Copper(I)-Zeolites as New Heterogeneous and Green Catalysts for Organic Synthesis

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Abstract: We have evaluated the potential of Cu^I-doped zeolites as heterogeneous catalysts for organic synthesis. Such catalysts proved to be easy to prepare, handle, recover, and recycle. They could be applied to different synthetic applications, such as [3+2] cycloadditions of alkynes with either azides or azomethine imines and the homocoupling of alkynes. These interesting characteristics make them highly attractive as catalysts for organic chemists, especially with regard to aspects of 'green chemistry'.

Key words: zeolite, copper, catalysis, green chemistry

1 Introduction

Increasing environmental concerns within the past decade have led to the emergence of so-called 'green chemistry'.[1] Within this 'green chemistry' context, we are looking for new classes of heterogeneous catalysts that are easy-to-handle and recyclable, but they can replace environmentally unfriendly reagents and/or solvents, and, at the same time, they can carry out the desired organic reactions with higher yield and better selectivity, while minimizing energy and waste.

Our interest in liquid or solid superacid-mediated organic transformations[2] recently led us to envisage exploiting the catalytic and discrimination properties of zeolites while combining this with the catalytic properties of selected metallic ions. Due to the large number of organic reactions promoted by copper salts or complexes,[3] we are currently exploring the potential of Cu^I-doped zeolites in organic synthesis. We reported here an update of our results in this new area, showing that such catalysts are able to promote efficiently different cycloaddition and coupling reactions. Such easy and efficient ways to perform reactions led us to coin the term 'zeo-click' for such processes (Figure 1) by analogy to the Sharpless 'click' chemistry principles.[4]

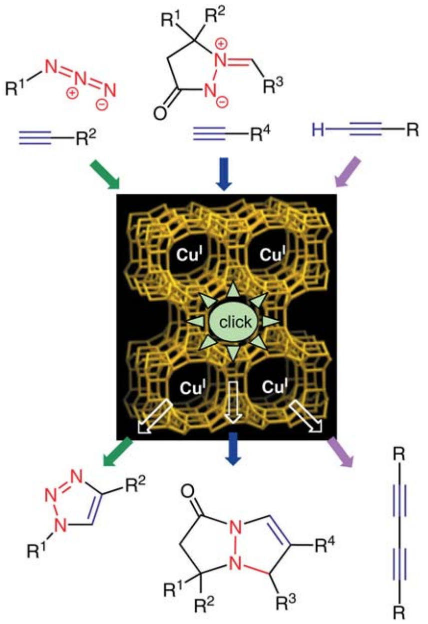

Figure 1 The zeo-click concept

2 Synthesis and Structure of Cu^I-Doped Zeolites

The ion-exchange properties of zeolites are well known and have been extensively exploited, *inter alia*, in water treatments.[5] For stability and solubility reasons, zeolites containing copper(II) could be easily prepared through such exchange. Cu^{II}-Zeolites are thus common and have

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been used for depollution processes such as NO_x reduction[6] and ammoniac oxidation.[7] They have also been utilized to improve the production of cyanamide from urea,[8] to convert syngas into methanol,[9] and for the carbonylation of methanol to dimethyl carbonate.[10] In contrast, zeolites containing copper(I) are scarce, probably due to the sensitivity of such species to redox processes and to the low solubility of Cu(I) salts in water. Cu^I-Zeolites have been obtained by ion-exchange from aqueous solutions of copper(II) acetate, copper nitrate, or copper(II) tetraamine nitrate with subsequent reduction under carbon monoxide or hydrogen at high temperatures.[11] A type of zeolite, the ferrierite, has been directly obtained by in situ formation of a copper(I) complex $[Cu(NH_3)_2]^+$ during the sol-gel preparation of the ferrierite itself.[12] Alternatively, Cu^I-zeolites could be obtained by interactions of H-zeolites with gaseous copper(I) chloride.[13] Surprisingly, the so-formed Cu^I-zeolites have always been studied in redox processes for depollution, in comparison with Cu^{II}-zeolites. No other application has so far been reported.

On this basis, we prepared Cu^I-doped zeolites from five representative zeolites, H-USY, H-Y, H-MOR, H-ZSM5, and H-β. They were prepared by heating the commercially available ammonium zeolites under nitrogen flow [Equation 1 (a)]. These acidic zeolites were then mixed with dry solid copper(I) chloride and the corresponding mixtures were heated under nitrogen flow at 350 °C or higher for 7–65 hours [Equation 1 (b)].

$$\text{H}_4\text{N—Zeolite} \xrightarrow[5\text{ h}]{550\ ^\circ\text{C}} \text{H—Zeolite} + \text{NH}_3 \quad \text{(a)}$$

$$\text{H—Zeolite} + \text{CuCl} \xrightarrow[7\text{–}65\text{ h}]{350\text{–}650\ ^\circ\text{C}} \text{Cu}^\text{I}\text{—Zeolite} + \text{HCl} \quad \text{(b)}$$

Equation 1 Preparation of Cu^I-doped zeolites

Although the temperature was below the melting point of copper(I) chloride (430 °C), copper(I) chloride was clearly able to sublimate at such temperatures and the nitrogen flow allowed it to diffuse within the zeolite, whatever its structure and internal shape. During this process, Cu^+ ions exchanged with the zeolite protons. HCl was indeed detected at the exhaust with each zeolite investigated. Several physical techniques confirmed that Cu^+ ions migrated within the zeolite crystalline framework, replacing zeolite protons at such relatively high temperatures. Interestingly, the Cu^+ loading could be tuned by varying the temperature and the contact time, from 80% at 350 °C to almost 100% at 650 °C.[14]

Biographical Sketches

Stefan Chassaing was born in 1975 in Haguenau, France. He studied physics and chemistry at the Louis Pasteur University in Strasbourg where, after also teaching in a secondary school for two years, he obtained his Ph.D. in 2006 under the supervision of Prof. Raymond Brouillard; his research focused on methods and their development and application to flavonoid synthesis. Following his doctoral studies, he remained for a further year at the Louis Pasteur University as a postdoctoral research associate in the group of Prof. Jean Sommer, where he contributed to the development of zeolite-based catalysts for organic synthesis. In 2007, he moved to Bordeaux, France, for a second postdoctoral stay in the group of Prof. Stéphane Quideau at the European Institute of Chemistry and Biology where he worked on ellagitannin chemistry and oxidative dearomatization of phenols. In 2008, he joined the group of Dr. Michel Baltas at the Paul Sabatier University in Toulouse as assistant professor. His current research interests focus on the synthesis and biological activity of natural products and analogues.

Patrick Pale studied at the University of Champagne-Ardenne, France, where he obtained his Ph.D. in 1982 under the direction of Profs. J. P. Pete and J. Muzart. After an industrial stay in a pharmaceutical company, he joined the group of Prof. L. Ghosez at Louvain-La-Neuve in Belgium for postdoctoral work on the development of azadienes. In 1984, he returned to the University of Champagne-Ardenne as a CNRS fellow. Working on rearrangements and reaction mechanisms with the late Prof. J. Chuche, he obtained a 'Doctorat d'Etat' in 1988, and then a research associate position at Harvard University in the group of Prof. G. Whitesides in 1988–1990. He returned to the University of Champagne-Ardenne, and took up his present position in 1995 as Professor of Organic Chemistry at the University L. Pasteur in Strasbourg. Subsequently, he was awarded Professor at the 'Institut Universitaire de France' from 1996 to 2001. His scientific interests include total synthesis of bioactive compounds, organometallic chemistry, asymmetric synthesis, carbohydrate chemistry, and enzymatic chemistry, and more recently chemistry in nanoreactors such as zeolites.

After this doping process, the zeolite structures were mostly preserved, as revealed by X-ray powder diffraction. However, depending on the duration of vaporization and the temperature, de-alumination occurred, leading to the formation of extra-framework aluminum species, inducing higher Lewis acidity of the modified zeolites.[15] Cu^I-Zeolites prepared at 350 °C exhibited fewer structural modifications, while those prepared at 650 °C were more affected. Crystallinity decreased under severe exchange conditions, from 86% for zeolites prepared at 350 °C to 65% for zeolite prepared at 650 °C for 15 hours, and even lower for prolonged calcination times. Moreover, the H/Cu exchange varied upon the calcination temperature and time. Cu^I-USY prepared at 350 °C still contained 20% protons, while none remained in Cu^I-USY prepared at 650 °C.[15]

3 Organic Synthesis with Cu^I-Doped Zeolites

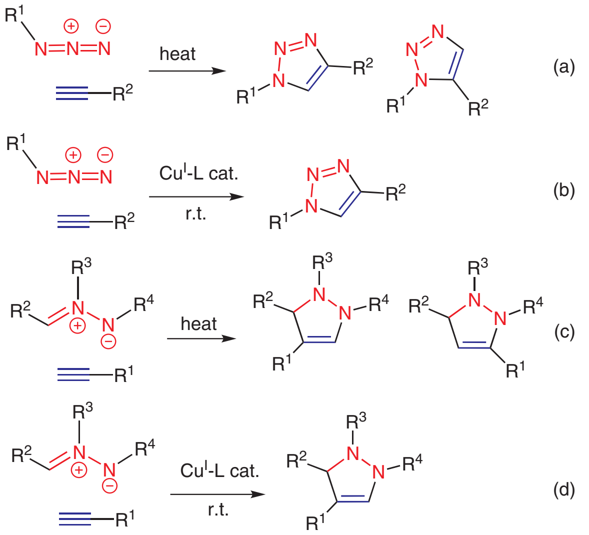
These so-formed Cu^I-doped zeolites were then investigated as new catalysts for specific problems in organic synthesis. To better comply with the principles of 'green chemistry',[1a] we applied such catalysts to reactions that are, in essence, economic in steps and atoms, such as cycloadditions and coupling reactions (Figure 1).

3.1 Cu^I-Zeolite-Catalyzed Cycloadditions

It is well known that cycloadditions can be catalyzed by Brønsted or, more conveniently, by Lewis acids. In parallel with the acceleration of the reaction, such catalysis usually reinforced regioselectivity, as amply demonstrated for [4+2] cycloadditions.[16] More recently, [3+2] cycloadditions have also been reinvestigated with catalysis in mind; a typical example is the Huisgen reaction. In this reaction, alkynes and azides were heated together, yielding a mixture of regioisomeric disubstituted 1,2,3-triazoles [Scheme 1 (a)].[17] Meldal and Sharpless independently found that copper(I) can catalyze the cycloaddition between alkynes and azides at room temperature regioselectively yielding 1,4-disubstituted 1,2,3-triazoles [Scheme 1 (b)].[18] This concomitant discovery led to a revival of the Huisgen cycloaddition and initiated a vast number of applications of this reaction.[19]

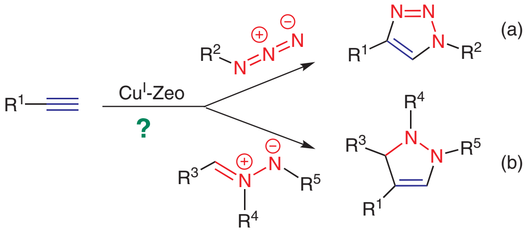
The lesser-known Dorn reaction allowed the preparation of pyrazolines from alkynes and azomethine imines. However, harsh conditions were usually required and this [3+2] cycloaddition led to mixtures of regioisomers in variable proportions and yields [Scheme 1 (c)].[20] In analogy with the Huisgen reaction, Fu recently developed a copper(I)-catalyzed version of the Dorn reaction. Copper catalysis improved the reaction and dramatically enhanced its regioselectivity [Scheme 1 (d)].[21]

Due to their inherent instability and their poor solubility, copper(I) salts must be used in the presence of ligands in these reactions. In the Meldal and Sharpless version, active catalytic species could also be in situ generated by reduction of copper(II) salts or by oxidation of copper turnings.



Scheme 1 [3+2] Cycloadditions catalyzed by copper compared to the original version. (a) Huisgen cycloaddition, (b) Meldal–Sharpless version, (c) Dorn cycloaddition, (d) Fu version.

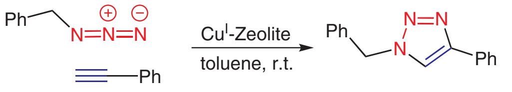
In contrast, several studies showed that the zeolite framework could behave like a ligand towards various inserted metal ions.[22] Therefore, and although copper zeolites have usually been used in redox reactions, we reasoned that immobilizing copper(I) ions into zeolites would stabilize them, the zeolite framework acting as a ligand. Doping as such zeolites would provide a stable, supported, and reusable copper(I) catalyst. Moreover, with such catalysts, discrimination could also be expected depending on the zeolite pore size and shape. We, thus, investigated Cu^I-zeolites as catalysts for the Huisgen and Dorn cycloaddition (Scheme 2).



Scheme 2 Cu^I-Zeolites as potential cycloaddition catalysts

Among the Cu^I-doped zeolites examined, Cu^I-USY proved to be the best for both reactions, giving the highest yields at room as well as at higher temperatures. USY contains a pore network made of adjacent large cages approximately 7.4 Å in diameter, the largest of the zeolite series investigated. With such large cages, Cu^I-USY was able to readily accommodate the two cycloaddition partners within its cages and promote the reaction.

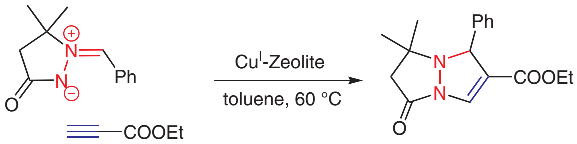
The Cu^I-USY-catalyzed Huisgen reaction could be performed at room temperature in any organic solvent, but the highest yields were achieved in toluene. Running the reaction at higher temperatures increased the reaction rate from overnight to a few hours with a slight increase in the yields.[23] A single regioisomer, the 1,4-disubstituted 1,2,3-triazole, was always formed regardless of the zeolite and solvent used (Scheme 3).[23]



	Cu^I-USY	Cu^I-Y	Cu^I-ZSM5	Cu^I-MOR	Cu^I-β	H-USY
yield	87%	75%	79%	79%	73%	0%

Scheme 3 Efficiency of the Cu^I-zeolite-catalyzed Huisgen cycloaddition between benzyl azide and phenylacetylene

In contrast, The Cu^I-USY-catalyzed Dorn reaction could only be performed in dichloromethane at room temperature, but the reaction was slow and the yields were moderate (40–58% yield in 24–48 h). However, at 60 °C, toluene was again the best solvent, giving very high yields in a rapid reaction (4 h, Scheme 4).[24] In this Cu^I-USY-catalyzed cycloaddition, a single regioisomer was again always obtained.



	Cu^I-USY	Cu^I-Y	Cu^I-ZSM5	Cu^I-MOR	Cu^I-β	H-USY
yield	95%	95%	80%	89%	69%	0%

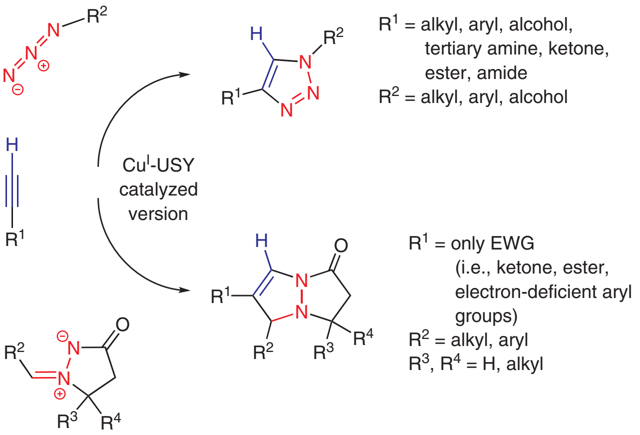
Scheme 4 Efficiency of the Cu^I-zeolite-catalyzed Dorn cycloaddition between (*Z*)-1-benzylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide and ethyl propiolate

These Cu^I-modified zeolites acted as true catalysts, since only 5–10 mol% was used.[25] Moreover, these catalysts could be easily recovered and recycled several times without any significant change in yield and conversion.[23,24]

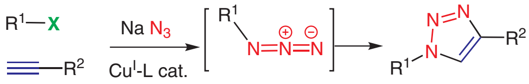
With Cu^I-USY as the catalyst (Scheme 5), the scope of these Cu^I-zeolite-catalyzed cycloadditions was explored. For the Huisgen reaction, it proved as broad as the now classical Meldal–Sharpless version; for the latter, only terminal alkynes reacted. In our Cu^I-USY-catalyzed version, only compounds having either free amino or acid group did not react.[23] The scope of the Dorn reaction proved also very similar to the one of the initial or Fu versions. Only terminal alkynes carrying sufficiently strong electron-withdrawing group reacted.

3.2 Cu^I-Zeolite-Catalyzed Cascade: Substitution and Cycloaddition

To go further along ‘green chemistry’ principles, we looked for a one-pot zeolite-catalyzed formation of triazoles. Since organic azides are usually prepared from the corresponding bromides by nucleophilic substitution, it was tempting to perform this step in the presence of terminal alkynes and Cu^I-USY as a catalyst in order to set up a Cu^I-zeolite-catalyzed cascade reaction (Scheme 6).



Scheme 5 Scope and limitations of the Cu^I-USY-catalyzed Huisgen and Dorn cycloadditions versions (EWG = electron-withdrawing groups)



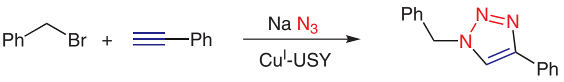
Scheme 6 One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from in situ generated azides

Benzyl bromide was, thus, placed under various conditions in the presence of sodium azide, phenylacetylene, and 10% of Cu^I-USY. Using the optimized conditions discussed above, no transformation could be detected (Table 1, entries 1, 2). Sodium azide was not readily soluble in such an apolar solvent. Adding a polar co-solvent did not help (entries 3, 4), but performing the reaction in more polar *N*,*N*-dimethylformamide led to the expected one-pot reaction; at room temperature, the expected triazole was directly obtained in a good overall yield (entry 5) while at higher temperatures in *N*,*N*-dimethylformamide the reaction was faster, giving a slightly better overall yield (entry 6). Interestingly, the same one-pot reaction also took place in the highly polar solvent water and with better efficiency since reaction times were decreased and overall yields increased (entries 7, 8). Again, high temperatures accelerated the reaction rate (entry 8 vs 7). Even more interesting, the triazole adduct precipitated out of the reaction mixture in water, facilitating its recovery as well as the recovery of the Cu^I-zeolite catalyst.

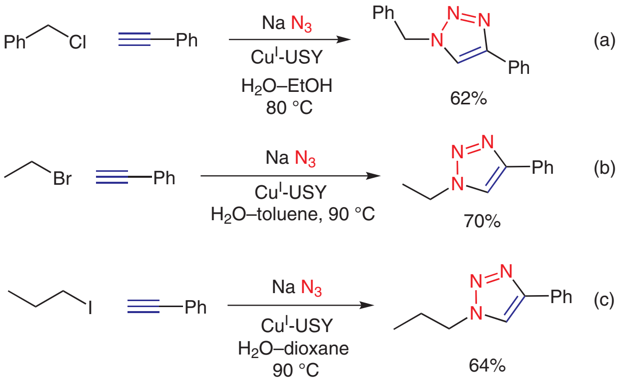
Interestingly, even chlorides could be engaged in such cascade reaction, but for solubility reasons, a mixture of solvent had to be used [Scheme 7 (a)]. Moreover, this one-pot process could be extended to aliphatic iodides or bromides, provided that the appropriate mixture of solvents was used, again for solubility reasons [Scheme 7 (b) and (c)].

This one-pot Cu^I-USY-catalyzed substitution–cycloaddition cascade seemed general and various aryl- or alkyl-substituted acetylene derivatives reacted under such conditions (Table 2). With arylacetylenes, this one-pot reac-

Table 1 Reaction Condition Optimization of One-Pot Synthesis of 1-Benzyl-4-phenyl-1,2,3-triazole from In Situ Generated Azides

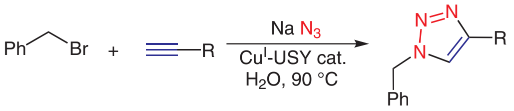


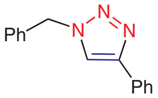
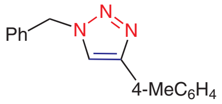
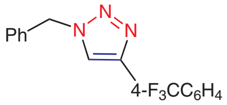
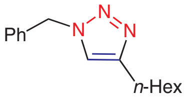
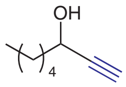
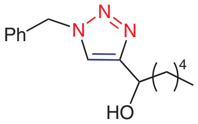
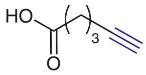
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	toluene	20	15	0
2	toluene	110	15	trace
3	toluene–THF	20	15-72	0
4	toluene–THF	80	15	trace
5	DMF	20	15	71
6	DMF	100	8	78
7	H$_2$O	20	9	90
8	H$_2$O	100	2	90



Scheme 7 One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from aliphatic bromides or iodides or benzyl chloride

Table 2 One-Pot Cascade Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Azides



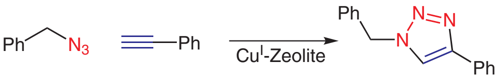
Entry	Alkyne	Product	Time (h)	Yield (%)
1	Ph—≡		2	90
2	4-MeC$_6$H$_4$—≡		2	89
3	4-F$_3$CC$_6$H$_4$—≡		2	98
4	*n*-Hex—≡		4	75
5			8	72
6		–	12	trace

tion in water proved to be more effective than the zeo-click reaction in toluene at room temperature.[23,24] Electronic effects had a stronger influence than in our previous zeo-click version. An electron-donating group on the phenyl moiety of phenylacetylene decreased the yield but not significantly (entry 2 vs 1), while a strong electron-withdrawing group increased the yield (entry 3 vs 2 vs 1). In contrast, alkylacetylenes were less reactive in this one-pot reaction in water compared to the zeo-click reaction in toluene at room temperature (entries 4 and 5).[23,24] As expected, the same limitations were observed under the one-pot water conditions as under the room temperature toluene conditions and no cycloaddition occurred with acetylenic derivatives containing free acid or amine groups (entry 6).

3.3 Cu^{I}-Zeolite-Catalyzed Cycloadditions: Mechanistic Investigations

The method by which the zeolite was prepared proved to be critical in the cycloaddition reactions examined. Under the conditions mentioned above, starting from benzyl azide and phenylacetylene, high yields of 1-benzyl-4-phenyl-1,2,3-triazole were achieved with zeolites prepared at 350 °C (Table 3, entries 1 and 2), while only modest yields were obtained with zeolites prepared at 650 °C (entries 4 and 5). Interestingly, the reaction could be sped up if performed under microwave irradiation, but only with Cu^{I}-USY prepared at 350 °C. Microwave proved deleterious when using Cu^{I}-USY obtained at 650 °C as catalyst (entry 5 vs 6).

Table 3 Cycloaddition between Phenylacetylene and Benzyl Azide in Toluene, Catalyzed by Differently Prepared Cu^{I}-USY, under Various Conditions



Entry	Catalyst[a]	Temp (°C)	Time (h)	Yield (%)
1	Cu^{I}-USY-350	20	15	83
2	Cu^{I}-USY-350	110	5	87
3	Cu^{I}-USY-350	110 (MW)	0.5	89
4	Cu^{I}-USY-650	20	15	37
5	Cu^{I}-USY-650	110	5	45
6	Cu^{I}-USY-650	110 (MW)	0.5	16

[a] Cu^{I}-USY-350: Cu^{I}-USY heated to 350 °C during preparation; Cu^{I}-USY-650: Cu^{I}-USY heated to 650 °C during preparation.

These results reflected the structural differences observed for Cu^I-zeolites prepared at various temperatures. As mentioned in Section 2, zeolites obtained at 350 °C did not exhibit morphological changes. Whatever the calcination temperature and duration, Cu^I-USY exhibited powder XRD patterns very similar to those of native USY. However, Cu^I-USY prepared at 350 °C still contained 20% acid sites/protons, while none remained in Cu^I-USY prepared at 650 °C.[15] The presence of protons could, thus, play a role in the Huisgen or Dorn cycloadditions.

For an in-depth view, reactions were performed in the presence of protic solvents. In methanol, the Cu^I-USY-catalyzed Huisgen reaction proceeded at room temperature, but was slower and less clean than the same performed in toluene (Table 4, entry 1). Surprisingly, excellent results were obtained in water (entries 2 and 3). High yields of triazole were achieved, whatever the reaction temperature (entry 2 vs 3). As before, zeolite prepared at 650°C gave less effective results (entries 4–6). Surprisingly, Cu^I-ZSM5, which gave the second best results in toluene (Scheme 3), proved to be a poor catalyst in water (entry 7), as well as in a mixture of solvent containing water (entry 8).

Table 4 Cycloaddition between Phenylacetylene and Benzyl Azide in Toluene, Catalyzed by Differently Prepared Cu^I-Zeolites in Various Protic Solvents

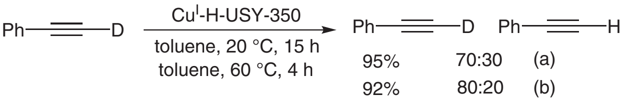
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Cu^I-USY-350	MeOH	20	15	61
2	Cu^I-USY-350	H_2O	20	9	90
3	Cu^I-USY-350	H_2O	100	2	90
4	Cu^I-USY-650	MeOH	20	15	42
5	Cu^I-USY-650	H_2O	20	15	35
6	Cu^I-USY-650	H_2O	100	5	41
7	Cu^I-ZSM5-350	H_2O	20	15	23
8	Cu^I-ZSM5-350	H_2O–CH_2Cl_2 (75:25)	20	15	42

[a] Cu^I-USY-350 or Cu^I-ZSM5-350: Cu^I-USY or Cu^I-ZSM5 heated to 350 °C during preparation; Cu^I-USY-650: Cu^I-USY heated to 650 °C during preparation.

For the Cu^I-USY-catalyzed Dorn reaction, this slowing effect of protic solvents was more dramatic. In methanol, the reaction, even performed at 60 °C, required 72 hours to give 20% of the cycloadduct, while in toluene only 4 hours was sufficient to give an almost quantitative yield (Scheme 4). Surprisingly, the second regioisomer could be detected in protic solvents.

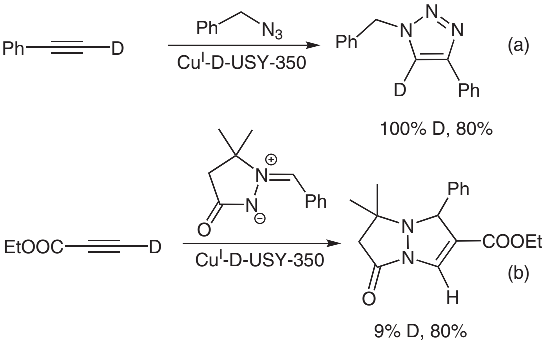
Hence, the Cu^I-USY-catalyzed Huisgen and Dorn cycloadditions could be performed in protic solvents, including water, but with variable results. External proton sources seemed mostly deleterious to the reaction, especially for the Dorn reaction, while internal protons seemed important for reaction efficiency.

To try to understand this discrepancy and shed some light on the mechanism of these Cu^I-USY-catalyzed reactions, reactions were performed with labeled materials. As mentioned above, Cu-zeolites prepared at 350 °C were the most active, but around 20% of the protons of the original zeolite remained. Control experiments revealed one role that these protons could play. Indeed, 1-deutero-2-phenylacetylene lost some deuterium when submitted to Cu^I-USY prepared at 350 °C,[26] but none in the presence of Cu^I-USY prepared at 650 °C or H-USY. Moreover, the exchange rate depended on reaction conditions (Scheme 8). These results showed that the remaining zeolitic protons were able to exchange acetylenic protons in the presence of copper, suggesting the in situ formation of a π-complex. Exchange processes via a π-complex have already been reported for silver ions, although in solution.[27]



Scheme 8 D/H-Exchange induced by Cu^I-USY on 1-deutero-2-phenylacetylene

To avoid such exchange, Cu^I-USY was prepared at 350 °C from deuterated USY,[28] so that the remaining acidic sites only were deuterated. With this zeolite, the Huisgen reaction was performed starting with 1-deutero-2-phenylacetylene and benzyl azide, while the Dorn reaction was applied to ethyl 3-deuteropropiolate (Scheme 9). In the former, all of the deuterium label was recovered in the adduct [Scheme 9 (a)], while in the latter, deuterium was almost completely lost [Scheme 9 (b)].

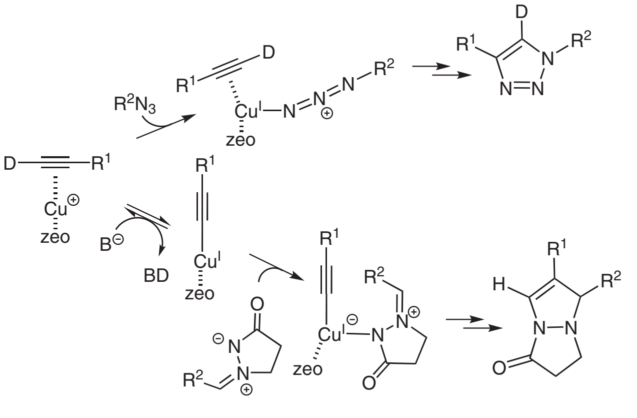


Scheme 9 Cu^I-Zeolite-catalyzed Huisgen and Dorn cycloadditions with deuterated alkynes and zeolite

These results revealed that acetylide was produced during the Dorn reaction while none was formed in the Huisgen reaction. Therefore, the intermediate π-complex evolved differently in each reaction. In the Huisgen reaction, the π-complex probably became a new π-complex after coordination of the azide, and further bond reorganization led to the 1,4-disubstituted triazole (Scheme 10, top). In the

Dorn reaction, the π-complex rearranged to a copper acetylide, the anionic part of the 1,3-dipole possibly acting as a base. Coordination of the dipole, again through its anionic part, led to a cuprate complex, which upon further bond reorganization gave the corresponding bicyclic pyrazolines (Scheme 10, bottom).

These possible mechanisms allowed understanding of the effects of protic solvents. In the Huisgen reaction, external protons could possibly interfere through solvation of the azide as well as by changing the solubility of the organic reagents. In contrast, external protons in the Dorn reaction might prevent the π-complex deprotonation step, possibly due to the 1,3-dipole, as well as further coordination to copper, dramatically reducing the reaction rate.

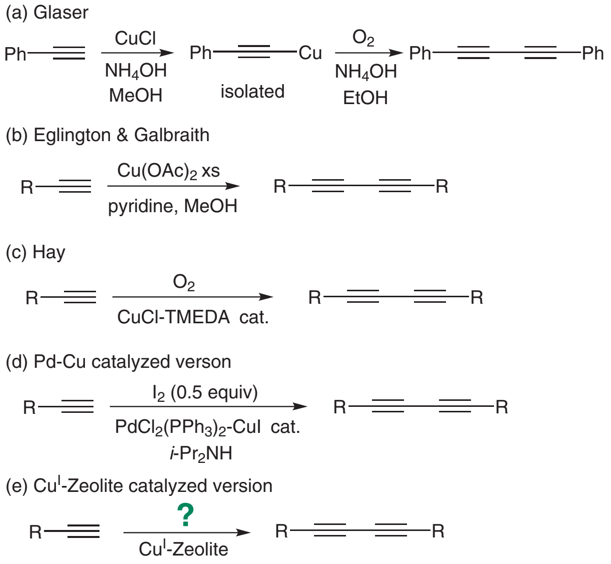


Scheme 10 Proposed mechanisms for Cu^I-zeolite-catalyzed cycloadditions explaining observed results using deuterated terminal alkynes

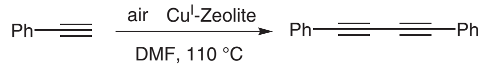
3.4 Cu^I-Zeolite-Catalyzed Coupling Reactions

Homocoupling of terminal alkynes is one of the oldest methods known for C–C bond formation, and one of the oldest involving a metal, in this case copper.[29] The so-obtained 1,3-diynes are an important motif found in natural products exhibiting interesting biological properties,[30] as well as in manmade compounds, such as oligo- and polymers,[31] organic conductors,[32] and conjugated connectors or synthetic receptors in molecular recognition.[33] Numerous methods have, thus, been developed and are still being developed to increase the efficiency and selectivity of alkyne homocoupling, especially under catalytic conditions [Scheme 11 (a–d)].[34] Surprisingly, few supported or heterogeneous versions of such homocoupling reactions have been described.[35] It was thus tempting to apply Cu^I-zeolites as a catalyst to this coupling [Scheme 11 (e)].

Phenylacetylene was used as the starting material to survey the catalysts and conditions for this Cu^I-zeolite-catalyzed homocoupling reaction. Solvent screening revealed that only the highly polar *N*,*N*-dimethylformamide led to the expected diyne product and the highest yield was achieved at high temperatures. As expected, dimerization only occurred under oxygen, but an air atmosphere was sufficient (Scheme 12).[36]



Scheme 11 Known alkyne homocoupling conditions promoted either by stoichiometric or catalytic amounts of copper (a–c) or by catalytic amount of palladium and copper (d), and proposal for a Cu^I-zeolite-catalyzed version (e)



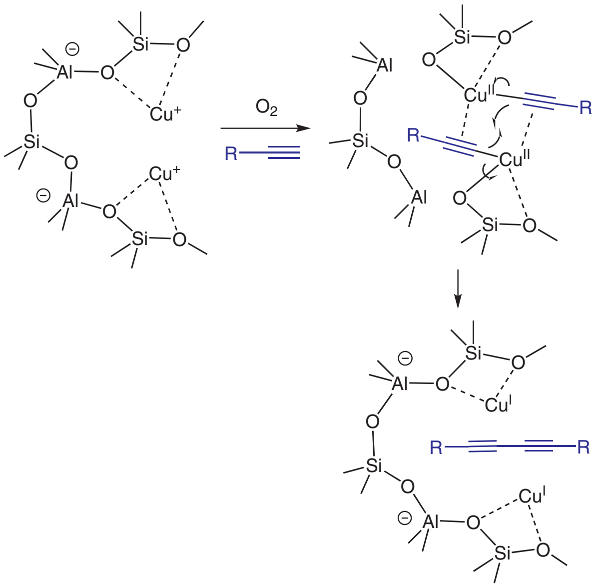
	Cu^I-USY	Cu^I-Y	Cu^I-ZSM5	Cu^I-MOR	Cu^I-β	H-USY
yield	97%	84%	12%	5%	19%	0%

Scheme 12 Cu-Zeolite-catalyzed dimerization of terminal alkynes

As for the preceding cycloadditions, Cu^I-USY was the most effective catalyst among the Cu^I-zeolites examined. Nevertheless, Cu^I-Y was fairly efficient. Surprisingly, the other Cu^I-zeolites were not as active as catalysts for this reaction (Scheme 12).

Such strong differences could be ascribed to the rigid shape of diynes and to the possible transition state of such a dimerization. Although still unknown, proposals have been made, involving dinuclear copper(II) alkyne–acetylide complexes.[34e] As demonstrated in the preceding section, Cu^I-zeolites obviously formed intermediate π-complexes in the presence of alkynes. Under oxygen, such complexes could reorganize to copper(II) acetylides and if two copper ions are present in the same zeolite pore, they can produce dinuclear copper(II) alkyne–acetylide complexes, suggested as intermediates in the homocoupling of terminal alkynes (Scheme 13). Therefore, only zeolites carrying the largest pores can accommodate such large complex intermediates. Moreover, the more copper loaded into the zeolite, increasing the probability of having more than one Cu$^+$ ion in the pore, the more efficient the catalyst should be. This is exactly what was observed.

This mechanistic proposal was also supported by a size effect observed by coupling alkynes of increasing sizes. Excellent yields were achieved for the formation of 1,3-diynes 12 to 15 Å long, indicating an optimal length for the coupling (Figure 2). Interestingly, this size optimum



Scheme 13 Proposed mechanism for the Cu^{I}-zeolite-catalyzed homocoupling reaction

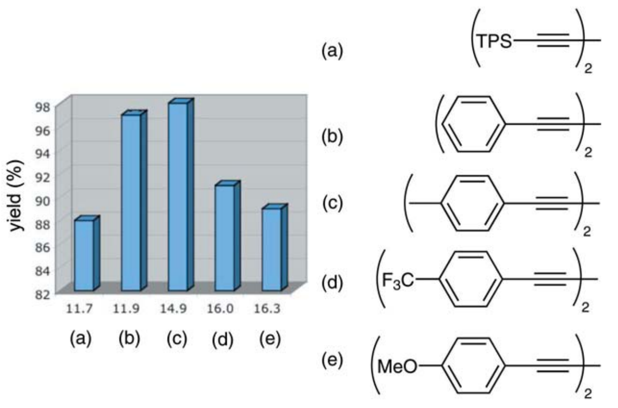
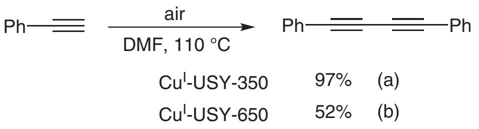


Figure 2 Effect observed on the yield (%) for the Cu^{I}-USY-catalyzed homocoupling reaction of 1,3-diynes of various sizes (Å)

perfectly fitted with the USY supercage size (13 Å), suggesting adequate accommodation of the dinuclear copper(II) alkyne–acetylide intermediate within the cage. Such an optimal supramolecular arrangement has led zeolites to be regarded as inorganic enzyme analogues, the so-called zeozymes.[37]

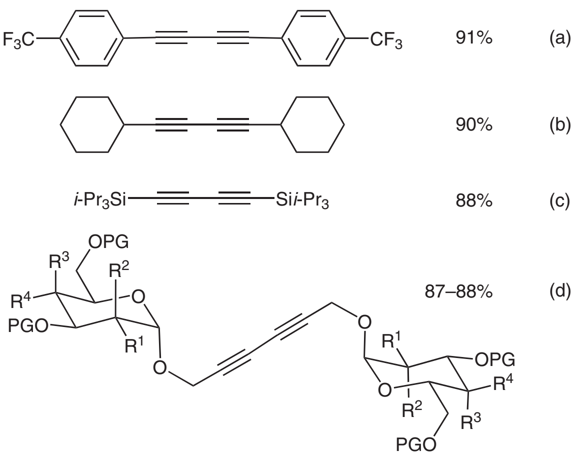
It is also worth noting that X-ray (XPS) experiments performed on Cu^{I}-USY before, during, and after its use as catalyst in the homocoupling of phenylacetylene confirmed that the oxidation state of the loaded copper varied from +I before use to +II during use (binding energy of Cu 2p$_{3/2}$: 932.8, 933.3, and 933.1 eV, respectively, as compared to Cu$_2$O and CuO; 932.8 and 933.3–934.4 eV, respectively). Interestingly, this study revealed that during the catalytic run only approximately 40% of the loaded copper ions were oxidized and that around 20% remained oxidized after use.[14]

As in the preceding cycloadditions, the way the Cu^{I}-zeolites were prepared was again critical. Cu^{I}-USY prepared at 350 °C was the most effective compared to Cu^{I}-USY prepared at 650 °C (Scheme 14).



Scheme 14 Effect of Cu^{I}-USY preparation on the efficiency of the phenylacetylene homocoupling reaction

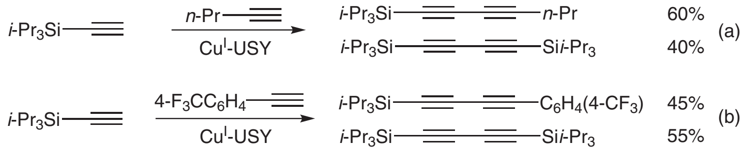
Under these conditions, a wide range of terminal alkynes could be dimerized, including aryl-, alkyl-, and silylacetylenes [Scheme 15 (a–c)]. Even propargyl glycosides could be dimerized under these conditions without any isomerization [Scheme 15 (d)]. Moreover, this method gave the highest yields compared to known routes.[38] The corresponding glycosylated hexa-2,4-diyne-1,6-diols are important compounds since they mimic the multivalent interactions between carbohydrates and proteins responsible for most of recognition and communication processes within cells, between cells, and between cells and viruses or bacteria. Such compounds could, thus, be applied to immunology, as drugs, or as synthetic vaccines.[39]



Scheme 15 Diynes obtained by Cu^{I}-USY-catalyzed homocoupling of aryl-, alkyl-, and silylacetylene derivatives and of propargyl glycosides

Capitalizing on reactivity differences of some alkynes and on the size effect mentioned above, we looked for selectivity in the formation of nonsymmetrical diynes. The 'small' (triisopropylsilyl)acetylene and pent-1-yne were submitted to the Cu^{I}-USY-catalyzed homocoupling conditions and the best fit, the heterodiyne 1-(triisopropylsilyl)hepta-1,3-diyne was, indeed, formed as the major product [Scheme 16 (a)]. As expected from the size limit observed (Figure 2), the combination of (triisopropylsilyl)acetylene with (4-trifluorophenyl)acetylene led to the heterodiyne, but with lower selectivity [Scheme 16 (b)].

Toward the same selectivity goal in alkyne coupling, a zeo-click variant of the Cadiot–Chodkewicz reaction[40] was examined. Various 1-bromoalk-1-ynes were submitted to different terminal alkynes in the presence of Cu^{I}-



Scheme 16 Nonsymmetrical Cu^I-USY-catalyzed coupling of various terminal alkynes

USY in different solvents (Table 5). Whatever the solvent and the nature of the substituent, almost no reaction took place and at best, less than 10% of the 1,3-diyne derived from the terminal alkyne engaged in the reaction was obtained (entries 1–9). Similar results were observed starting from the corresponding 1-iodoalk-1-ynes. Under these conditions, the halogenated alkynes could not be recovered, suggesting their reaction with copper(I) ions loaded into USY, but without further evolution.

Table 5 Cadiot–Chodkewicz-Type Heterocoupling Attempts via the Reaction between 1-Bromoalkynes and Terminal Alkynes

Entry	Bromoalkyne	Alkyne	Conditions[a]	Yield (%)
1	Ph—≡—Br	4-MeC$_6$H$_4$—≡	toluene	0[b]
2			CH$_2$Cl$_2$	trace[c]
3			THF	trace[c]
4			MeCN	trace[c]
5			DMF	98
6		4-MeOC$_6$H$_4$—≡	DMF	trace[c]
7		4-F$_3$CC$_6$H$_4$—≡	DMF	9[c]
8		*n*-Hex—≡	DMF	0[b]
9	*n*-Hex—≡—Br	4-F$_3$CC$_6$H$_4$—≡	DMF	0[b]

[a] Cu^I-USY (0.3 to 1 equiv), r.t. to reflux; concomitant and sequential additions were examined.

[b] The starting terminal alkyne was recovered.

[c] The homocoupling product derived from the terminal alkyne was detected or isolated.

4 Conclusion

Copper(I)-modified zeolites were, for the first time, used as catalysts in organic synthesis. They proved to be very efficient catalysts for various cycloadditions as well as for the homocoupling of terminal alkynes.

Easy to prepare, handle, recover, and recycle, such heterogeneous catalysts offer, thus, an interesting alternative to more conventional homogeneous catalysts in organic synthesis. Moreover, they exhibit typical characteristics of 'green chemistry' towards synthetic applications.

All starting materials were commercial and were used as received. The zeolites used were those that had been prepared at 350 °C, except in the few cases where the role of this preparation temperature was being examined. The reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F$_{254}$, Merck) using UV light and *p*-anisaldehyde for visualization. Column chromatographies were performed on silica gel 60 (0.040–0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were recorded on a 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 are reported relative to residual solvent as an internal standard (chloroform-*d*$_1$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C).

Cu^I-USY; Typical Procedure

Commercial NH$_4$USY was loaded in an oven and heated at 550 °C for 4 h giving H-USY. H-USY (1 g) and CuCl (475 mg, 1.1 equiv) were mixed using a mortar and charged in a closed reactor. The mixture of powders was heated at 350 °C under N$_2$ flow, quantitatively yielding Cu^I-USY. The same procedure was applied to other zeolites.

Cu^I-Zeolite-Catalyzed [3+2] Cycloaddition of Azides and Terminal Alkynes; General Procedure

To a suspension of Cu^I-USY (50 mg, 0.1 equiv) in toluene (1.5 mL) was added the azide (1.3 mmol, 1.0 equiv) and then the terminal alkyne (1.6 mmol, 1.2 equiv). The mixture was stirred at r.t. overnight (15 h) and then it was taken up in CH$_2$Cl$_2$ (15 mL). The solid catalyst was removed by filtration over Nylon membranes (0.20 μm) and washed with CH$_2$Cl$_2$. Solvent evaporation provided the resulting triazole, usually of sufficient purity (from NMR spectra).

Cu^I-Zeolite-Catalyzed Cascade from Halides, Sodium Azide, and Terminal Alkynes; General Procedure

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in solvent (3 mL) (see Table 1) was added successively NaN$_3$ (1.1 mmol, 1.1 equiv), the halide (1.0 mmol, 1 equiv), and then the terminal alkyne (1.0 mmol, 1 equiv). For reactions performed in H$_2$O, the mixture was filtered, then extracted with EtOAc (3×5 mL). The combined organic layers were then dried (anhyd MgSO$_4$), filtered, and concentrated under vacuum, providing the resulting triazole, usually of sufficient purity (from NMR spectra).

1-Benzyl-4-phenyl-1,2,3-triazole[23,26]

From BnBr: To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H$_2$O (3 mL) was added NaN$_3$ (71.5 mg), BnBr (171 mg), and then phenylacetylene (102 mg). The mixture was heated at 90 °C for 2 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (212 mg, 90%).

From BnCl: To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H$_2$O–EtOH (1:1, 3 mL) was added NaN$_3$ (71.5 mg), BnCl (126 mg), and then phenylethyne (102 mg). The mixture was heated at 78 °C for 5 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (146 mg, 62%).

1-Benzyl-4-tolyl-1,2,3-triazole[23,26]

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H$_2$O (3 mL) was added NaN$_3$ (71.5 mg), BnBr (171 mg) and then (4-methylphenyl)acetylene (116 mg). The mixture was heated at 80 °C for 2 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (222 mg, 89%).

1-Benzyl-4-[4-(trifluoromethyl)phenyl]-1,2,3-triazole

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H_2O (3 mL) was added NaN_3 (71.5 mg), BnBr (171 mg) and then [4-(trifluoromethyl)phenyl]acetylene (170 mg). The mixture was heated at 90 °C for 2 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (296 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.90 (m, 2 H), 7.74 (s, 1 H), 7.66–7.63 (m, 2 H), 7.43–7.31 (m, 5 H), 5.59 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1, 136.9, 135.0, 134.2 (q, $^2J_{C\text{-}F}$ = 31 Hz), 129.3, 129.0, 128.0, 127.1 (q, $^1J_{C\text{-}F}$ = 268 Hz), 125.7, 125.8, 120.2, 54.4.

1-Benzyl-4-hexyl-1,2,3-triazole[41]

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H_2O (3 mL) was added NaN_3 (71.5 mg), BnBr (171 mg), and then oct-1-yne (110 mg). The mixture was heated at 90 °C for 4 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (160 mg, 66%).

1-Benzyl-4-(1-hydroxyhexyl)-1,2,3-triazole

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H_2O (3 mL) was added NaN_3 (71.5 mg), BnBr (171 mg) and then 3-hydroxyoct-1-yne (126 mg). The mixture was heated at 90 °C for 8 h, then cooled, filtered and extracted as mentioned above, leading to the expected triazole (186 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (s, 1 H), 7.24–7.16 (m, 3 H), 7.13–7.09 (m, 2 H), 5.31 (s, 2 H), 4.75 (t, *J* = 6.6 Hz, 1 H), 4.45 (br s, 1 H, OH), 1.76–1.66 (m, 2 H), 1.38–1.15 (m, 6 H), 0.80–0.73 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 134.8, 128.9, 128.5, 127.9, 120.9, 66.6, 53.7, 37.3, 31.6, 25.1, 22.5, 14.0.

1-Ethyl-4-phenyl-1,2,3-triazole[42]

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H_2O–toluene (1:1, 3 mL) was added NaN_3 (71.5 mg), 1-bromoethane (108 mg), and then phenylacetylene (102 mg). The mixture was heated at 90 °C for 12 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (121 mg, 70%).

1-Propyl-4-phenyl-1,2,3-triazole

To a suspension of Cu^I-USY (20 mg, 0.1 equiv) in H_2O–dioxane (1:1, 3 mL) was added NaN_3 (71.5 mg), 1-iodopropane (170 mg), and then phenylacetylene (102 mg). The mixture was heated at 90 °C for 15 h, then cooled, filtered, and extracted as mentioned above, leading to the expected triazole (120 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2 H), 7.71 (s, 1 H), 7.47–7.30 (m, 3 H), 4.37 (t, *J* = 7.2 Hz, 2 H), 1.98 (sextuplet, *J* = 7.2 Hz, 2 H), 0.99 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 130.7, 129.0, 128.9, 128.1, 125.7, 52.1, 23.8, 11.1.

Cu^I-Zeolite-Catalyzed [3+2] Cycloaddition of Azomethine Imines and Terminal Alkynes; General Procedure

To a suspension of Cu^I-USY (7 mg, 0.05 equiv) in toluene (2 mL) was added pyrazolidin-3-one ylide (0.4 mmol, 1.0 equiv) and then the terminal alkyne (0.48 mmol, 1.2 equiv). The mixture was heated to 60 ° for 4 h, then cooled to r.t. The catalyst was then removed by filtration over Nylon membranes (0.20 μm) and washed with CH_2Cl_2. Solvent evaporation provided the resulting adduct usually of sufficient purity (from NMR spectra). Column chromatography was performed when necessary.

Cu^I-Zeolite-Catalyzed Homocoupling of Terminal Alkynes; General Procedure

To a suspension of Cu^I-USY (70 mg, 0.3 equiv) in DMF (3 mL) was added the terminal alkyne (1 mmol, 1.0 equiv). The mixture was stirred at 110 °C vigorously overnight (15 h) and then it was taken up in CH_2Cl_2 (25 mL) and filtered over Nylon membranes (0.20 μm). After washing with 0.1 M HCl (3 × 25 mL), the organic layer was dried ($MgSO_4$) and filtered. Solvent evaporation provided the resulting diyne, usually with >95% purity (from NMR).

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