatalysts.[19] This latter topic appears to be strongly related to the field of "click" chemistry. In fact, several recent authoritative reviews were focused to the following aspects of nanoscale copper-containing catalysts: (*i*) the multicomponent synthesis of 1,2,3-triazoles,[20] (*ii*) the "click" chemistry of copper

nanoparticles[21,22] in water as the solvent,[23] (*iii*) the role of "click" dendrimers in triazole synthesis[24] and (*iv*) the use of CuO nanoparticles in the azide-alkyne cycloaddition.[25]

The scope of the present review article is to present the state of the art of inorganic nanocatalysts applied to 1,3-dipolar cycloadditions with emphasis to the various metals involved, their structure, characterisation and recyclability and, when interesting, their preparation. Although intended for an audience of organic chemists, it was avoided to produce a mere list of hundreds of cycloadducts that would result rather tedious. Whenever possible, emphasis has been given to improvements with respect to cycloadditions performed with the usual (non-nano) catalysts.

For the sake of simplicity, the results will be summarised according to the 1,3-dipole type. In the case of the azide-alkyne cycloaddition, further subdivision will be made according to the nature of the metal-based catalyst, namely its unsupported or supported nature.

Alessandro Ponti received his MSc in Chemistry and PhD in Chemical Sciences from the University of Milano. After a post-doc stay at the ETH in Zurich, he joined the Consiglio Nazionale delle Ricerche where he now is senior research scientist at SCITEC. His research interest mainly focuses on magnetic nanoparticles and computational chemistry, spanning from fundamental issues to applications in catalysis and nanotechnology. He is member of AI Magn and of the Editorial Board of the journal *Molecules*.

Giorgio Molteni, born in 1963, received his MSc and PhD in Chemistry at the University of Milan. Since 2001 he was appointed Assistant Professor at the Chemistry department of the same University. He explored the synthetic, mechanistic and theoretical aspects of 1,3-dipolar cycloadditions. Recently, his research activity rely upon the catalysis of cycloadditions by metal-oxide nanoparticles and the behaviour of 1,3-dipolar species in aqueous medium. He is member of the National centre of Pericyclic Reactions.

2. Structure and characterisation of the nanocatalysts

Several types of nanocatalysts are discussed in the following sections. To set a framework for the ensuing discussion, we briefly describe the morphological and functional features of the nanocatalysts to be reviewed. Of course, the most distinctive

feature of nanocatalysts is that they comprise particles with nanometric size and, consequently, high surface/volume ratio. Nanoparticles thus expose a large number of active sites to the surrounding environment and, also thanks to their usually convex shape, minimally impede mass-transfer of reactants to and products from their surface. Clearly, these are beneficial properties for catalysis and are shared with homogeneous catalysts. However, nanocatalysts also share favourable properties with heterogeneous catalysts, such as durability and ease of recovery. Indeed, nanocatalysts have been considered as a "bridge between homogeneous and heterogeneous catalysis".[26] Another peculiar feature of nanoparticle-based catalysts is that the inorganic nanoparticles may play different roles. They can serve as: (*i*) the catalyst itself, when catalytic sites are present at the surface of the inorganic core, (*ii*) a high-area support for grafting catalytic moieties, and (*iii*) a convenient "handle" for the recovery of the nanocatalyst by filtration or centrifugation or, even better, by magnetic separation when magnetic nanoparticles are used. Each of these functions can be incorporated in the nanocatalyst design independently. However one should recall that, when exploiting function (*ii*) and/or (*iii*), the possibility that the nanoparticle is not innocent, i.e., that it interferes with the ongoing chemical transformations, should be kept in mind.[27]

The morphology and structure of nanoparticle-based catalysts is diverse according to the exploited functions. In the simplest case, the nanocatalyst consists of inorganic (usually crystalline) nanoparticles possessing active sites at the surface (Figure 1a). For instance, in the following many examples can be found where copper-containing nanoparticles are effective catalyst for the azide-alkyne cycloaddition. It is noteworthy that inorganic nanoparticles can be active catalysts for cycloadditions also when coated with chemisorbed organic molecules (Figure 1a).[28] In another strategy, the inorganic nanoparticles are decorated with catalytic moieties, *e.g.*, organic catalysts,[29,30] metal complexes,[31,32] or other nanoparticles (Figure 1b,c).[33] The advantages of this strategy are the easy separation of the catalyst from the reaction mixture, especially when magnetic nanoparticles are employed, and a possible improvement of the catalytic activity thanks to multi-presentation of the active sites.[34] In both strategies, the nanoparticle inorganic core can be coated with a silica shell.[35] Finally, catalytic nanoparticles can be grafted onto a support thus realizing a nanoparticle-based heterogeneous catalyst (Figure 1d).
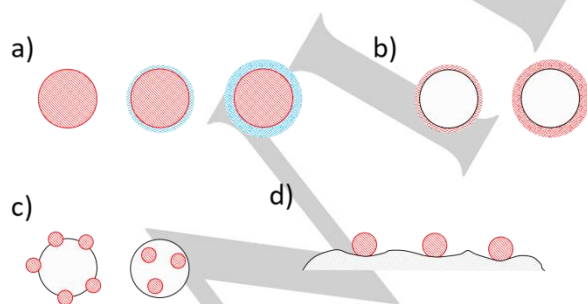

Figure 1. Schematic picture of the structure types of the nanocatalysts for 1,3-dipolar cycloadditions. The catalytic moiety is highlighted in red. a) Catalytic nanoparticles (left: bare, middle: coated with small molecules, right: polymer coated). b) Non-catalytic nanoparticles decorated with catalytic moieties directly grafted onto the nanoparticle (left) or attached to polymer chains (right). c) Non-catalytic nanoparticles decorated with smaller catalytic nanoparticles either outside (left) or within (right) the supporting nanoparticles. d) Catalytic nanoparticles grafted on an inert support.

In some cases, the support also is in the nanometric scale.[33] In this strategy, the nanoparticles are protected from chemical degradation and prevented from aggregating, a problem often plaguing unsupported nanoparticles during recycling. It should however be recalled that magnetic recovery of nanocatalysts based on magnetic nanoparticles is effective only when (at least partial) aggregation has occurred.[36]

Otherwise, the catalytic nanoparticles can be separated by filtration/centrifugation. Of course, a decreased mass-transfer to and from the supported nanoparticles should be expected.

The characterization of the nanocatalyst (before and after use) is of course critical to understand its behaviour. A reasonably complete characterization requires a non-negligible effort since it should include at least the morphology (size and shape, usually by transmission electron microscopy, TEM), and the crystal structure and composition of the inorganic nanoparticles. The latter are best investigated both at the macro- and nanoscale to achieve both a global and a nanoscale picture of the sample. The former obviates the sampling problem of nanoscale characterization and the latter obviates the averaging problem of macroscale characterization. For crystal structure, one could use X-ray diffraction on a macroscopic sample[18] whereas electron diffraction (carried out in a TEM) allows one to analyse specimen regions 10-100 nm across[28] and HR-TEM provides data equivalent to diffraction from single nanocrystals.[37] To get insight into the nanoparticle chemical composition, ICP methods are accurate and affordable (but destructive) at the macroscale[38] while specialized TEM techniques (electron energy loss spectroscopy, EELS, and mapping, ESI; energy-dispersive X-ray spectroscopy, EDX), are required at the nanoscale.[39] Composition mapping with nanometric resolution is especially important when heterogeneous composition is expected (*e.g.*, core-shell nanoparticles) or possible (*e.g.*, MFe_2O_4 nanoparticles).

When the nanoparticles are coated with passivating ligands, the structure and composition of the latter is usually known (although checking is advisable) but the ligand density should be measured (by thermogravimetric analysis, TGA, or elemental CHN analysis),[40] especially when the availability of active sites at the inorganic surface is important. When the nanoparticles are decorated with catalytic moieties, the latter should be characterized as to their chemical nature and their loading with respect to the nanoparticle core and/or passivating coating measured. For instance, in the case of decoration with an organic catalyst, one should ascertain by infrared spectroscopy the presence and integrity of the catalyst after decoration[40] and after use[28] and its loading by CHN or TGA analysis[41] or by quantification of the catalyst remaining in solution after decoration. Finally, when metal-containing nanoparticles are used, either as catalysts or as catalyst support, one should be aware that leached metal ions can act as homogeneous catalyst for the desired reaction or for unwanted ones. Testing for metal leaching from the nanoparticles under reaction conditions [38,42] and checking the effect of purposely dissolved metal ions are both advisable.[43]

Even a brief outline of the numerous characterization techniques that have been applied to characterize cycloaddition nanocatalysts is beyond the scope of this review. We just highlight two less-common methods found in the literature reviewed in this article.

The use of copper-containing nanocatalyst is prominent in this Review because of the importance of the copper(I)-catalysed azide-alkyne cycloaddition pioneered by Sharpless.[44]

Nanoparticles containing Cu(0) or Cu(I) undergo oxidation when exposed even briefly to air. It is therefore important to investigate the oxidation state and the crystal phase of the copper nanocatalyst. X-ray photoelectron spectroscopy (XPS) provides quantification of the oxidation state (or chemical environment) of any element since it disperses the recorded signal according to the atomic orbital energies. XPS proved effective to identify and quantify the copper oxidation states.[18,45,46] XPS is a surface technique having a penetration depth of a few nm. Thus, XPS quantitatively pictures the oxidation state of the copper atoms/ions near the nanoparticle surface, which are the catalytically active sites, providing a basis to understand the catalyst activity. XPS has also been used to prove the absence of surfactant coating on Cu_2O nanoparticles.[47]

Single-molecule optical imaging and spectroscopy has been used to identify the actual catalytic agent in the azide-alkyne cycloaddition catalysed by Cu nanoparticles.[42] The technique relies on using dye-tagged azide and alkyne which are passed in a microflow reactor coated with Cu nanoparticles. After the formation of the triazole product, the two dyes are close enough for resonance energy transfer (FRET) to occur, which is optically detected by a fluorescence microscope. This method was able to detect single cycloaddition events and to demonstrate that the cycloaddition occurs at the Cu nanoparticles. It was also shown that leached Cu ions may at most contribute 5% of the theoretical yield.

Finally, it is interesting to note that in very few cases computational modelling has been applied to get insight into nanocatalysed 1,3-dipolar cycloadditions. This is surprising since, on one hand, the importance of calculations in understanding surface catalysis is well established[48] and, on the other hand, 1,3-dipolar cycloadditions have been a favourite playground of computational chemists since long.[49,50] The experimental outcome of the nitrilimine-alkene cycloaddition catalysed by spinel-structure iron oxide nanoparticles led to the proposal of a mechanism involving as a key step the accelerated dehydrochlorination of the precursor chlorohydrazone on the nanoparticle surface (see Scheme 7, intermediate 9). Model calculations based on the density functional theory (DFT) in a cluster approach supported the proposed mechanism.[43] It has been recently shown that the azide-alkyne cycloaddition is catalysed by copper-free nanoparticles such as magnetite, Mn and Co ferrite, MnO, and MnS nanoparticles. Focusing on magnetite, a more thorough DFT approach was used where the nanoparticle surface was modelled as either an iron oxide cluster or an infinite magnetite surface. It was shown that the end-on adsorption of the azide on iron sites at the magnetite surface brings about a strong hybridization of the azide and iron orbitals leading to a decreased HOMO-LUMO gap and the opening of easier reactive channels.[28]

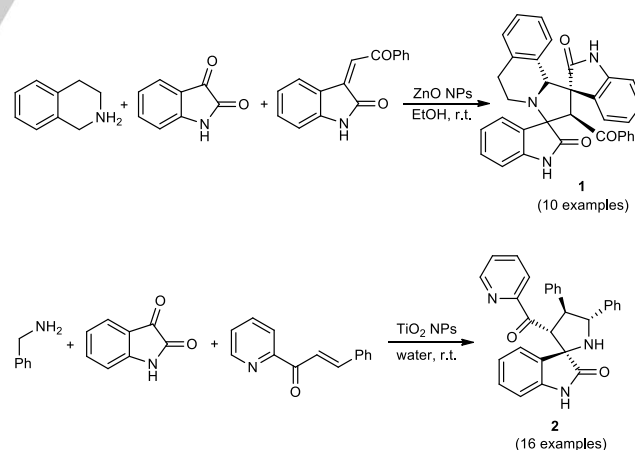## 3. Azomethine ylide, azomethine imine and nitrone cycloadditions

Heterogeneous silica-supported silver(0) nanoparticles are able to catalyse the stereoselective cycloaddition between 2'-hydroxychalcones and the azomethine ylide intermediates generated in situ from proline and *p*-tolualdehyde (Scheme 1). The major *exo*-isoxazolidine stereoisomer depicted in Scheme 1 was obtained with 85 : 15 ratio. Starting from different dipolarophilic counterparts, 18 examples of functionalised

pyrrolidines were obtained with quite variable combined yields (25-99%) and *exo/endo* ratio (between 95 : 5 and 63 : 37).[51] However, since the best results for these three-component cycloadditions were obtained in boiling acetonitrile, the involvement of the usual thermal route cannot be excluded. As far as the catalyst is concerned, it was prepared starting from silver(I) tetrafluoroborate in the presence of tetrabutylamino borohydride as the reducing agent, followed by the addition of chromatography-grade silica gel and subsequent drying *in vacuo* at 220°C. Although no data of the nanoparticles size are available, the catalyst reusability was verified in the case of the reaction depicted in the Scheme 1. Seven runs were performed without significant loss of activity.
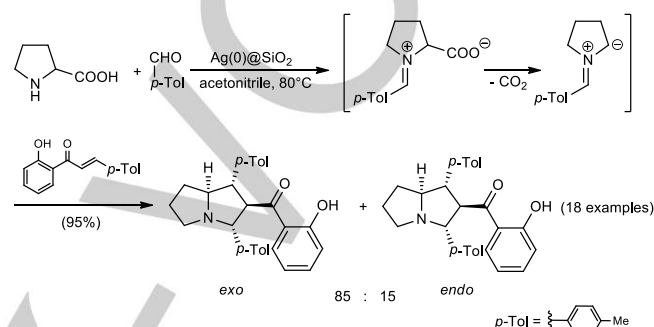
Scheme 1. Three-component cycloaddition of non-stabilised azomethine ylides catalysed by Ag(0)@SiO$_2$ nanoparticles.

Three-component reactions based onto the intermolecular azomethine ylide cycloaddition have been also exploited in the presence of unsupported, partially aggregated zinc(II) oxide or TiO$_2$ nanoparticles. As can be seen in Scheme 2 both di-spiroindolizidinebisoxindoles **1** and spiroxindole-pyrrolidine **2** skeletons were obtained at room temperature in ethanol or water (1: 10 examples, 83-97% yield; 2: 16 examples, 80-94% yield).


Scheme 2. Three-component cycloaddition of azomethine ylides catalysed by unsupported partially aggregated ZnO or TiO2 nanoparticles.

The initial condensation between tetrahydroisoquinoline (or benzylamine) and isatine provide the precusor of the azomethine ylide intermediate whose subsequent cycloaddition onto the appropriate dipolarophile gives the target molecules **1**[52] and **2**[53] as single stereoisomers. Curiously enough, these

reactions occur in the absence of a basic agent, in contrast with both uncatalysed[54] and metal-catalysed[55] azomethine ylide cycloadditions. Inexpensive ZnO nanoparticles were tested in order to determine their recyclability. Unfortunately, the efficiency of the nanocatalyst declined at every cycle, and after the third one the nanoparticles resulted as aggregates. In the case of TiO_2 nanoparticles, four catalytic runs were performed for the reaction depicted in Scheme 2 to investigate their recyclability. The recovery amount of this latter nanocatalyst was always > 90% at every step.

Switching the attention to the azomethine imine 1,3-dipole, the stereoselective synthesis of julolidine alkaloids analog **3** was accomplished starting from the corresponding *O*-allyl-pyridoquinoline derivative by intramolecular azomethine imine cycloaddition catalysed by unsupported bare (*i.e.*, non-coated) $MgSiO_3$ NPs.[56] As is depicted in Scheme 3, the initial condensation between *N*-methylglycine and the formyl group of the precursor was followed by a cyclisation to an oxazolidinone intermediate. Subsequent loss of carbon dioxide gave the non-stabilised azomethine imine whose intramolecular cycloaddition gave (3a*S**, 13b*R**)-**3** with 78% yield. The $MgSiO_3$ nanocatalyst[57] was collected by simple filtration and was recycled only a couple of times without significant decrease in the isolated yields. However, the beneficial effects of $MgSiO_3$ NPs on the cycloaddition may be appreciated by considering that in the presence of MgO NPs the isolation yield of product **2** was considerably lower (30%), and no reaction occurred without catalyst. By using the same protocol with α-aminoacids other than *N*-methylglycine, 15 more julolidine alkaloid analogs were synthesised with 65-85% cycloaddition yield.
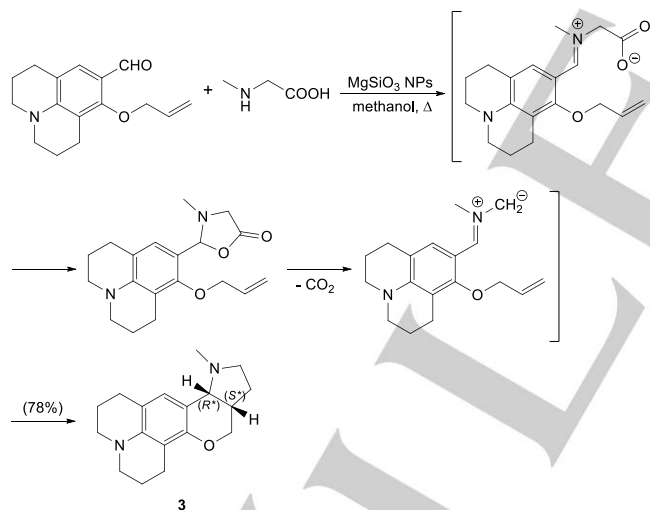

Scheme 3. Intramolecular cycloaddition of non-stabilised azomethine imines in the presence of $MgSiO_3$ nanocatalyst.

The examples of nanoparticle-catalysed intermolecular cycloadditions of nitrones (azomethine oxides) rely upon the use of nanocatalysts comprising iron oxide nanoparticles decorated with an organic catalyst. These magnetic nanoparticles often represent valuable catalysts due to the ease of their preparation and recovery by an external magnet. In addition, nanometric iron oxides display good recyclability, low toxicity and can be prepared starting from inexpensive reagents.[58]

It was found that MacMillan's imidazolidinone-based nanocatalyst **4** was able to promote the asymmetric cycloaddition between nitrones and α,β-unsaturated aldehydes (Scheme 4) affording 20 examples with combined cycloadducts yields up to 96% and endo/exo ratio up to 95 : 5.[29] The diastereoselectivity towards the *endo* isoxazolidine is consistent with previous results obtained *via* the organocatalytic route.[59] Furthermore, both reaction conditions and performance of the two complementary approaches are comparable. As far as the recyclability of nanocatalyst **4** is concerned, the reaction between *C,N*-dibenzylnitrone and (*E*)-crotonaldehyde was performed four times with no substantial decrease in yield (89-94%) and with no appreciable decrease of stereocontrol. The recovery of **4** was always achieved quantitatively by using an external magnet.
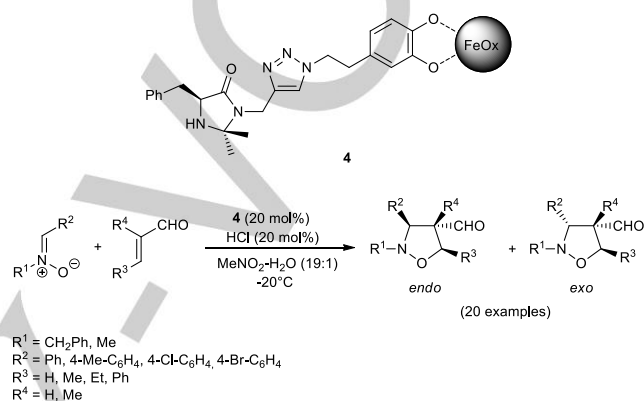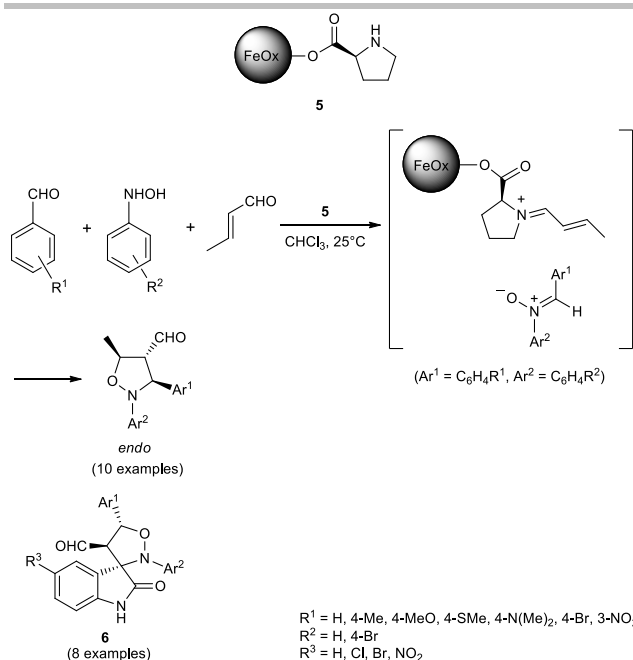

Scheme 4. Diastereoselective nitrone cycloaddition catalysed by FeOx NPs decorated with MacMillan's imidazolidinone-based nanocatalyst 4.

L-proline-decorated nanocatalyst **5** was used successfully in the diastereoselective nitrone cycloaddition to α,β-unsaturated aldehydes. The (3*S*,4*R*,5*S*)-isoxazolidines (*endo*-isomers) depicted in Scheme 5 were obtained with 87-89% yield and are the result of the three-component reaction between *N*-aryl-hydroxylamines, aromatic aldehydes and the appropriate dipolarophile.[30]

This latter specie should be the iminium intermediate, which arises from the condensation between the L-proline supported on the nanocatalyst and crotonaldehyde. The diastereo-preference towards the *endo*-isoxazolidines as well as the observed *e.e.* and yields are consistent with early results obtained according to the organocatalytic route pursued by using prolinols as the organocatalysts.[60] In the presence of the nanocatalyst **5** short reaction times and good isoxazolidine yields were observed. The suspended nanocatalyst was recovered and recycled five times without significant loss of its catalytic activity. The application of this protocol was extended to the reactions of *N*-arylhydroxylamines and crotonaldehyde with substituted isatins, obtaining spiroisoxazolidines **6** with 89-93% yield.

As far as supported nano-iron oxides catalysts are concerned, an example of silica-coated nanomagnetite ($Fe_3O_4@SiO_2$) was exploited in the [3+2] cycloaddition between fullerene and *N*-phenyl-*C*-4-nitrophenylnitrone affording the corresponding functionalised fullerene derivative **7** (Scheme 6).[61]

Scheme 5. Diastereoselective-three component nitrone cycloaddition catalysed by FeOx NPs decorated with L-proline (**5**).
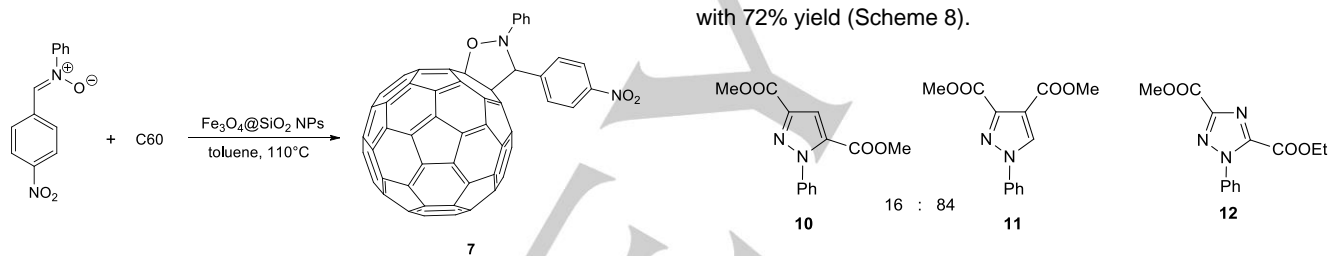
Scheme 6. Cycloaddition between fullerene and *N*-phenyl-*C*-4-nitrophenyl nitrone.

4. Nitrilimine cycloadditions

Nitrilimine cycloadditions to ethylenes, acetylenes and activated nitriles have been exploited in the presence of catalytic amounts (4.2 mol %) of oleic-acid-coated iron oxide nanoparticles with diameter = 11.9 ± 1.0 nm.[43] As expected from Frontier Molecular Orbital (FMO) calculations,[49] the reactions with monosubstituted ethylenes were fully regioselective giving 4,5-dihydropyrazoles **8** with 78-92% yield (Scheme 7). The presence of iron oxide nanoparticles allowed to carry out the cycloadditions at milder conditions compared to the "metal free" thermal processes.[62] Furthermore, the separation step by column chromatography can often be avoided. The labile intermediate **9** (R^1 = H) resulting from the interaction between hydrazonoyl chlorides and an undercoordinated iron(III) ion at the nanoparticle surface has been proposed to explain this favourable behaviour. The nanometric iron-oxide catalyst was recovered and recycled twice by using an external magnet.
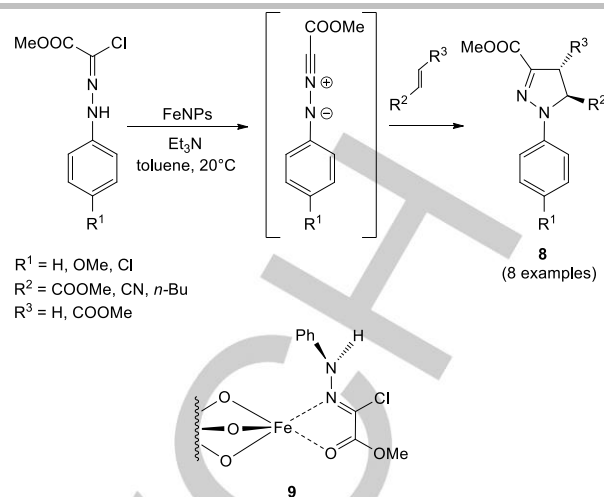
Scheme 7. Nitrilimine cycloadditions to ethylenes catalysed by oleic-acid-coated iron oxide nanoparticles.

The same protocol was applied to triple-bonded dipolarophiles, namely acetylenes and activated nitriles. The cycloaddition with methyl propiolate gave a mixture of the corresponding isomeric pyrazoles **10** and **11** with 67% overall yield, while the activated nitrile group of ethyl cyanoformate gave the 1,2,4-triazole **12** with 72% yield (Scheme 8).

Scheme 8. Products arising from nitrilimine cycloadditions to methyl propiolate and ethyl cyanoformiate catalysed by oleic-acid-coated iron oxide nanoparticles.

5. Azide cycloadditions

It is well-known that the celebrated copper(I)-catalysed azide-alkyne cycloaddition has acquired the status of the quintessential "click" reaction.[63] Undoubtedly, this process constitutes a robust and versatile route to the selective synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles, notwithstanding it has been recognised that it is not an ubiquitously-attractive process[64] due to the cytotoxicity of the residual copper ions.[65] However, as will be seen in the next sections, this problem can be largely overcomed by using appropriate nanocatalysts that display very low metal loadings and negligible leaching.

The discussion of the azide-alkyne cycloadditions catalysed by nanoparticles is divided according to the unsupported or supported nature of the nanocatalyst. For the sake of clarity, the data are further grouped according to the metal that constitutes the effective catalytic site.

5.1. Unsupported nanocatalysts

Nanoparticles without coating have been scarcely studied in the azide-alkyne cycloadditions due to their tendency to agglomeration.[21] On the other hand, appropriate nanoparticle

coating provided effective nanocatalysts that are well-dispersed within the reaction medium, thus increasing the catalytic surface available. In several cases, this strategy can circumvent the requirement of heterogeneous catalysts in which the nanoparticles are tied up to a special support.

5.1.1. Unsupported copper nanoparticles

Three pioneering studies in the field of "click" cycloadditions by means of unsupported copper nanocatalysts date since 2005. It was found that the use of a catalytic amount of Cu(0)-nanosized, activated powder in water-t-butanol mixtures gave the corresponding 4-substituted-1,2,3-triazoles without the need of any additive (Scheme 6, 6 examples, 80-99% yield).[66] On the other hand, the presence of an amine hydrochloride salt promoted the formation of copper acetylide that was able to catalyse the regioselective cycloaddition giving the target triazoles with 83-95% yield (Scheme 9, 16 examples).[67] It was reasoned that the slightly acidic environment ensured by the presence of an amine hydrochloride salt was required to induce the partial dissolution of Cu(0) and, subsequently, trigger the generation of the Cu(I) catalytic species.
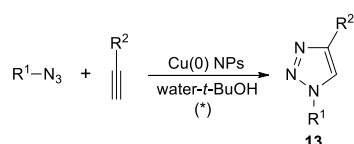
Ref. 66: Cu(0) NPs, water-t-BuOH, 25°C, 6 examples

R^1 = Ph, CH$_2$Ph

R^2 = Ph, CH$_2$OH, CH(OH)Ph

Ref. 67: Cu(0) NPs, Et$_3$NH$^+$Cl$^-$, water-t-BuOH, r.t., 16 examples

R^1 = CH$_2$Ph, CH$_2$COOEt, ... NBoc, ... NH·HCl, ... COOH, ...

R^2 = Ph, COOH, COOMe, COOEt, CH$_2$Ph, CH$_2$OPh, CH$_2$OH, CH$_2$NHBoc, CH$_2$SEt

Ref. 68: Cu(0)@Cu$_2$O NPs, toluene, r.t., 11 examples

R^1 = Ph, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

R^2 = COOMe, Ph, CH$_2$OH, CH$_2$Br, (CH$_2$)$_4$OH, CH(OH)Ph, CH$_2$NH$_2$
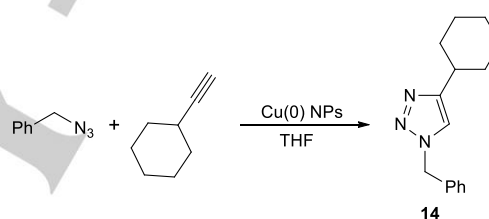
Scheme 9. Azide-alkyne cycloadditions catalysed by Cu(0) nanoclusters.

Finally, the scope of the investigation described above was broadened by isolating and thoroughly characterising the core-shell Cu(0)@Cu$_2$O nanoparticles, including their behaviour to air. A set of 3 arylazides and 7 terminal alkynes was investigated to span a wide range of functional groups featuring largely different electronic demand. Reaction outcomes were high irrespective of R^1 and R^2, as required for a genuine "click" reaction (Scheme 9, 11 examples, 89 - >95% product yield).[68] In these three early studies the Cu(0) or Cu(0)@Cu$_2$O nanocatalysts were added as 10-20 mol% relative to the azide, a comparable amount used for a genuine "click" cycloaddition.[63] The copper nanocatalysts were not recovered.

Stable Cu(0) nanoparticles coated with poly(*N*-vinyl-2-pyrrolidone) were synthesised by reduction in air of the suitable Cu(II) salt with hydrazine or ascorbic acid in formamide or in dimethylformamide and in the presence of poly(*N*-vinyl-2-pyrrolidone) as the stabilising agent. These Cu(0) nanoparticles were fully characterised using TEM, SEM, XRD, and UV-visible spectroscopic techniques and were found to be effective

nanocatalysts for the cycloaddition between terminal alkynes and azides. Nine examples of 1,4-disubstituted-1,2,3-triazoles were obtained starting from a set of four azides and four terminal alkynes with 91-97% yield. The durability of the Cu(0) nanocatalyst was investigated in four successive reactions without loss of catalytic activity. Further use led to aggregation of the nanoparticles giving agglomerates up to 60 nm. It needs to be added that the nanoparticle agglomeration did not affect their catalytic efficiency to a large extent.[69]

Another interesting method to access the Cu(0) nanoparticles was developed starting from copper(II) chloride by using lithium metal as the reducing agent in tetrahydrofuran. In the subsequent azide-alkyne cycloaddition, the presence of triethylamine was shown to be indispensable for the reaction to take place. An increase of triethylamine concentration over the stoichiometric amount allowed to shorten the reaction time in the reaction between benzylazide and cyclohexylacetylene (Scheme 10 and Table 1, entries 9-11), while the concentration of Cu(0) nanoparticles did not affect the triazole yield for a given reaction time (Table 1, entry 6-8). Starting from a set of seven azides and ten terminal alkynes, 29 examples of 1,4-disubstituted-1,2,3-triazoles were obtained, but the nanocatalyst could not be recovered at the end of the reaction due to the truly colloidal nature of the resulting mixture.[45,70]

Scheme 10. Benzylazide-cyclohexylacetylene cycloaddition catalysed by Cu(0) nanoparticles.

Table 1. Cycloaddition between benzylazide and cyclohexylacetylene catalysed by Cu(0) nanoparticles.

Entry	Cu NPs[a] (mol %)	Additive (mol)	T (°C)	Time (h)	Yield (%)
1	100	—	25	12	0
2	100	Et$_3$N (1)	25	1	98
3	100	Et$_3$N-PVP[b] (1)	25	3	58
4	20	Et$_3$N (1)	25	6	98
5	10	Et$_3$N (1)	25	6	98
6	5	Et$_3$N (1)	25	24	98
7	2	Et$_3$N (1)	25	24	100
8	1	Et$_3$N (1)	25	24	100
9	10	Et$_3$N (3)	25	0.5	99
10	10	Et$_3$N (2)	25	0.5	99
11	10	Et$_3$N (1)	65	0.5	100
12	10	Et$_3$N (1)	65	24	75
13	10	Et$_3$N (1)	65	24	71

[a]Cu(0) nanoparticles. [b]Poly(*N*-vinyl-2-pyrrolidone).

The reaction of deuterated phenylacetylene with benzylazide in the presence of Cu(0) nanoparticles gave near-to-quantitative deuterium incorporation into the correponding 1-benzyl-4-phenyl-5-deutero-1,2,3-triazole **16** (Scheme 11). From a

mechanistic standpoint, this and other labeling experiments demonstrate that the protonolysis or deuteriolysis of the intermediate copper(I) triazolide complex **15** occurs *in situ*, and the proton or deuterium transfer from the alkyne must be very efficient.[70] It may be recalled that the generation of **15** as labile intermediate was perceived on the basis of the accepted catalytic cycle proposed in the "click" copper azide-alkyne cycloaddition (CuAAC), as well as other metal-mediated azide-alkyne cycloadditions.[71]
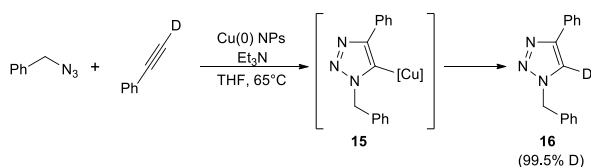
Scheme 11. Benzylazide-deuterophenylacetylene cycloaddition catalysed by Cu(0) nanoparticles.

The use of unsupported copper-containing nanocatalysts was applied successfully in the synthesis of some relevant synthetic targets. However, in all the examples depicted in the Scheme 12 the nanocatalyst was not recovered at the end of the reaction sequence. The triazole-steroid derivative **17** was obtained from 17α-ethynylestradiol and benzylazide with nearly quantitative yield after 30 min.[45] A microwave-assisted protocol developed for the construction of 2-amino-1*H*-imidazole-triazole conjugates **18** showed moderate to high preventive activity against biofilms of *S. Typhimurium*, *E. coli*, *P. aeruginosa* and *S. aureus*.[72]
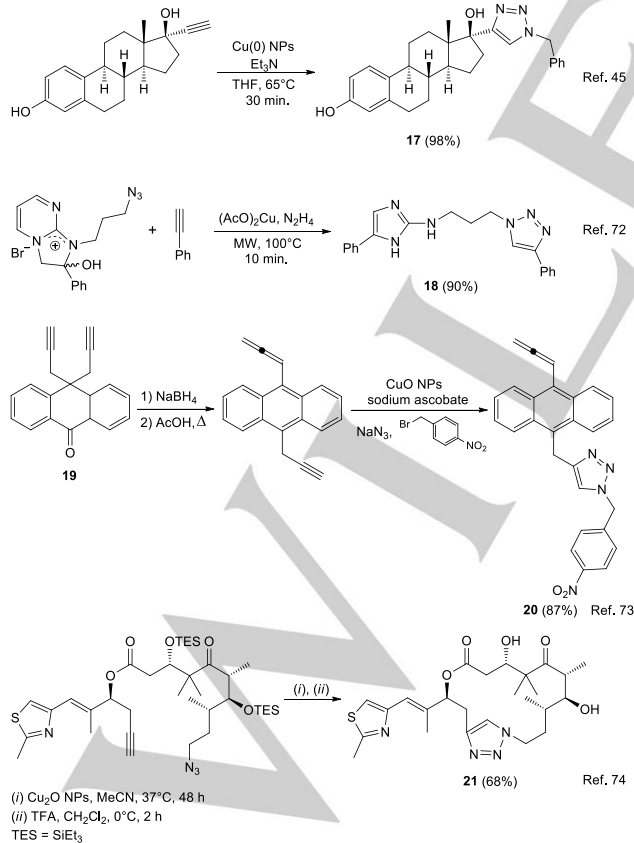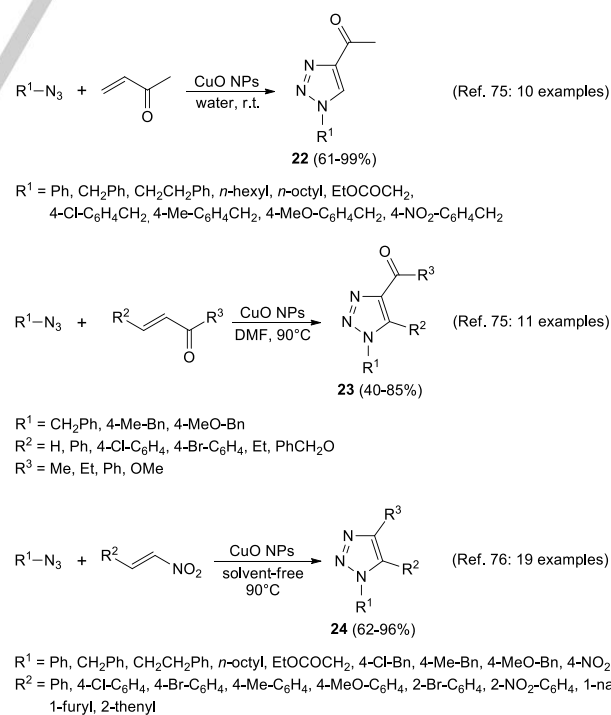

Scheme 12. Synthetic applications with unsupported *C*-containing nanoparticles.

The synthesis of mono-, bis- and tris-triazole derivatives can be accomplished using 10,10-dipropargyl-9-anthrone **19** as a key starting material.[73] The reaction with alkyl- or benzyl-bromides and sodium azide in the presence of 10 mol% of CuO nanoparticles along with 20 mol% sodium ascorbate in water afforded a wide variety of triazole derivatives. It is worthwhile mentioning that the allene moiety remains unaffected during the cycloaddition step. The triazole **20** is able to undergo extended assembly in the solid state forming a zig-zag supramolecular structure stabilized by π-π and C–H/π interactions.

In the total synthesis of the triazole-epothilone analogue **21**, the key step to generate the macrocyclic- and the triazole-ring was to apply Cu$_2$O nanoparticles. Computational modelling of **21** allowed to investigate the correlation between its conformation and bioactivity against the breast cancer cell line MCF-7.[74]

Switching the attention to the +2 oxidation state of copper in the absence of reducing agents, it has been reported that the oxidative cycloadditions between azides and activated ethylenes, namely acroleyn, methyl vinyl ketone, chalcones[75] and nitro olefins,[76] were feasible in the presence of unsupported suspended CuO nanoparticles. After the optimisation of both the solvent and the catalytic species, starting from a set of ten azides and 22 olefins, 40 examples of 1,4-disubstituted-1,2,3-triazoles were obtained with 40-99% yield (Scheme 13). In all the cases described, the azide cycloaddition to unsymmetrically 1,2-disubstituted ethylenes was found to be fully regioselective. It was possible to recover the copper(II) nanoparticles from the reaction mixture by centrifugation followed by washing with ethyl acetate and drying in a hot air oven. The so-obtained recovered nanoparticles were proven to be active for four cycles. From the mechanistic point of view, it was suggested that the presence of molecular oxygen dissolved in the reaction solvent (namely, the atmospheric oxygen), could promote the oxidation of the 1*H*-4,5-dihydro-1,2,3-triazole primary cycloadducts to the fully unsaturated species **22**-**24**.

R^1 = Ph, CH$_2$Ph, CH$_2$CH$_2$Ph, *n*-hexyl, *n*-octyl, EtOCOCH$_2$,
4-Cl-C$_6$H$_4$CH$_2$, 4-Me-C$_6$H$_4$CH$_2$, 4-MeO-C$_6$H$_4$CH$_2$, 4-NO$_2$-C$_6$H$_4$CH$_2$

R^1 = CH$_2$Ph, 4-Me-Bn, 4-MeO-Bn
R^2 = H, Ph, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, Et, PhCH$_2$O
R^3 = Me, Et, Ph, OMe

R^1 = Ph, CH$_2$Ph, CH$_2$CH$_2$Ph, *n*-octyl, EtOCOCH$_2$, 4-Cl-Bn, 4-Me-Bn, 4-MeO-Bn, 4-NO$_2$Bn
R^2 = Ph, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 2-Br-C$_6$H$_4$, 2-NO$_2$-C$_6$H$_4$, 1-naphtyl, 1-furyl, 2-thenyl

Scheme 13. Azide-alkene cycloadditions in the presence of CuO nanoparticles.

To this point, since there are no literature evidence that copper(II) is able to catalyse the azide cycloadditions, some considerations must be formulated. First, the azide cycloadditions with chalcones and nitroalkenes were performed at 90°C, in DMF and in solvent-free conditions, respectively (see Scheme 13). In these conditions a thermal cycloaddition can occur, followed by atmospheric oxygen oxidation of the above-mentioned primary cycloadduct, although the scarce thermal stability of 1H-4,5-dihydro-1,2,3-triazoles is known.[77] Second, methylvinylketone (MVK) reacted well in water at r.t. (see Scheme 13). To this respect, it should be recalled that abnormally high reaction rates were experienced in the cycloaddition between MVK and phthalazinium-2-dicyano-methanide or pyridazinium dicyanomethanide[78] in water. Such a peculiar behaviour was attributed to balanced hydrophobic effects and special hydrogen bonding interactions between water and MVK, the latter being named a "superdipolarophile".[79]

5.1.2. Unsupported copper-iron or -iron oxide nanoparticles

The favourable features of magnetic nanoparticles related to the ease of catalyst recovery, their prompt availability and environmental-friendly behaviour have been briefly sketched in section 4. In the case of the azide-alkyne cycloaddition, three types of magnetically recoverable copper nanocatalysts have been successfully used: well-dispersed glutathione-copper(I)-decorated magnetite **25**,[31] partially aggregated copper ferrite (CuFe$_2$O$_4$)[80] and partially aggregated copper(0)/iron(0).[81,82] The regiochemical course of the azide-alkyne cycloaddition and the cycloaddition extent depends upon the presence of copper in the nanocatalyst. Mixtures of isomeric 1,2,3-triazoles are obtained with low yield in the absence of copper, while 1,4-disubstituted-1,2,3-triazoles arise selectively in the presence of copper-based nanocatalyst, possibly through a "click-like" mechanism, notwithstanding a catalytic cycle has not been proposed.[31,82] As an example, the cycloaddition between benzylazide and phenylacetylene shows the behaviour in Scheme 14 and Table 2. Although the results obtained by different Authors may appear sometimes conflicting (Table 2, entries 3 and 4), the different experimental conditions should be by kept in mind.
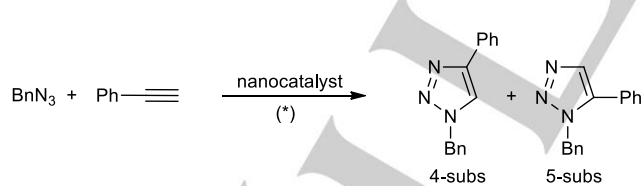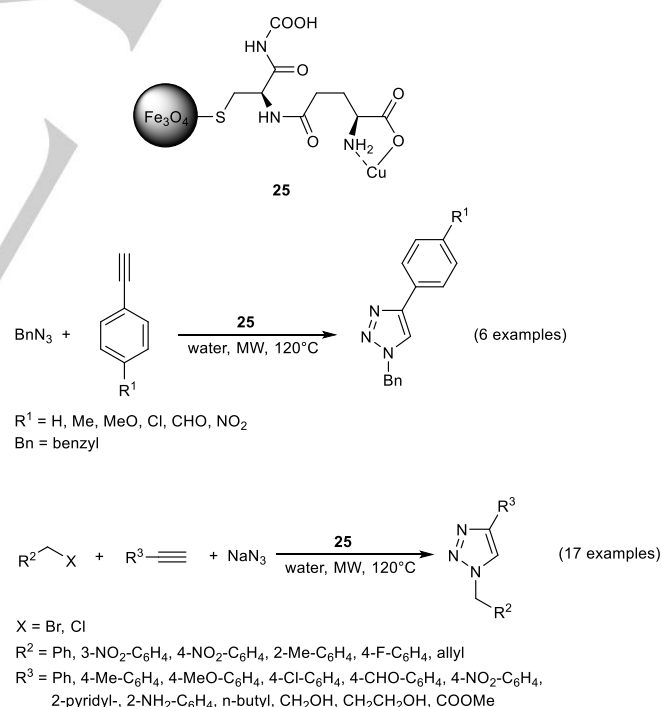

(*)
Ref. 31: water, MW, 120°C, 10 min.
Ref. 80: water, 70°C (BnN$_3$ generated *in situ* by BnBr + NaN$_3$)
Ref. 82: water, r.t., 12 h

Scheme 14. Nanocatalysed benzylazide-phenylacetylene cycloaddition.

Table 2. Nanocatalysed benzylazide-phenylacetylene cycloaddition.

Entry	Nanocatalyst	Combined yield 4-subs + 5-subs	Product ratio 4-subs/5-subs	Ref.
1	None	< 5	—	82
2	Fe(0)	< 5	—	82
3	CuFe$_2$O$_4$	< 5	—	82
4	CuFe$_2$O$_4$	93	100 : 0	80
5	CuFe$_2$O$_4$ + sodium ascorbate	96	100 : 0	82
6	Cu(0)@Fe(0)	93	100 : 0	82
7	Fe$_3$O$_4$	20	50 : 50	31
8	Fe$_3$O$_4$-glutathione	20	50 : 50	31
9	Fe$_3$O$_4$-Cu(0)	80	75 : 25	31
10	glutathione-copper(I)-Fe$_3$O$_4$ (**25**)	99	100 : 0	31

By using the bimetallic glutathione-copper(I)-decorated nanocatalyst **25**, 23 1-benzyl-4-substituted-1,2,3-triazoles were obtained in superheated water by microwave (MW) irradiation with 80-99% yield (Scheme 15).[31] It was possible to obtain these triazoles via one-pot multi component reaction catalysed by **25** starting from the corresponding benzyl bromides or chlorides (Scheme 15). The nanocatalyst **25** was recovered magnetically and reused at least three times without any change in activity.

R^1 = H, Me, MeO, Cl, CHO, NO$_2$
Bn = benzyl

X = Br, Cl
R^2 = Ph, 3-NO$_2$-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$, 2-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, allyl
R^3 = Ph, 4-Me-C$_6$H$_4$, 4-MeO-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-CHO-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$, 2-pyridyl-, 2-NH$_2$-C$_6$H$_4$, n-butyl, CH$_2$OH, CH$_2$CH$_2$OH, COOMe

Scheme 15. Azide-alkyne cycloadditions catalysed by bimetallic glutathione-copper(I)-Fe$_3$O$_4$ nanocatalyst **25**.

The one-pot multicomponent reaction catalysed by CuFe$_2$O$_4$ was performed by the *in situ* generation of the azide from the corresponding activated halides (benzyl or phenacyl bromides or chlorides, 8 substrates) and sodium azide followed by

cycloaddition to the appropriate acetylene (phenyl-, naphthyl- or alkyl-diacetylenes, 8 substrates). 23 Examples of 1,4-disubstituted-1,2,3-triazoles were obtained with 74-93% yield. The copper ferrite nanocatalyst was recovered magnetically and reused three times with little loss of catalytic activity.[80]

As far as suspended Cu(0)/Fe(0) nanocatalysts are concerned, their application to the regioselective azide-alkyne cycloaddition prompted to 28 examples of 4-substituted-1,2,3-triazoles with 49-98 % yield.[81,82] The active nanocatalyst was prepared in two different ways: from iron powder and $CuSO_4$ in deoxygenated water[81] and from $FeSO_4$ + sodium borohydride and $CuSO_4$ in water.[82] In the first case, the cycloaddition between benzylazide and phenylacetylene was completed in six hours after the 15th run at 30°C, and the time conversion curve profiles showed no change of the reaction rate after 10 runs, showing that the copper source can be used multiple times.[81] In the second case the nanocatalyst was recovered with an external magnet and reused under stringent inert conditions up to five times with no appreciable decrease in yield.[82]

5.1.3. Unsupported iron oxide nanoparticles

Since the discovery of the copper(I)-catalysed azide-alkyne "click" reaction, a huge number of 1,4-disubstituted-1H-1,2,3-triazoles have been obtained and, as it is described in section 5.1.1, the nanocatalysed version of such a transformation also gives the same heterocyclic ring.

The use of colloidal nanoparticles of Earth-abundant, first-row transition metal oxides and sulfide, namely magnetite (Fe_3O_4), manganese and cobalt ferrite, ($MnFe_2O_4$, $CoFe_2O_4$), manganese(II) oxide (MnO) and sulfide (α-MnS), were used as catalysts in the cycloaddition between azides and methyl propiolate. Mixtures of regioisomeric 1H-1,2,3-triazoles were always obtained with mild conditions (toluene, 45°C) and good combined yields (62-99%). Unfortunately, compared to the Huisgen-type (thermal) cycloadditions,[83] the catalytic effect of these latter nanoparticles is such to increase the reaction rate without significantly enhancing the regioselectivity in favour of the 4-substituted-1,2,3-triazoles.[84] This behaviour may be ascribed to the reversible formation of a labile intermediate arising from the interaction between the azide and the uncoordinated metal ion at the nanoparticle surface that is able to react with the alkyne faster than the free azide. Density functional theory (DFT) calculations support a mechanistic hypothesis that attributes the increased cycloaddition rate to the adsorption of the azide onto to the nanocatalyst surface. The ferrite nanocatalysts was recovered by an external magnet and reused without significant loss of catalytic activity.
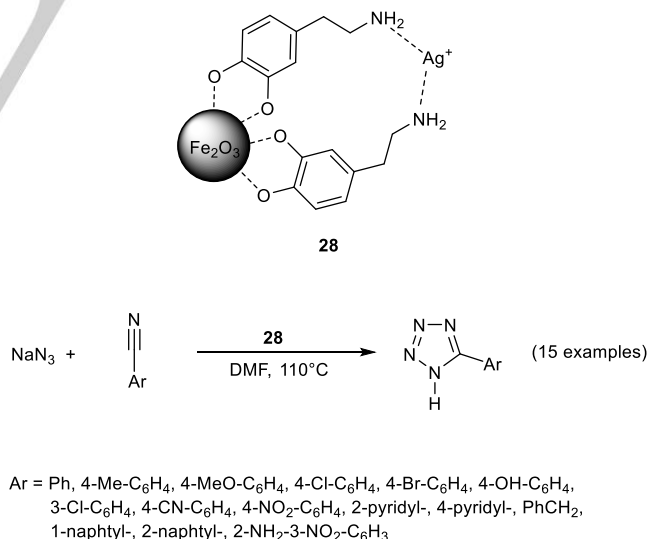
On the other hand, the access to the isomeric 2-substituted-2H-1,2,3-triazoles is still rare.[85] This latter ring type was successfully approached by reacting chalcones with sodium azide in the presence of catalytic amounts of commercially available nano-Fe_2O_3 (<d> < 50 nm), followed by the addition of activated aryl halides. In Scheme 16 is reported the reaction between chalcone **26** and 2-nitro-fluorobenzene, however 19 examples of 2-substituted-2H-1,2,3-triazoles **27** were obtained starting from a set of 12 chalcones and 3 aryl halides with 59-93 % yield.[86] Triazoles **27** were formed via an oxidative cycloaddition. As a proof of this statement, the reaction between **26**, 2-nitro-fluorobenzene and sodium azide was conducted in the absence of oxygen (nitrogen atmosphere) obtaining cycloadduct **27** with 40% yield. Furthermore, no reaction occurred in the absence of the nanocatalyst under aerobic

conditions. To this point, it was concluded that atmospheric oxygen behaves as the oxidant only in the presence of the nanocatalyst. It was also supposed by the Authors that the Fe(III) species could be responsible for the oxidation, and atmospheric oxygen regenerates the catalytically active species by re-oxidation of the low-valent iron intermediates. The Fe_2O_3 nanocatalyst was recovered magnetically and reused three times with little loss of catalytic activity.
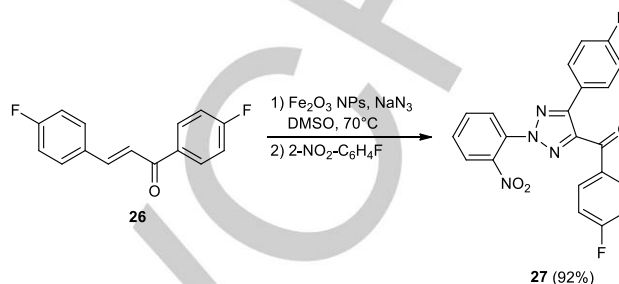
Scheme 16. Synthesis of 2H-1,2,3-triazole **27** from chalcone **26**, sodium azide and 2-nitro-fluorobenzene in the presence of Fe_2O_3 nanocatalyst.

The synthesis of 5-substituted-1H-tetrazoles (15 examples, 70-94% yield) has been pursued by direct cycloaddition between nitriles and sodium azide in the presence of dopamine-silver(I)-decorated maghemite (**28**, Scheme 17).[41] No recycling of the magnetic specie **28** has been attempted in the case of the above reaction. Furthermore, since this transformation is carried out in dimethylformamide at 110°C, the (non-catalytic) thermal pathway can be envisaged. In fact, successful sodium azide-nitrile cycloadditions were carried out in the absence of any catalyst.[87]


Ar = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OH-C_6H_4, 3-Cl-C_6H_4, 4-CN-C_6H_4, 4-NO_2-C_6H_4, 2-pyridyl-, 4-pyridyl-, $PhCH_2$, 1-naphtyl-, 2-naphtyl-, 2-NH_2-3-NO_2-C_6H_3

Scheme 17. Synthesis of 5-substituted-1H-tetrazoles by direct cycloaddition between nitriles and sodium azide in the presence of magnetic species **28**.

5.1.4. Unsupported silver(I) oxide nanoparticles

Nanoscale silver(I) oxide has received much less attention as a catalyst for organic synthesis compared to copper oxides. However, due to the known chemical and crystallographic

similarity of Ag$_2$O and Cu$_2$O, it was perceived that Ag$_2$O nanoparticles could be used as a catalyst for the azide-alkyne cycloaddition. In this respect, colloidal Ag$_2$O nanoparticles coated with oleic acid (<d> = 5.3 nm, σ_d = 1.3 nm) were investigated.[88] By reacting an equimolecular mixture of aryl azides and terminal alkynes in the presence of catalytic amounts of Ag$_2$O nanoparticles, the corresponding 1-aryl-4-substituted-1,2,3-triazoles were obtained with 50-95% yield (9 examples). It is worth noting the loss of regioselectivity of the reactions between electron-poor azides, namely 4-nitrophenylazide, towards methyl propiolate. This behaviour was rationalised by proposing a catalytic cycle in which the key intermediate **29** leads to the corresponding 4-substituted-1,2,3-triazoles. On the basis of the corresponding σ+ Hammett constants, the ability of electron poor 4-nitrophenylazide to act as a ligand may be by far less effective than that of 4-methoxyphenylazide. In the former case the intermediacy of **29** is partly ruled out providing mixtures of the corresponding regioisomers. The Ag$_2$O nanocatalyst was not recovered.
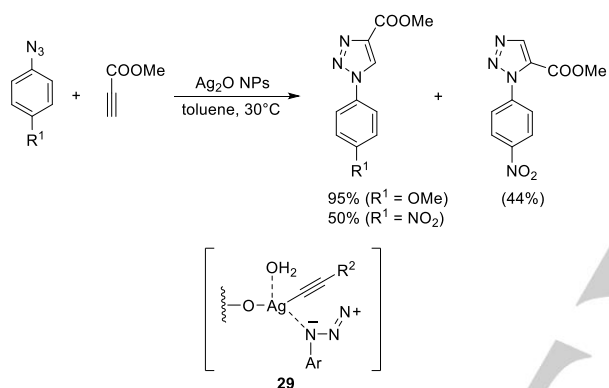
Scheme 18. Cycloaddition between arylazides and methyl propiolate catalysed by Ag$_2$O nanoparticles.

5.1.5. Unsupported miscellaneous nanoparticles

ZnO[89] and Bi$_2$WO$_6$[90] nanoparticles have been used as catalysts in the cycloaddition between benzylazide and β-nitrostyrenes. In both cases the reactions were carried out in water at 80°C giving 1-benzyl-5-phenyl-1,2,3-triazole as the major cycloadduct (16 examples, 79-92% yield). Large amounts of these nanoparticles were required (ZnO: 10 mol%, Bi$_2$WO$_6$: up to 30% mol), and the intervention of a thermal cycloaddition cannot be ruled out in these conditions. To this respect, it is useful to recall that cycloadditions between azides and terminal alkynes in hot water are often regioselective in the absence of any catalytic specie.[91] Anyway, as far as catalyst recyclability is concerned, ZnO and Bi$_2$WO$_6$ nanoparticles were recovered and reused up to six and four cycles, respectively, for the same reaction without loss in the catalytic activity.
A further example of cycloaddition between benzylazide and phenylacetylene was also performed in the presence of Bi$_2$WO$_6$ nanoparticles and bulk copper(II) sulfate/sodium ascorbate giving 1-benzyl-4-phenyl-1,2,3-triazole.[90]

5.2. Supported nanocatalysts

The use of supported nanocatalysts relies upon their robustness and efficiency compared to the unsupported counterparts because of their higher stability and resistance to nanoparticle aggregation. Generally speaking, with the use of supported nanocatalysts the metal loading can be significantly decreased and the catalyst can be recovered and recycled easily, though time-consuming procedures like filtration or centrifugation are required. Furthermore, various kinds of inorganic supports that display high surface area can be used to immobilize metal nanoparticles, namely activated carbon, alumina and montmorillonite, silica coated iron species, metal oxides and organic supports. All the following azide-alkyne cycloadditions are concerned with the use of copper nanocatalysts and will be presented according to the support type.

5.2.1. Carbon as support

(Non-nano) copper(0) on charcoal (Cu/C) was found to be an active catalyst for the "click" cycloaddition between preformed azides and terminal alkynes.[92] In fact, reaction rates experienced an increase when carried out in the presence of triethylamine or by microwawe irradiation, and some substrates reacted rapidly at room temperature. Furthermore, the order of addition of reagents is not important, the catalyst is not air- or moisture-sensitive and is easily recoverable and reusable. Furthermore, the use of carbon-supported nanocatalysts enables the *in situ* generation of the organic azides making the experiments safe, and waste is reduced to a sodium chloride (or bromide) aqueous solution. A one-pot protocol for the three-component reaction between terminal alkynes, sodium azide and alkyl halides in the presences of 1 mol% of copper(I) on carbon as the heterogeneous catalyst was exploited in refluxing water. The Cu(I) nanoparticles immobilised on activated carbon were prepared by a two-step procedure: (*i*) refluxing of the activated carbon with a solution of nitric acid, its subsequent water-washing and vacuum drying, and (*ii*) refluxing of the oxidized activated carbon with a solution of CuI in ethanol. Eighteen examples of 4-substituted-1,2,3-triazoles were obtained with 69-91% yields, and the three-component reaction was suitable for the synthesis of triazolo-azacrown ethers and triazolo-anthraquinones (Scheme 19).[93] The recyclability of Cu(I)/C catalyst was investigated in the reaction between phenylacetylene, benzyl bromide and sodium azide. The Cu(I)/C catalyst was recovered by filtration and was reused without further purification. After ten runs, the recovered Cu/C catalyst was found to contain 9.83% (w/w) of Cu(I), very close to the initial 9.97% (w/w) value (less than 1.40% leaching during all the reaction cycles).
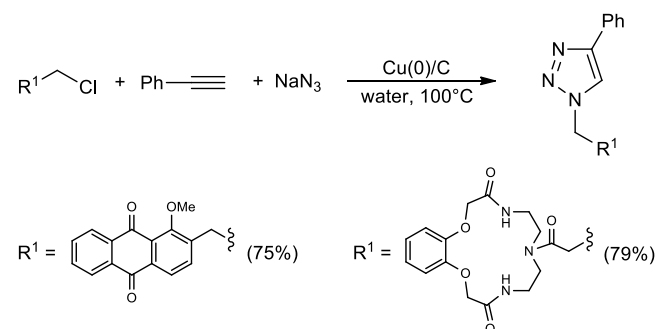
Scheme 19. Synthesis of triazolo-azacrown ethers and triazolo-anthraquinones *via* three component cycloaddition catalysed by Cu(I)/C.

A variety of copper(0) catalysts was prepared by addition of the support to a suspension of Cu(0) nanoparticles generated by copper(II) chloride reduction with lithium metal.[94] Benzyl bromide and phenylacetylene were used as model substrates in the three-component cycloaddition with sodium azide in water to test the activity of the different catalysts (Scheme 20, Table 3). Cu(0) nanoparticles on activated carbon gave the best results in terms of cycloadduct yield after both the first and second run (Scheme 19 and Table 3, entry 2), the catalyst was recovered by filtration and reused, leading to the 1-benzyl-4-phenyl-1,2,3-triazole cycloadduct in quantitative yield along five consecutive cycles. Further 13 examples of this three-component reaction and one example of its intramolecular version were pursued (76-99% yield). The Cu(0)/C catalyst obtained with the electrochemical discharge method of nanometric copper onto amorphous carbon furnished seven further examples (78-98% yield) of the above three-component cycloaddition. The latter catalyst was recovered and reused 5 times without significant decrease in activity.[95]
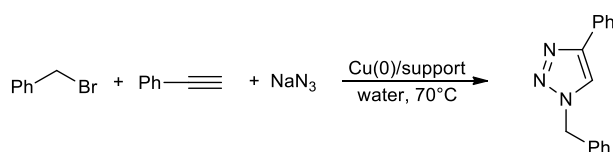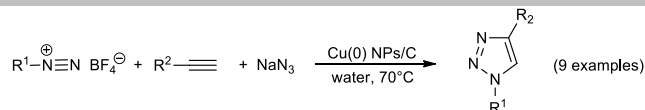

Scheme 20. Cu(0) NPs/supported catalysts in the three-component cycloaddition between benzyl bromide, phenylacetylene and sodium azide in water at 70°C.

Table 3. Cu(0) NPs/supported catalysts in the three-component cycloaddition between benzyl bromide, phenylacetylene and sodium azide in water at 70°C.

Entry]	Support [mol% Cu(0)]	Time (h)	Yield (%)[a]
1	activated carbon [5]	7	100
2	activated carbon [1]	3	100 [100]
3	graphite [5]	14	80
4	graphite [1]	7	90
5	magnetite [1]	9	100
6	alumina [1]	9	100
7	TiO$_2$ [1]	24	74
8	MgO [1]	24	16
9	ZnO [1]	24	57
10	Aluminium silicate [1]	6	100 [19]

[a] In square brackets: second run.

The three-component synthesis of 4-substituted-1,2,3-triazoles was also accomplished in the presence of Cu(0)/C catalyst starting from diazonium salts (9 examples, 71-92% yield) and aromatic amines (10 examples, 64-95% yield) as the azide precursor (Scheme 21).[96]

R^1 = Ph, 4-MeO-C$_6$H$_4$, 4-MeCO-C$_6$H$_4$, 4-CN-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$
R^2 = Ph, 4-MeO-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 2-pyrido, SiMe$_3$
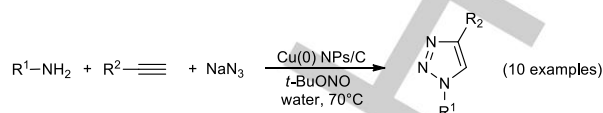
R^1 = Ph, 4-MeO-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 3-Cl-C$_6$H$_4$, 2-Cl-C$_6$H$_4$, 1-naphtyl
R^2 = Ph, cyclohexyl, n-butyl

Scheme 21. Cu(0) NPs/supported catalysts in the three-component cycloaddition between benzyl bromide, phenylacetylene and sodium azide in water at 70°C.

Despite the small amount of catalyst utilised, it was recovered by filtration and reused, leading to 1-benzyl-4-phenyl-1,2,3-triazole cycloadduct in excellent yields along five consecutive cycles. No detectable leaching of copper was observed.

Starting from non-activated alkenes, it was developed a one-pot protocol for the synthesis of 1,2,3-triazoles that is based onto two consecutive click reactions: (*i*) the azidosulfenylation of the carbon-carbon double bond and (*ii*) the azide-alkyne cycloaddition (Scheme 22, 12 examples, 19-91 % overall yield). The former transformation is possible only in the presence of the nanoscale copper(0)/carbon catalyst (Scheme 23, Table 4) obtained by lithium metal reduction of CuCl$_2$ followed by addition of activated carbon. In fact, none of the bulk commercial copper catalysts listed in Table 4 were active in the first step of the overall reaction. Unfortunately, the catalyst reutilization was inefficient due to catalyst poisoning by sulfur.[97]
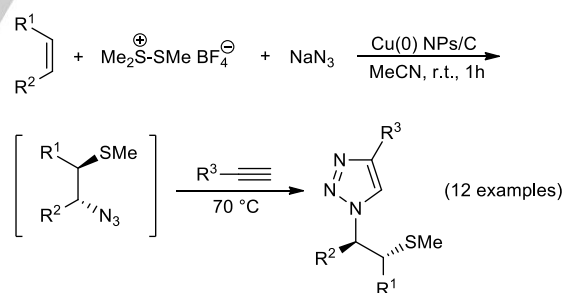
R^1 = R^2 = -(CH$_2$)$_4$-, -(CH$_2$)CH=CH(CH$_2$)-, -CH$_2$OCH$_2$-, (CH$_2$)$_2$CH$_3$
R^1 = H, R^2 = n-hexyl
R^3 = Ph, 4-MeO-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, n-hexyl

Scheme 22. Cu(0) NPs/supported catalysts in the multicomponent azidosulfenylation-azide-alkyne cycloaddition in acetonitrile.
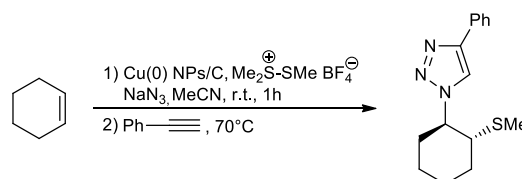
Scheme 23. Cu(0) NPs/supported catalysts in the multicomponent cyclohexene-dimethyl(methylthio)sulfonium tetrafluoroborate-sodium azide-phenylacetylene reaction.

Table 4. Cu(0) NPs/supported catalysts in the multicomponent cyclohexene-dimethyl(methylthio)sulfonium tetrafluoroborate-sodium azide-phenylacetylene reaction.

Entry	Catalyst (Cu, mol%)	Yield (%)
1	Cu metal (1)	—[a]
2	CuCl (1)	—[a]
3	CuCl$_2$ (1)	—[a]
4	Cu$_2$O (1)	—[a]
5	CuO (1)	—[a]
6	Cu(0) NPs/C	81

[a] Not detected.

The feasibility of the cycloaddition between terminal alkynes and organic azides generated *in situ* in aqueous medium was also demonstrated in the presence of a non-colloidal catalyst comprising copper ferrite nanoparticles supported on carbon nanotubes. With this nanocatalyst 18 examples of 4-substituted-1,2,3-triazoles were obtained with 57-92% yield).[98]

An efficient three-component reaction between epoxides, sodium azide and terminal alkynes was exploited in water at r.t. in the presence of catalytic amounts of [meso-tetrakis(2-chlorophenyl) porphyrinato] copper(II) **30** as homogeneous catalyst. 4-Substituted-1,2,3-triazoles were obtained in the presence of such a copper (II) catalyst with 78-93% yields (16 examples). The heterogeneous nanocatalyst **31** was then prepared by impregnation of **30** onto activated multi-walled carbon nanotubes, and the above-mentioned three-component reaction was run in the presence of **31**. The same 4-substituted-1,2,3-triazoles as above were obtained with slightly better yields (84-95%),[99] see Scheme 24 for selected examples. To assess the applicability of both catalysts **30** and **31** on a preparative scale, the reaction between phenyloxirane and phenylacetylene was performed on a 50-mmol scale and was found to proceed similarly to the smaller scale reaction (with catalyst **30**: 85%, with catalyst **31**: 90%, to be compared with the first-row reaction in Scheme 21). In order to investigate the stability of the catalyst **31**, IR spectra were taken on the freshly-prepared catalyst and after ten runs. No notable changes appeared. Furthermore, the catalytic activity of **31** remained nearly unchanged on the basis of cycloadducts yields and with less than 0.40% catalyst leaching after ten runs.

To account for the peculiar catalytic activity of the two copper(II) species **30** and **31**, the Authors asserted that the porphyrinato-copper structure with the central tertiary nitrogen bond, providing electron density at copper, should be much more catalytically active than those in which the porphyrin ligand is not involved (*sic*).[99]
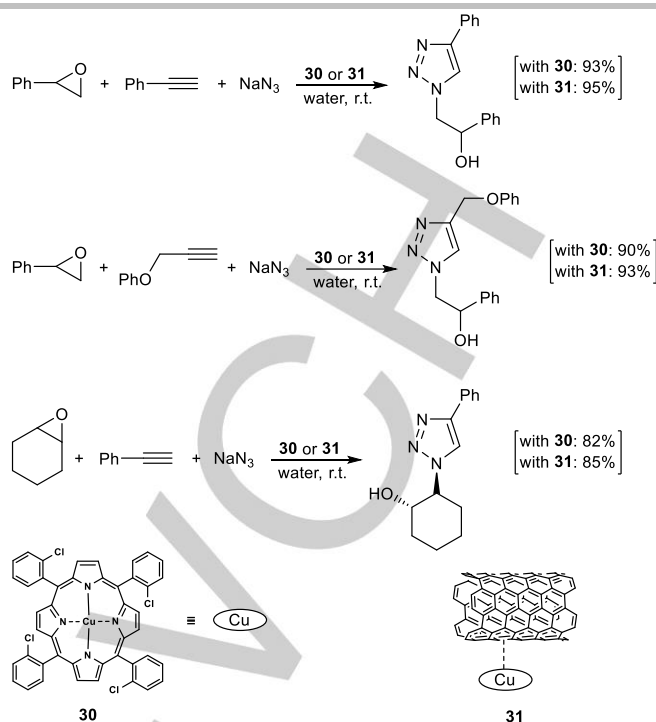
Scheme 24. Porphyrinato-Cu(II) **30** and porphyrinato-Cu(II)@C-nanotubes **31** in the three-component reaction between epoxides, sodium azide and terminal alkynes in water.

5.2.2. Alumina and montmorillonite as supports

Copper(0) nanoparticles on alumina (Al$_2$O$_3$) were used for the preparation of 1,4-substituted-1,2,3-triazoles by the three-component reaction between terminal alkynes, sodium azide and activated alkyl halides. The supported Cu(0) nanoparticles were prepared starting from copper(II) acetylacetonate in the presence of aluminum isopropoxide, that acts both as the reducing agent and the aluminium source. The Cu(0) NPs/Al$_2$O$_3$ catalyst allowed clean reactions for a variety of substrates (9 examples, 5-92% triazole yield). In particular, good yields were obtained for the reaction involving phenylacetylene with different activated alkyl halides, while the reaction outcome of propargyl alcohol was strongly depentent upon the alkyl halide (Scheme 25).[38] The behaviour of these reactions was camparable to that attained with the bulk catalysts Cu(OH)$_x$/Al$_2$O$_3$[100] and Cu(0)/Al$_2$O$_3$ under ball-milling.[101] However, some experiments highlighted the lack of catalyst hitching and its good reusability after three runs. Recycle experiments evidenced that some nanoparticle agglomeration has scarce influence on the reactivity.[38]
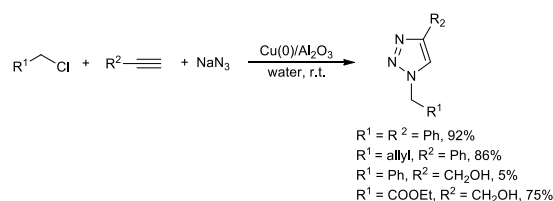
Scheme 25. Alkyl halide-sodium azide-alkyne three component cycloaddition catalysed by Cu(0)/Al$_2$O$_3$.

The cycloaddition between preformed azides and terminal alkynes was carried out in the presence of a catalyst obtained by immobilising Cu(0) nanoparticles on aluminium oxydroxide [AlO(OH)] fiber, obtaining 15 examples of 4-substituted-1,2,3-triazoles with 72-95% yield.[102] Similarly to the above Cu(0)/Al$_2$O$_3$ catalyst, the Cu(0)/AlO(OH) one was prepared by heating at 160°C the appropriate mixture of copper(II) chloride and aluminum *sec*-butoxide. The latter catalyst was recycled five times without significant loss of activity. Montmorillonite belongs to the smectite group, is a clay that possesses a sheet structure with alternating layers of linked silica tetrahedra and alumina octahedra; this layers are interleaved by positively charged alkali or alkaline-earth ions.[103] The modification of such complex structure was carried out by activation with sulfuric acid to generate nanopores able to act as "hosts" for the Cu(0) nanoparticles. The latter catalyst was obtained by impregnation of the modified montmorillonite with copper(II) acetate, followed by reduction with sodium borohydride. The cycloaddition between alkylazides and terminal alkynes was carried out in the presence of the so-obtained heterogeneous catalyst leading to eight 4-substituted examples with 83-95% yield. *Bis*-1,2,3-triazoles **32** and **33** were also obtained (Scheme 26).[104] The recyclability of the Cu(0)/montmorillonite catalyst was investigated in the phenylacetylene/1-azidodecane and the 1,6-heptadiyne/1-azidoadamantane cycloadditions. In both cases the catalyst was recovered by simple filtration and reused for three runs without appreciable loss of the catalytic activity.
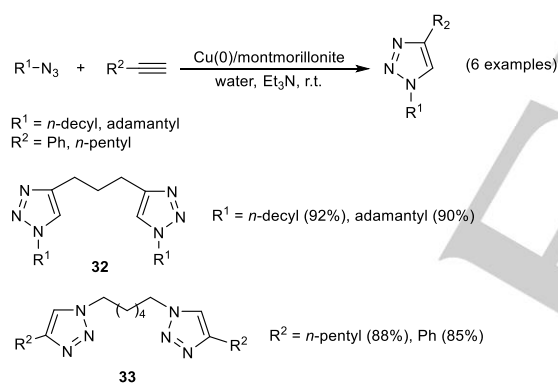
Scheme 26. Alkyl azide-alkyne cycloaddition catalysed by Cu(0)@montmorillonite.

Zeolites are crystalline aluminosilicates showing framework structures that contain regular channels or cavities, these cavities contain water molecules and metal cations usually belonging to group 1 or 2.[103] Copper(I)-doped zeolites have been used as non-nano copper(I)-supported catalysts giving very good results with both preformed azides and in three-component reactions.[105]

5.2.3. Silica-coated iron-containing nanoparticles as supports

A magnetically recoverable catalyst consisting of copper(0) nanoparticles supported on partially-aggregated silica-coated maghemite nanoparticles was prepared by reduction of anhydrous CuCl$_2$ with lithium metal and a catalytic amount of 4,4'-di-*t*-butylbiphenyl as electron carrier in the presence of maghemite nanoparticles. The so-obtained Cu(0) NPs-
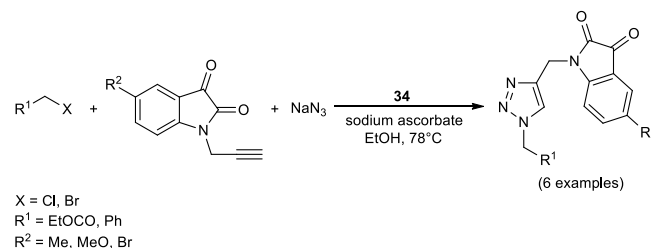
Fe$_2$O$_3$@SiO$_2$ nanocatalyst was effective towards the three component cycloaddition between alkyl halides, sodium azide and terminal alkynes in water (12 examples, 50-98% yield). This copper-based catalyst was also effective towards the Glaser alkyne dimerization and the three-component synthesis of propargylamines under solvent free conditions.[33] The degree of copper leaching in the three-component cycloaddition was below the atomic absorption spectrometry sensitivity threshold, but the study of the catalytic performance over three consecutive cycles of catalyst recovery and reuse was experienced only in the case of the three-component synthesis of propargylamines.

Magnetically separable FeO$_x$@SiO$_2$ nanoparticles decorated with copper(II)-complexed 2-iminopyridine ligand **34** behaved as an efficient nanocatalyst for the three-component reaction between alkylhalides, sodium azide and terminal alkynes which provide 22 examples of 1,4-disubstituted-1,2,3-triazoles (Scheme 27).[106]

The catalyst **34** was obtained by precipitation of mixed iron(III) oxides and hydroxides followed by addition of tetraethyl orthosilicate. The resulting FeO$_x$@SiO$_2$ nanoparticles were then submitted to decoration with 3-aminopropyl-triethoxysilane, condensation with acetyl pyridine and final complexation with copper(II) acetate. The recycling experiments of nanocatalyst **34** were realised for the three-component reaction between benzyl bromide, sodium azide and phenylacetylene. It was possible to recover the catalyst by an external magnet, and after six runs SEM and TEM analyses showed that no significant changes occurred both in morphology and nanoparticle size of the catalyst. However, the isolation yield of 1-benzyl-4-phenyl-1,2,3-triazole cycloadduct steadily decreased from 96% of the first run to 78% of the sixth one.
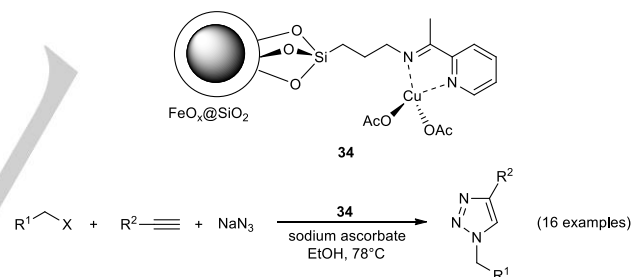
Scheme 27. Alkyl halide-sodium azide-alkyne three component cycloaddition catalysed by FeOx@SiO$_2$ nanoparticles decorated with the copper(II)-complexed 2-iminopyridine ligand **34**.

A composite heterogeneous copper(II) catalyst based on poly(ionic liquid)-coated magnetic nanoparticles was prepared by polymerization of 3-methoxycarbonyl-1-vinylimidazolium chloride in the presence of surface-modified vinyl-functionalized

ferrite nanoparticles. First, the co-precipitation of FeCl$_3$ and FeCl$_2$ in an ammonia solution led to the formation of Fe$_3$O$_4$ nanoparticles (MNPs). Then, a layer of SiO$_2$ was coated on the Fe$_3$O$_4$. Next, the surface of so-obtained Fe$_3$O$_4$@SiO$_2$ nanoparticles was modified with vinyl-functionalized Fe$_3$O$_4$ nanoparticles. Copolymerization with vinyl-ionic liquids was initiated by aza-*bis*-isobutyrronitrile (AIBN) in the presence of 1,4-butane-diyl-3,3'-*bis*-1-vinylimidazolium dibromide (BVD) as a cross-linking agent. During the polymerization, the magnetic Fe$_3$O$_4$ core was entrapped into the cross-linked polymer matrix and covalently attached to the polymer chains. As the final step, copper(II) sulfate was loaded onto the support surface by coordination with free carboxylate groups giving the composite catalyst **35**.

The activity of this catalyst was tested in the three component reaction between primary halides or tosylates, sodium azide and terminal alkynes affording 29 examples of 1,4-disubstituted-1,2,3-triazoles with 82-99% yield (Scheme 28).[40] These reactions were realised in aqueous medium at r.t. As far as the cycloadduct yields are concerned to the benzylbromide-sodium azide-phenylacetylene model reaction, the catalytic performances of **35** was comparable with that obtained in the presence of the previously reported non-nano Cu/SiO$_2$ catalyst.[107] Nanocatalyst **35** was stable and didn't show aggregation, furthermore no copper leaching was observed. As far as catalyst recyclability is concerned, the reaction between benzylbromide, phenylacetylene and sodium azide was studied under optimized reaction conditions. The magnetically-recovered catalyst **35** was reused for ten times without a significant decrease in catalytic activity. However, after the fifth run longer reaction times were required, which is possibly due to the mass loss of catalyst during its separation and washing procedures.
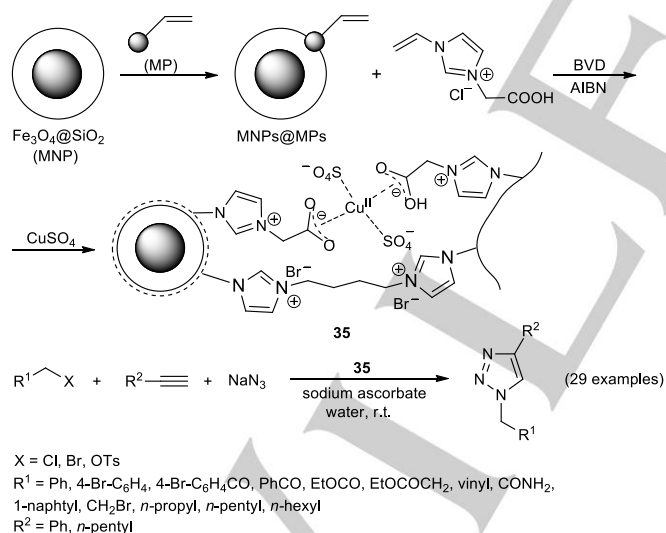
Scheme 28. Alkyl halide-sodium azide-alkyne three component cycloaddition with copper(II)-poly(ionic liquid)-coated magnetic nanocatalyst **35**.

Copper nitride nanoparticles were supported on a mesoporous, silica microsphere containing iron nitride superparamagnetic microsphere. Iron nitride phases containing Fe$_3$N as a major component were formed within the mesoporous silica by using two immiscible iron precursors which were subject to annealing at 700°C in NH$_3$ (Fe$_3$N@SiO$_2$). Then, the formation of the copper

nitride nanoparticles was done by infiltrating a copper source into the Fe$_3$N@SiO$_2$ microsphere by annealing at 250°C in NH$_3$. The final Cu$_3$N/Fe$_3$N@SiO$_2$ catalyst had an average diameter of approximately 500 nm. This catalyst exhibits a very good activity toward the azide-alkyne cycloaddition, giving 15 examples of 1,4-disubstituted-1,2,3-triazoles with 60-91% yields (Scheme 29).[108] The Cu$_3$N/Fe$_3$N@SiO$_2$ catalyst could be separated by an external magnet, and its recycling experiments were tested for the benzylazide-phenylacetylene cycloaddition. After five runs the catalyst was still effective and the copper leaching is less likely to occur during the the consecutive cycloadditions.
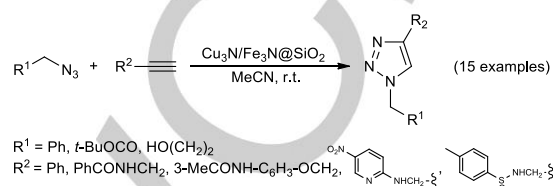
Scheme 29. Azide-alkyne cycloaddition catalysed with Cu$_3$N/Fe$_3$N@SiO$_2$.

5.2.4. Metal oxides

The cycloaddition between benzylazide and phenylacetylene was successfully realised in the presence of ZnO-Cu$_2$O core-branch nanoparticles. This catalyst was prepared by injection of copper(II) acetylacetonate in a hot solution of zinc(II) acetylacetonate hydrate and (poly)vinylpyrrolidone. Prior to injection of the copper precursor, uniform ZnO nanospheres with an average diameter of 101± 4 nm were obtained as aggregates of small particle domains. After the reaction, CuO nanocubes were uniformly generated on the surface of the ZnO spheres. The above cycloaddition was performed in a 2 : 1 water-*t*-butanol mixture at r.t. at different catalyst concentration. In the presence of 3 mol% of ZnO-CuO the cycloaddition was complete after 5 min. with 80% cycloadduct yield. By decreasing the catalyst concentration to 1 mol% the yield dropped to 21% in 10 min. From a mechanistic standopint, it was supposed that the excess amount of phenylacetylene could behave as a reductant able to convert CuO into the Cu$_2$O active catalyst. It was also inferred that ultrasonic irradiation played a critical role in activating the original Cu(II) surface and generating the Cu(I) species. As far as catalyst recyclability is concerned, after five consecutive runs a significant damage from the original core-branch nanostructure was not found.[39]

Gold nanoparticle-catalysed synthesis of 1,4-disubstituted-1,2,3-triazoles in aqueous medium was performed in the presence of nanoporous titania-supported gold(0) nanoparticles. The catalyst was prepared through the deposition-precipitation method by adding the porous TiO$_2$ nanoparticles to a solution of HAuCl$_4$ previously neutralizedto pH 7. Centrifugation followed by calcination at 350°C gave Au(0)@TiO$_2$ nanoparticles. The azide-alkyne cycloaddition carried out in the presence of the Au(0)@TiO$_2$ nanocatalyst gave 25 examples of triazole cycloadducts in 20-30 min. with 87-97% yields, the proposed mechanism is based on a catalytic cycle that strongly resemble the copper(I)-catalysed "click" cycloadditions. Au(0)@TiO$_2$ nanocatalyst was recycled five times in the reaction between phenacyl azide with ethyl propiolate with little loss in cycloadduct yield at a 30 min. reaction time. It is tentatively believed that the catalytic activity was not really diminished, the decrease in

cycloadduct yield could be due to the mass loss of the catalyst.[109]

5.2.5. Organic supports

Some examples of the azide-alkyne cycloaddition have been reported in which the copper nanoparticle catalyst is supported onto organic aggregates, namely diacetylene-polyethylene glycol copolymer micelles and nanocellulose.

A colloidal catalyst was developed through the encapsulation of copper(I) oxide nanoparticles in polydiacetylene micelles. Micelles were first produced from the assembly of amphiphilic units made of a lipophilic diacetylene chain and a polyethyleneglycol polar head (DAPEG). The Cu_2O@DAPEG catalyst was applied to the azide-alkyne cycloaddition carried out in aqueous medium obtaining 12 examples of 1,4-disubstituted-1,2,3-triazoles with 40-99% yields. The reaction did not require heating or a controlled atmosphere. Recycling experiments were performed on the cycloaddition between *S*-azidomethyl thiophenol and phenylacetylene, four subsequent cycloadditions did not evidenced any loss of catalyst activity.[46]

A methodology based upon the use of copper(0) nanoparticles supported on nanocellulose [Cu(0)NPs/NC] was fruitful in the synthesis of 1,4-disubstituted-1,2,3-triazoles carried out in glycerol as the solvent at r.t. (14 examples, 68-99% yields).[110] To prepare the Cu(0) nanoparticles on nanocellulose, an aqueous nanocellulose suspension was added with $CuSO_4$. Copper reduction with hydrazine followed by drying at 100°C gave well dispersed nanoparticles with average particle size of 6-7 nm. The recyclability of Cu(0)NPs/NC was tested in the cycloaddition between phenylacetylene and benzyl azide for five runs. The activity of the catalyst showed a little decrease in terms of the cycloadduct yield from 99% (first run) to 90% (fifth run). No significant copper leaching was observed (ICP analysis). Naturally-occurring cellulose has also been employed as a support for the immobilization of copper(I) ions in order to catalyse the azide-alkyne cycloaddition in water at r.t. Very good cycloadducts yields were obtained, and the non-nano catalyst was recovered and reused for five runs.[111] Similar performance occurred with a (non-nano)copper-chitosane catalyst.[112]

6. Conclusions

The applications of nanoparticle-based catalysts to the 1,3-dipolar cycloadditions of various dipolar species, namely azomethine-ylides and -imines, nitrone, nitrilimines and azides were summarised. As general consideration, all the catalysts displayed good performances in terms of cycloadduct yield, and very often the cycloaddition regioselectivity leads to a single product. This is particularly true in the case of copper-based catalysts, which behave as a genuine "click" additive. The advantages by operating with unsupported nanocatalyst rely upon their easy preparation. However, nanoparticle dissolution sometimes prevented the catalyst recovery in the case of non-magnetic nanoparticles. To this respect, non-magnetic nanoparticles supported onto an inorganic or organic core can be easily filtered off from the reaction mixture. Compared to their unsupported counterpart, supported nanoparticles are advantageous since: (*i*) low metal loading is required, (*ii*) multicomponent cycloadditions can be realised, and (*iii*) the cycloadditions can be carried out in pure water.

In nearly all the reactions reviewed, the performance of nanoparticle-based catalysts was superior compared to

commercial bulk catalysts; this behaviour should be due to the nanometric dimension of the active nanoparticles.

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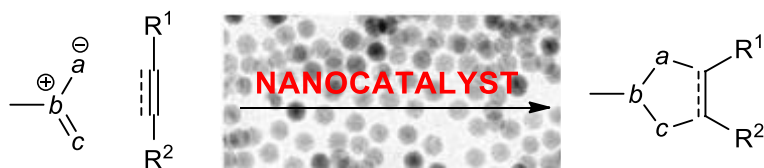
This first attempt to cover the whole field of inorganic nanocatalysts applied to 1,3-dipolar cycloadditions gives emphasis to the various metals involved, their structure, characterisation and recyclability and, when interesting, their preparation. Although intended for an audience of organic chemists, emphasis has been given to improvements with respect to cycloadditions performed with the usual (non-nano) catalysts. For the sake of clarity, the results were summarised according to the 1,3-dipole type, namely azomethine ylides, azomethine imines, nitrone, nitrilimine and azides.

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