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"Click Chemistry" in Zeolites: Copper(I) Zeolites as New Heterogeneous and Ligand-Free Catalysts for the Huisgen [3+2] Cycloaddition

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Abstract: For the first time, copper(I)-exchanged zeolites were developed as catalysts in organic synthesis. These solid materials proved to be versatile and efficient heterogeneous, ligand-free catalytic systems for the Huisgen [3+2] cycloaddition. These cheap and easy-to-prepare catalysts exhibited a wide scope and compatibility with functional groups. They are very simple to use, easy to remove (by filtration), and are recyclable (up to three times without loss of activity). Investigations with deuterated alkynes and deuterated zeolites proved that this Cu^I-zeolite-catalyzed "click" reaction exhibited a mechanism different from that reported for the Meldal–Sharpless version.

Keywords: click chemistry · copper · cycloaddition · heterogeneous catalysis · zeolites

Introduction

The "click chemistry" term, first proposed by Sharpless et al.,[1] has been coined for reactions that: "*are modular, wide in scope, high yielding, create only inoffensive by-products (that can be removed without chromatography), are stereospecific, simple to perform and that require benign or easily removed solvent.*" Not surprisingly, such criteria are very close to those of green chemistry and, until now, only a few processes meeting these requirements have been identified.[1,2] In this context, the copper-catalyzed 1,3-dipolar cycloaddition of alkynes and azides that yields 1,2,3-triazoles is undoubtedly the premier example of a click reaction.

Originally disclosed by Huisgen, the noncatalyzed cycloaddition of alkynes and azides required high temperatures and usually gave a mixture of regioisomeric triazoles in variable yields.[3] Sharpless[4] and Meldal[5] independently reported that copper(I) catalysis significantly enhances the cycloaddition between alkynes and azides, exclusively affording 1,4-disubstituted 1,2,3-triazoles in very good yields even at room temperature. Although recent mechanistic aspects have suggested copper acetylides as key intermediates in this reaction, the in situ formation of such intermediates is not unambiguously proven.[6]

With high regioselectivity, 100 % atom economy, and convenient product isolation, the click version of Huisgen cycloaddition has been increasingly used in various applications ranging from chemical[7] and combinatorial[8] synthesis, bioconjugation, and biology[9] to materials science, especially polymer and dendrimer synthesis.[10] For example, this reaction has been applied to the formation of anti-HIV compounds,[11] selective β_3 adrenergic receptor inhibitors,[12] antibacterial compounds,[13] potent antihistaminic compounds,[14] as well as agrochemicals.[15] 1,2,3-Triazoles themselves have also found extensive industrial use as corrosion inhibitors,[16] dyes,[17] and photostabilizers.[18] Furthermore, it is worth noting that triazoles could become important pharmacophores in future drug discovery because they are stable, nonharmful, and could mimic peptide bonds from a steric and electronic point of view, without the same sensitivity towards hydrolytic cleavage.[1b,19]

The copper(I) species required in the catalyzed version of the Huisgen cycloaddition are either added directly as cuprous salts, usually with stabilizing ligands,[5,20] or more often generated from copper(II) salts with reducing agents.[4] Metallic copper[21] or clusters[22] can also be employed, but although an inexpensive copper source, the corresponding cat-

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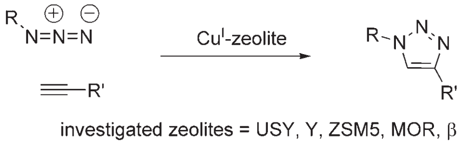
alytic systems present some drawbacks: 1) oxidative agents are required, 2) reactions are relatively slow, and 3) a significant amount of catalyst is necessary. As copper(I) salts are quite prone to redox processes, nitrogen- or phosphorus-based ligands must be added to protect and stabilize the active copper catalyst during the cycloaddition reaction. Nevertheless, formation of undesired byproducts, primarily diacetylenes and bistriazoles, was often observed.[4,23]

These problems and the wide applicability of this reaction led us to explore the possibility of an attractive click-compatible heterogeneous version. As click chemistry mediated by a source of heterogeneous copper(I) is very rare,[21,22,24] we looked for such catalysts and focused on zeolites in connection with our interest in solid acid-catalyzed chemistry, as well as in superacid-mediated organic transformations.[25] In this context, copper(I)-modified zeolites attracted our attention, these solid materials having been recently described and characterized but surprisingly never used for organic transformations.[26]

In continuation of our preliminary results,[27] herein we report in more detail the scope and limitations of this first click chemistry in zeolites, as well as some evidence for the mechanism of this copper(I)-zeolite-catalyzed Huisgen reaction (Scheme 1).



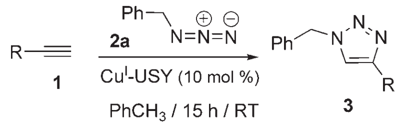
Scheme 1. Copper(I)-zeolite-catalyzed Huisgen reaction.

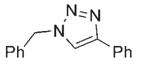
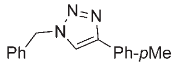
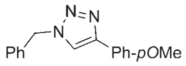
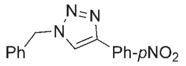
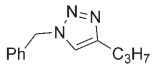
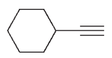
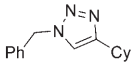
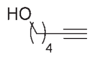
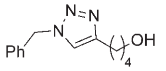
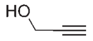
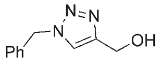
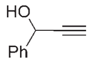
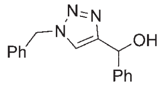
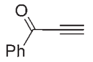
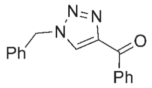
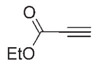
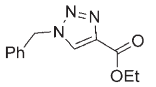
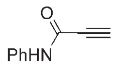
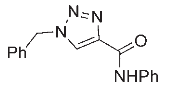
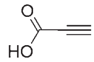
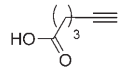
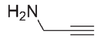
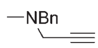
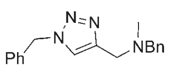
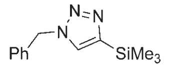
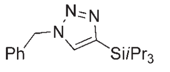
Results and Discussion

Scope and compatibility with functional groups: From a practical point of view, copper(I)-modified zeolites must accept a variety of substrates as large as possible, which have different sizes and carry different functional groups. Therefore, the scope of the copper(I)-zeolite-catalyzed Huisgen reaction was explored with Cu^I-USY, which proved to be the best catalyst (see next section and Table 3).

In one series of experiments, terminal alkynes bearing different functional groups **1a–r** were submitted to benzyl azide **2a** in the presence of Cu^I-USY as catalyst (Table 1). As illustrated by the reaction of **1a** and of its substituted analogues **1b–d** (Table 1, entries 1–4), aryl substituents allowed for an efficient cycloaddition, giving the expected adducts **3a–c** as single regioisomers in high to excellent yields (Table 1, entries 1–4). Contrarily to the now "classical" click reaction,[4,5] electron-donating or -withdrawing groups clearly alter the reactivity of the acetylenic partner. Electron-donating groups decreased yields and the more electron donating the group, the lower the yield (Table 1, entry 3 vs. 2 vs. 1). The presence of a strong electron-withdrawing group on the benzene moiety also decreased yields (Table 1, entry 4 vs. 1). These results were reminiscent of the typical delicate

Table 1. Cu^I-zeolite-catalyzed cycloadditions of benzyl azide **2a** with various alkynes.[a]



Entry	Alkyne		Product		Yield [%][b,c]
1	Ph—≡	**1a**		**3a**	83
2	*p*-MePh—≡	**1b**		**3b**	76
3	*p*-MeOPh—≡	**1c**		**3c**	69
4	*p*-O_2NPh—≡	**1d**		**3d**	64
5	C_3H_7—≡	**1e**		**3e**	85
6					traces[d]
7		**1f**		**3f**	89[e]
8		**1g**		**3g**	88
9		**1h**		**3h**	64
10		**1i**		**3i**	83
11		**1j**		**3j**	52[f]
12		**1k**		**3k**	76[f]
13		**1l**		**3l**	87
14		**1m**	–	–	0[d]
15		**1n**	–	–	0[d]
16		**1o**	–	–	0[d]
17		**1p**		**3m**	92
18	Me_3Si—≡	**1q**		**3n**	traces[d]
19	*i*Pr_3Si—≡	**1r**		**3o**	traces[d]
20	Me_3Si—≡—Ph	**1s**	–	–	–
21	Me_3Si—≡—C_4H_9	**1t**	–	–	–
22	H_7C_3—≡—C_3H_7	**1u**	–		–

[a] Reagents and reaction conditions: **1** (1.2 equiv), **2a** (1.0 equiv), 1 M solution concentration, 10 mol % Cu^I-USY,[31] toluene, 15 h, room temperature. [b] Yields of isolated pure product. [c] Only the 1,4-adduct was formed and isolated unless otherwise noted. [d] Mainly recovery of the starting materials. [e] Reaction performed at 80 °C. [f] Unidentified byproducts were formed.

balance of frontier orbital controls in the noncatalyzed cycloaddition of azides,[28] but without the associated regioselectivity variations since only 1,4-adducts were produced in our conditions whatever the alkynes.

Alkyl-substituted acetylenes reacted efficiently when the alkyl chain was linear (Table 1, entry 5), but very slowly at room temperature when the chain was branched (Table 1, entry 6). However, at higher temperature, complete conversion was restored and the regioselectivity was still in favor of the 1,4-adduct, the latter being again the sole product isolated (Table 1, entry 7). Such behavior is not surprising in zeolites, for which the internal shape dramatically influences chemical transformations.[29]

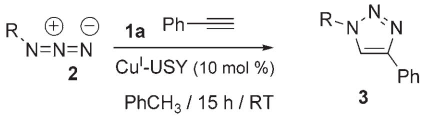
Hydroxy-substituted alkynes, such as **1g–i**, also gave the expected adducts **3g–i** as single regioisomers in good to high yields (Table 1, entries 8–10). The conjugated ketone **1j** seemed to decompose under the reaction conditions, even at room temperature, and byproducts were formed. Even if the expected triazole could be isolated, the yield of triazole **3j** was therefore lower (Table 1, entry 11). It is worth noting that terminal ynones are known to be particularly sensitive compounds.[30] However, the corresponding esters or amides, **1k** or **1l**, proved fully compatible with the reaction conditions. Although the conjugated amide **1l** was converted very efficiently into the 1,4-disubstituted triazole **3l** (Table 1, entry 13), the ester **1k** gave some side products but was still very effective, giving the triazole **3k** in good yield (Table 1, entry 12).

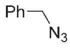
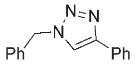
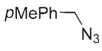
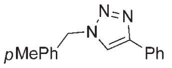
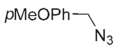
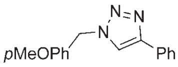
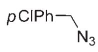
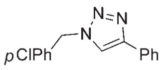
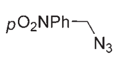
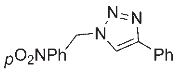
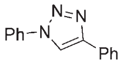
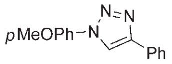
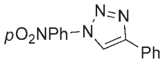
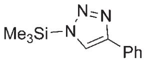
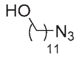
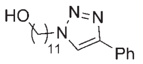
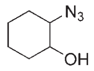
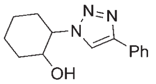
Not surprisingly, free acetylenic acids did not react under these conditions, even when the acid function was far from the reactive acetylenic moiety as for **1n** (Table 1, entries 14 and 15). The free carboxylic acid function probably interacted with the zeolite framework and the starting materials were recovered. For similar reasons, free acetylenic amines did not react (Table 1, entry 16) but protected ones, such as **1p**, were easily converted to the expected triazole **3m**, again as a single regioisomer, in excellent yield (Table 1, entry 17). Acetylenes silylated with either a small or a large group to scrutinize a possible size discrimination (respectively **1q** and **1r**) led only to small amounts of the expected triazoles **3n** and **3o** (Table 1, entries 18 and 19).

Disubstituted acetylenes, either silylated (**1s**, **1t**) or alkylated (**1u**), did not react under these conditions, the starting materials being recovered (Table 1, entries 20–22). Note that only two examples of Cu-catalyzed cycloaddition reactions of internal alkynes are known so far.[20d,e]

In a second series of experiments, various azides bearing different groups **2a–k** were submitted to phenylacetylene **1a** in the presence of Cu^{I}-USY as catalyst (Table 2). Electron-donating or -withdrawing groups on benzyl azides only slightly affected the reactivity (Table 2, entries 2–5 vs. 1). Nevertheless, electron-donating groups slightly favored the reaction, increasing yields, and it seems that the more electron donating the group, the higher the yield (Table 2, entry 3 vs. 2 vs. 1). Electron-withdrawing groups slightly disfavored the reaction, lower yields being obtained. Within these groups, chlorine exhibited the largest effect (Table 2, entry 4 vs. 5). Nevertheless, a single regioisomer was still produced whatever the substitution and yields of isolated products remained good to excellent (67–94 %).

Table 2. Cu^{I}-zeolite-catalyzed cycloadditions of phenylacetylene **1a** with various azides.[a]



Entry	Azide		Product		Yield [%][b,c]
1		**2a**		**3a**	83
2		**2b**		**3p**	91
3		**2c**		**3q**	94
4		**2d**		**3r**	67
5		**2e**		**3s**	76
6	Ph–N$_3$	**2f**		**3t**	59
7	pMeOPh–N$_3$	**2g**		**3u**	61
8	pO$_2$NPh–N$_3$	**2h**		**3v**	traces[d]
9	Me$_3$Si–N$_3$	**2i**		**3w**	< 10[d]
10		**2j**		**3x**	78
11		**2k**		**3y**	63

[a] Reagents and reaction conditions: **1a** (1.2 equiv), **2** (1.0 equiv), 1 M solution concentration, 10 mol % Cu^{I}-USY,[31] toluene, 15 h, room temperature. [b] Yields of isolated pure product. [c] Only the 1,4-adduct was formed and isolated unless otherwise noted. [d] Mainly recovery of the starting materials.

In contrast with these results and with those of the first series (Table 1, entries 2–4 vs. 1), when the phenyl group is directly linked to the reactive azide, electronic effects are more pronounced (Table 2, entries 6–8 vs. 1–5) and they significantly alter the reactivity. Phenyl azide **2f** or its analogue with a *para*-methoxy group **2g** gave the expected triazoles **3t** and **3u** as single regioisomers but with significantly lower yields than benzyl azide **2a** (Table 2, entries 6–7 vs. 1). With a strong electron-withdrawing group, almost no reaction was observed and only traces of the expected triazole **3v** were detected (Table 2, entry 8 vs. 6 and 7). In a similar way, trimethylsilyl azide **2i** yielded only a small amount of the corresponding triazole **3w** (Table 2, entry 9).

As in the other series (Table 2 versus Table 1), alkyl azides react very efficiently when they are primary, but slightly less when they are secondary, both reacting with a very high regioselectivity (Table 2, entries 10 and 11). Indeed, the single 1,4-adduct **3x** was isolated in high yield from the reaction of 11-azidoundecanol **2j** (Table 2, entry 10), whereas the secondary 2-azidocyclohexanol **2k** only gave the 1,4-disubstituted triazole **3y** but in lower yield (Table 2, entry 11). As before, the bulkiness of the reagents seemed to affect their reactivity, but not the regioselectivity of the cycloaddition.

These series of results clearly show that the scope of this heterogeneous version of the Huisgen "click" reaction is very broad, the reaction being as compatible with functional groups as the Meldal–Sharpless version. Moreover, the recovery of the products proved to be greatly facilitated, because filtration and solvent evaporation usually provided pure 1,4-disubstituted triazoles. The copper(I) zeolite click reaction is thus often easier and more practical, as well as more general than the procedures now commonly used for the Huisgen click reaction.

Catalyst survey: Although protection of copper(I) ions by zeolite frameworks was already established,[26] we addressed the question of the stability of such a copper(I) reagent as catalyst in organic reactions. Keeping the Cu^{I} zeolites under air changed their aspect (color changed from brown to greenish) but did not alter their reactivity. Indeed, Cu^{I}-USY was still active as catalyst after prolonged air exposure (Figure 1). It is nevertheless worth noting that in this case, undesirable byproducts[32] were detected in small amounts, slightly lowering yields, contrarily to catalysts not exposed to air (Figure 1). As a consequence, even if the surface of the catalyst clearly evolved after prolonged air exposure, these results clearly showed the effective stabilization of copper(I) species by the zeolite framework but also suggested that the reaction is occurring inside the zeolite framework.

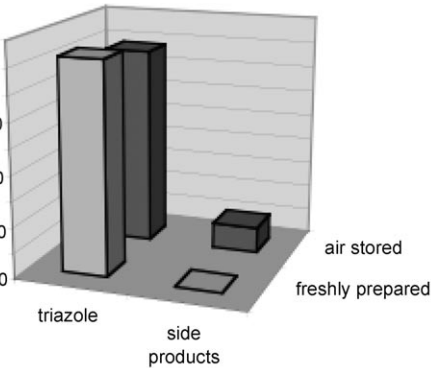


Figure 1. Influence of the copper(I) zeolite storage on the catalyzed Huisgen reaction between **1a** and **2a** to give **3a**.

Besides ease of handling and purification, another eco-friendly interesting aspect of heterogeneous catalysts relies on catalyst recovery and recycling. To look at this aspect, we performed several times the reaction between **1a** and **2a** with the same Cu^{I}-USY catalyst, the latter being filtered and reused after each run. As shown in Figure 2, the Cu^{I}-USY catalyst could be recycled up to three times without significant loss of activity (runs 1–3). However, after the fourth reuse of the catalyst, the catalyst efficiency dramatically decreased (run 5 vs. runs 1–4).

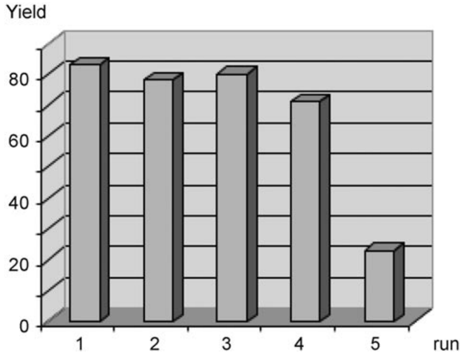


Figure 2. Recovery studies: cycloaddition of **1a** to **2a** successively catalyzed by the same recovered Cu^{I}-USY.

In parallel, we examined whether leaking of active species from the zeolite framework is occurring or not. To do so, Cu^{I}-USY was suspended with the reaction solvent (toluene) and stirred for 2 h, and the resulting suspension was filtered, which led to a clear and colorless solution. Phenylacetylene **1a** and benzyl azide **2a** were added. After stirring overnight at room temperature, the starting materials were the main compounds identified but the cycloadduct **3a** could be detected, although in low amount ($\leq 5\%$; Figure 3). Control experiments revealed that no traces of **3a** could be detected without Cu^{I}-USY catalyst or with untreated USY, and thus it seems that some residual Cu active species are leaking from the Cu^{I}-exchanged USY, catalyzing the cycloaddition but at a rate by far slower than the Cu^{I}-USY-catalyzed reaction (<5 vs. 83% yield after 15 h). The question, under investigation, is to know whether any leaked Cu^{I} species are coming from the outer surface of the catalyst or from its internal volume.

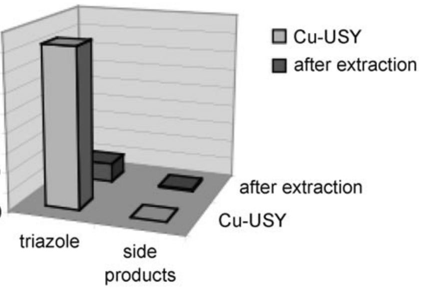


Figure 3. Leaking studies: comparison of the cycloaddition of **1a** to **2a** in the presence of either Cu^{I}-USY or a solution resulting from Cu^{I}-USY extraction.

Mechanistic investigations: For a better understanding of this reaction we embarked on mechanistic studies, and sought clues on the role of zeolite structures and on the mechanism itself.

Zeolites are solid acids mainly characterized by their topologies (cage or channel type), pore size (typically 6 to 8 Å), and acidity (correlated to the Si/Al ratio).[33] To look for correlations between structure and catalytic properties, five representative zeolites, H-USY, H-Y, H-MOR, H-ZSM5, and H-β, were modified by CuCl treatment according to a reported solid-state exchange procedure.[34] Their behavior in the Huisgen reaction was screened with the archetypal cycloaddition of phenylacetylene **1a** with benzyl azide **2a** (Table 3).

Table 3. Behavior of Cu^I zeolites in the cycloaddition of **1a** to **2a**.[a]

Entry	Catalyst	Temperature [°C]	Time [h]	Yield [%][b]	Acidic sites number [mmol g^{-1}]	Pore diameter [Å]	Topology type
1	Cu^I-Y	RT	15	68	6.67	7.4×7.4	cage
2	Cu^I-USY	RT	15	83	4.39	7.4×7.4	cage
3	Cu^I-MOR	RT	15	69	1.48	6.5×7.0 3.4×3.8	channel
4	Cu^I-ZSM5	RT	15	63	1.04	5.1×5.5 5.3×5.6	channel
5	Cu^I-β	RT	15	47	0.90–1.23	7.6×6.4 5.5×5.5	channel
6	Cu^I-Y	110	5	75	6.67	7.4×7.4	cage
7	Cu^I-USY	110	5	87	4.39	7.4×7.4	cage
8	Cu^I-MOR	110	5	79	1.48	6.5×7.0 3.4×3.8	channel
9	Cu^I-ZSM5	110	5	79	1.04	5.1×5.5 5.3×5.6	channel
10	Cu^I-β	110	5	73	0.90–1.23	7.6×6.4 5.5×5.5	channel
11	H-USY	RT	15	–[c]	6.67	7.4×7.4	cage

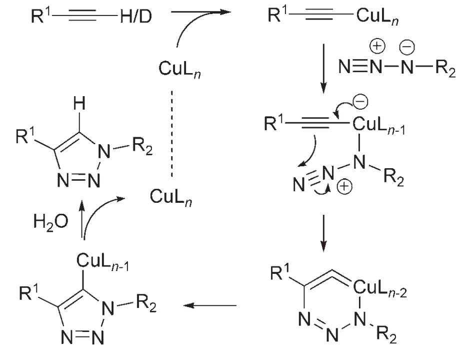
[a] Reagents and reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv), 1 M solution concentration, 10 mol% catalyst,[31] toluene. [b] Yields of isolated pure product **3a** after complete conversion unless otherwise stated. [c] Mainly recovery of the starting materials.

If one considers that copper ions exchanged protons during CuCl treatment of the zeolite,[34] it was surprising not to see a clear correlation between the number of active sites and yields. From 1 to 6 mmol g^{-1}, the yields only slightly varied from 63 to 69% at room temperature and from 73 to 79% at reflux, except for Cu-USY (Table 3, entry 2 vs. 1, 3–5 and 7 vs. 6, 8–10). At room temperature, the channel-type zeolites appeared less efficient than the cage-type zeolites (Table 3, entries 4, 5 vs. 1, 2), the Cu-MOR being nevertheless as good as Cu-Y (Table 3, entry 3 vs. 1). As expected, these differences vanished at reflux, and only Cu-β remained a less effective zeolite whatever the temperature (Table 3, entries 5 vs. 1–4 and 10 vs. 6–9). Clearly, the modified USY seemed the best compromise between number of sites and topology; its efficiency as catalyst was revealed by a net increase in yields whatever the temperature (Table 3, entries 2 vs. 1, 3–5 and 7 vs. 6, 9–10). A control experiment with unmodified USY highlighted the key role of copper since no transformation occurred under these conditions (Table 3, entry 11 vs. 2). Therefore, the zeolite framework alone is not constraining and activating the reagents enough and no reaction occurred, in contrast to organic encapsulating systems known to promote the reaction and favor the 1,4-regioisomer in non-copper-catalyzed Huisgen cycloaddition.[35]

Incorporation and stability of copper(I) ions in the zeolite framework have been established,[26] but we nevertheless tried to get a better view of the H/Cu exchange process. To do so, we applied the H/D titration method that we developed for the determination of acidic sites in zeolites.[31,36] The catalyst was activated at 350 °C under N_2 flow prior to titration to remove adsorbed water and any other molecules that could have diffused into the zeolite pores.

This H/D titration method proved to be very effective and allowed us to quantify the number of acidic sites exchanged in the copper(I)-modified zeolites. For example, native USY contained 3.71 mmol of H^+ per gram of solid, but after treatment with CuCl at 350 °C, its number of acid sites decreased to 0.81 mmol of H^+ per gram. This result revealed that exchange of H^+ by Cu^+ indeed took place and its extent was around 78%.

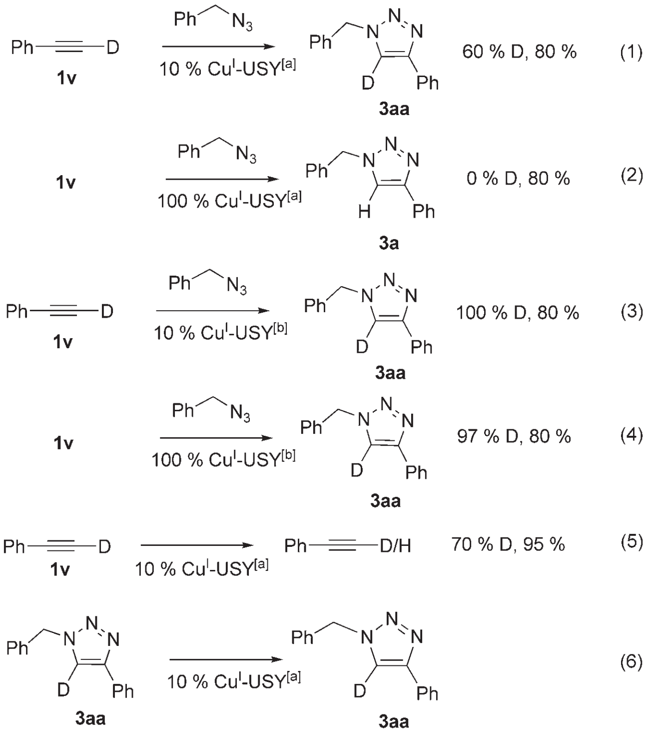
To get a deeper insight into the mechanism of the present copper(I)-zeolite-catalyzed reaction, experiments with deuterated samples were performed. The mechanism proposed for the copper(I)-catalyzed Sharpless–Meldal version of the Huisgen reaction relies on the intermediate formation of copper acetylides (Scheme 2).[6] Therefore, if such species



Scheme 2. Proposed mechanism of the copper(I)-catalyzed Sharpless–Meldal version of the Huisgen reaction.[6]

were also formed within zeolites, deuteroalkynes would not give deuterated triazoles.

For this study, the commercially available deuterophenylacetylene **1v** was used and submitted to copper(I)-modified USY. The same experiments were then repeated with a deuterated copper(I) zeolite.[37] The results of these experiments are compiled in Scheme 3.



Scheme 3. Copper(I)-zeolite-catalyzed cycloadditions with either deuterated alkyne or deuterated zeolite. a) from regular zeolite; b) from deuterated zeolite.

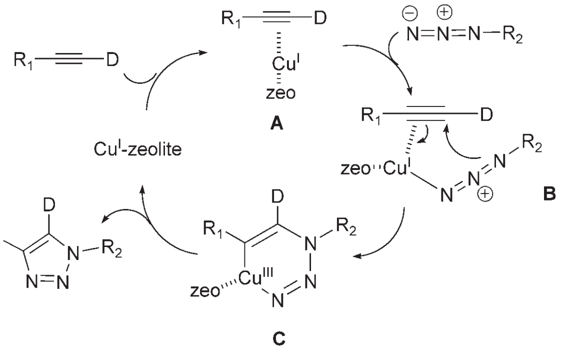
When deuterophenylacetylene **1v** was placed in the presence of benzyl azide in our standard catalytic conditions, the triazole **3aa** was obtained with a yield similar to that obtained with phenylacetylene (see Table 1, entry 1). Interestingly, NMR spectra revealed the presence of vinylic deuterium together with proton, the ratio being in favor of the deuterated triazole (60:40; Scheme 3, [Eq. (1)]). The product was still deuterated after the reaction, and thus the intermediate formation of copper acetylide as suggested in the "classical" Cu click reaction (Scheme 2)[6] is *not the major* pathway in the zeolite version.

Control experiments with deuterated adducts showed that no exchange occurred in such heterocycles under these conditions (Scheme 3, [Eq. (6)]). However, control experiments revealed that deuterated phenylacetylene **1v** undergoes H/D exchange (Scheme 3, [Eq. (5)]), probably with residual acidic protons of the copper(I)-exchanged zeolite. As demonstrated above, the copper(I) zeolite prepared at 350 °C still contains 20 % of protons in its active sites. Therefore, these protons could be responsible for the H/D exchange observed with deuterophenylacetylene.

To check this hypothesis, deuterophenylacetylene **1v** was submitted again to benzyl azide but in the presence of a stoichiometric amount of copper(I) zeolite. In this case, the triazole obtained did not contain deuterium, as expected if H/D exchange occurred (Scheme 3, [Eq. (2)]).

If the starting zeolite is already deuterated,[37] no H/D exchange would be possible and the deuterium label within the starting material should stay during the reaction if no other process occurs. As expected, copper(I) zeolite obtained from a deuterated zeolite catalyzed the click reaction without any loss of deuterium, whatever the amount of catalyst used (Scheme 3, [Eqs. (3) and (4)]). Therefore, this set of results clearly showed that the mechanism of the zeolite-catalyzed Huisgen reaction is different from the Meldal–Sharpless version, and *did not involve copper acetylide.*

H/D exchanges of terminal alkynes are known to be accelerated in the presence of metal salts, especially with silver salts. It has been demonstrated that π coordination is responsible for this effect.[38,39] It is therefore possible that, within the Cu zeolite framework, formation of a π complex occurred between the alkyne and copper(I) ions linked to the zeolite framework (Scheme 4, **A**). Such coordination will favor the H/D exchange and thus explains the results observed (Scheme 3, [Eqs. (1) and (2)]).



Scheme 4. Proposed mechanism for copper(I)-zeolite-catalyzed cycloadditions.

More interestingly, this π coordination helped the understanding of what could happen within zeolites. Indeed, further coordination of an incoming azide to a copper ion linked to the zeolite framework could be envisaged. This would lead to the formation of a new complex where the triple bond and the azide are coordinated to copper (**B** in Scheme 4). This complex could evolve in a process similar to *syn* nucleophilic addition to a π complex (for example, carbocupration). The azide would thus add to the terminal end of the coordinated alkyne, leading to a metallacycle (**C** in Scheme 4). Reductive elimination would then give the triazole adduct, regenerating the copper(I) active species linked to the zeolite. Note that a similar mechanism has recently been proposed for a Ru-catalyzed version of the click reaction.[40]

Conclusion

We have shown for the first time that copper(I)-modified zeolites can be used as catalysts in organic synthesis. With such catalysts, we have developed a simple and efficient ligand-free catalytic system for the [3+2] cycloaddition of terminal alkynes with azides. This heterogeneous method offers a wide scope, tolerates numerous functional groups, and provides a very high regioselectivity, with only the 1,4-disubstituted 1,2,3-triazole regioisomer being formed. Moreover, this heterogeneous copper(I)-modified zeolite catalyst can be reused three times without loss of activity. Various investigations suggested a mechanism different from the click reaction.

Experimental Section

General: All starting materials were commercial and were used as received. The reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F_{254}, Merck) with UV light and *p*-anisaldehyde for visualization. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck) with mixtures of ethyl acetate and cyclohexane as eluent. Evaporation of solvents was conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Melting points (m.p.) were measured in open capillary tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer FTIR 1600 spectrometer (KBr disk) and values are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts δ and coupling constants J are given in ppm and Hz, respectively. Chemical shifts δ are reported relative to residual solvent as an internal standard (chloroform-d_1: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C; methanol-d_4: 3.31 ppm for ^1H and 49.15 ppm for ^{13}C). Carbon multiplicities were determined by DEPT135 experiments. Electron impact (EI) and electrospray ionization (ESI) low-/high-resolution mass spectrometry (HRMS) was carried out at the mass spectrometry department of the Service Commun d'Analyses, Institut de Chimie, Strasbourg.

General procedure for the Cu^I-zeolite-catalyzed [3+2] cycloaddition of azides and terminal alkynes: Azides **2** (1.3 mmol, 1.0 equiv) and then alkynes **1** (1.6 mmol, 1.2 equiv) were added to a suspension of Cu^I-USY (50 mg, 0.1 equiv)[31] in toluene (1.5 mL). After stirring for 15 h at room temperature (unless otherwise stated), the mixture was extracted overnight with dichloromethane (15 mL). After the catalyst was removed by filtration, solvent evaporation provided the resulting crude product, usually at >95 % purity as judged by NMR spectroscopy. Column chromatography was performed when necessary.

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3c): By using the general procedure, benzyl azide **2a** and 1-ethynyl-4-methoxybenzene **1c** provided the triazole **3c** as an off-white solid. Yield 69 %; m.p. 145 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.74–7.70 (m, 2H), 7.57 (s, 1H), 7.41–7.28 (m, 5H), 6.95–6.90 (m, 2H), 5.55 (s, 2H), 3.82 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.6, 148.1, 134.7, 129.1, 128.7, 128.0, 127.0, 123.2, 118.7, 114.2, 55.3, 54.2 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{16}H_{15}N_3O$: 266.1248 $[M+H]^+$; found: 266.1234.

1-Benzyl-4-(4-nitrophenyl)-1*H*-1,2,3-triazole (3d): By using the general procedure, benzyl azide **2a** and 1-ethynyl-4-nitrobenzene **1d** provided the triazole **3d** as a yellow solid. Yield 64 %; m.p. 168 °C; IR: $\tilde{\nu}$=1601, 1504, 1456, 1330, 1229, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.28–8.24 (m, 2H), 7.99–7.95 (m, 2H), 7.80 (s, 1H), 7.43–7.32 (m, 5H), 5.61 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/MeOD 1:1): δ=147.9, 146.5, 137.2, 134.9, 129.7, 129.5, 128.7, 126.7, 124.8, 122.5, 54.9 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{15}H_{13}N_4O$: 281.1033 $[M+H]^+$; found: 281.1039.

1-Benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (3f): By using the general procedure with a reaction temperature of 80 °C, benzyl azide **2a** and 1-ethynylcyclohexane **1f** provided the triazole **3f** as an off-white solid. Yield 89 %; m.p. 106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.39–7.33 (m, 3H), 7.26–7.23 (m, 2H), 7.14 (s, 1H), 5.48 (s, 2H), 2.78–2.70 (m, 1H), 2.04–2.00 (m, 2H), 1.79–1.68 (m, 4H), 2.04–2.00 (m, 2H), 1.40–1.24 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=154.2, 135.0, 129.0, 128.5, 128.0, 119.1, 54.0, 35.3, 33.0, 26.1, 26.0 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{15}H_{19}N_3$: 242.1612 $[M+H]^+$; found: 242.1710.

4-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)butan-1-ol (3g): By using the general procedure, benzyl azide **2a** and 5-hexyn-1-ol **1g** provided the triazole **3g** as an off-white solid. Yield 88 %; m.p. 80 °C; IR: $\tilde{\nu}$=3107, 3056, 4 2931, 2928, 2900, 2861, 1554, 1493, 1453, 1431, 1360, 1332, 1309, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.33–7.28 (m, 3H), 7.21–7.18 (m, 3H), 5.42 (s, 2H), 3.60 (t, J=6.3 Hz, 2H), 2.66 (t, J=7.2 Hz, 2H), 1.73–1.66 (m, 2H), 1.63–1.51 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=148.4, 134.7, 128.9, 128.4, 127.8, 120.7, 61.8, 53.8, 31.9, 25.4, 25.1 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{13}H_{18}N_3O$: 232.1444 $[M+H]^+$; found: 232.1473.

***N*-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)-*N*-methylbenzylamine (3m)**: By using the general procedure, benzyl azide **2a** and *N*-(1-ethynylmethyl)-*N*-methylbenzylamine **1p** provided the expected triazole **3m** as a yellow solid. Yield 92 %; m.p. 52 °C; IR: $\tilde{\nu}$=3038, 3024, 2796, 2758, 1493, 1453, 1437, 1418, 1389, 1360, 1329, 1309, 1266, 1220, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.38–7.34 (m, 4H), 7.30–7.24 (m, 7H), 5.52 (s, 2H), 3.69 (s, 2H), 3.52 (s, 2H), 2.21 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=145.9, 138.6, 134.8, 129.1, 129.0, 128.6, 128.2, 128.0, 127.0, 122.3, 61.4, 54.1, 52.1, 42.1 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{18}H_{21}N_4$: 293.1761 $[M+H]^+$; found: 293.1738.

11-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)undecan-1-ol (3x): By using the general procedure, 11-azidoundecan-1-ol **2j** and phenylacetylene **1a** provided the expected triazole **3x** as an off-white solid. Yield 78 %; m.p. 113 °C; IR: $\tilde{\nu}$=3036, 3009, 2931, 2857, 1719, 1604, 1466, 1433, 1359, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/MeOD 1:1): δ=8.02 (s, 1H), 7.78–7.75 (m, 2H), 7.44–7.37 (m, 2H), 7.35–7.28 (m, 1H), 4.39 (t, J=7.1 Hz, 2H), 3.52 (t, J=6.8 Hz, 2H), 1.96–1.90 (m, 2H), 1.52–1.45 (m, 2H), 1.40–1.14 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$/MeOD 1:1): δ=148.4, 130.9, 129.5, 128.9, 126.3, 121.2, 62.8, 51.2, 33.1, 30.9, 30.3, 30.2, 30.0, 29.6, 29.5, 27.1, 26.4 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{19}H_{30}N_3O$: 316.2383 $[M+H]^+$; found: 316.2376.

2-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)cyclohexan-1-ol (3y): By using the general procedure, 2-azidocyclohexan-1-ol **2k** and phenylacetylene **1a** provided the triazole **3y** as an off-white solid. Yield 63 %; m.p. 177 °C; IR: $\tilde{\nu}$=3009, 2946, 2864, 1601, 1484, 1454, 1433, 1353, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.75 (s, 1H), 7.72–7.68 (m, 2H), 7.40–7.28 (m, 3H), 4.21–4.03 (m, 2H), 3.55 (d, J=3.7 Hz, 1H), 2.25–2.17 (m, 2H), 2.06–1.88 (m, 4H), 1.53–1.40 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=147.2, 130.5, 128.9, 128.2, 125.7, 119.7, 72.7, 67.2, 33.8, 31.7, 24.9, 24.2 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{14}H_{17}N_3ONa$: 266.1264 $[M+Na]^+$; found: 266.1249.

Detailed experimental procedures and NMR spectra of all new compounds and of most of the known compounds are given in the Supporting Information.

Acknowledgements

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