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Click Chemistry in Cu^{I}-zeolites: The Huisgen [3 + 2]-Cycloaddition

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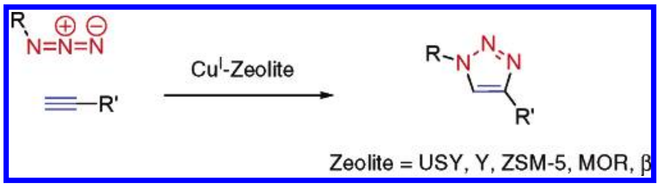
ABSTRACT



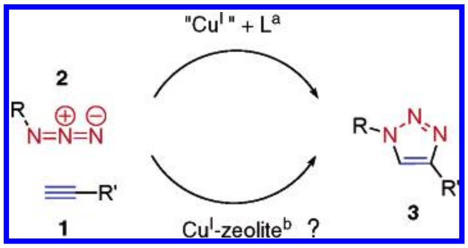
Cu^{I}-exchanged solids based on zeolite materials were investigated for the first time as catalysts in organic synthesis. The catalytic potential of these materials was evaluated in the Huisgen [3 + 2]-cycloaddition. Five Cu^{I}-exchanged zeolites were examined and Cu^{I}-USY proved to be a novel and efficient heterogeneous ligand-free catalyst for this "click chemistry"-type transformation.

The development of synthetic tools able to connect highly functionalized fragments still constitutes an exciting challenge for organic chemists. The so-called "click chemistry" establishing heteroatom linkages between unsaturated building blocks is probably the most effective way to connect molecules.[1] Among them, the Cu^{I}-catalyzed version[2] of the Huisgen [3 + 2]-cycloaddition[3] between a terminal alkyne **1** and an azide **2** is to date the most practical and useful "click" reaction, regioselectively affording 1,4-disubstituted 1,2,3-triazoles **3** (Scheme 1).[4,5]

In this reaction, the active Cu^{I} catalytic species are directly formed from Cu^{I} salts in the presence of ligands[2a,6] or prepared in situ by reduction of Cu^{II} salts[2b] or by oxidation of Cu turnings.[7] More flexible, supported, and reusable catalysts would clearly improve the scope of this click reaction.[8]

Involved in zeolite and other solid acid-catalyzed chemistry,[9] we were aware of the possibility of modifying such catalysts. Because Cu^{I}-modified zeolites have been recently described and characterized,[10] we thus wondered if such heterogeneous Cu^{I} species would catalyze the Huisgen reaction and give rise to click chemistry. We show here that Cu^{I}-zeolites are indeed an effective ligand-free catalyst for the Huisgen [3 + 2]-cycloaddition (Scheme 1).

Scheme 1



^{a} Classical catalytic system (L = ligand). ^{b}Investigated catalytic system.

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(1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137.

(2) For pioneering reports on a Cu^{I}-catalyzed variant, see: (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. For a recent review, see: (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51−68.

(3) (a) Huisgen, R.; Szeimis, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494−2507. (b) Huisgen, R. In *1,3-Dipolar Cycloadditional Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176. (c) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613−628.

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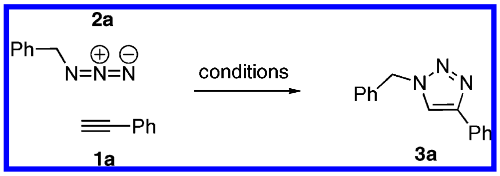
Because zeolites are solids mainly characterized by their topologies (cage or channel-type), pore size (typically 6−8 Å), and acidity (correlated to the Si/Al ratio), we prepared a series of catalysts derived from five representative zeolites, e.g., H-USY, H-Y, H-MOR, H-ZSM5, and H-β,[11] by subjecting them to CuCl treatment.[12] It is noteworthy that the incorporation as well as the stabilization of $\mathrm{Cu^{I}}$ ions in zeolite frameworks have been largely demonstrated in previous reports.[10]

The classical cycloaddition of phenylacetylene **1a** with benzyl azide **2a** was used to explore the efficiency of these $\mathrm{Cu^{I}}$-modified zeolites (Tables 1 and 2).

Without any catalyst, this reaction did not take place in toluene at room temperature (Table 1, entry 1), but led to a 1:1 mixture of regioisomers after a prolonged reaction time at reflux (Table 1, entry 2). With CuCl alone as the catalyst, the reaction was still very slow but yielded a single regioisomer (Table 1, entry 3). In sharp contrast, the modified zeolites $\mathrm{Cu^{I}}$-USY, $\mathrm{Cu^{I}}$-Y, $\mathrm{Cu^{I}}$-MOR, $\mathrm{Cu^{I}}$-ZSM5, and $\mathrm{Cu^{I}}$-β gave the expected adduct even at room temperature as a single regioisomer (Table 1, entries 4−13). Good to high yields were obtained in refluxing toluene (entries 5, 7, 9, 11, and 13) and even at room temperature, except for $\mathrm{Cu^{I}}$-β (entry 12 vs 4, 6, 8, and 10). $\mathrm{Cu^{I}}$-USY clearly appeared as

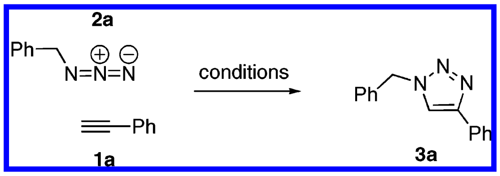
Table 1. Screening of Catalysts for the Cycloaddition of Phenylacetylene **1a** to Benzyl Azide **2a**[a]



entry	catalyst	temp (°C)	time (h)	yield (%)[b,c]
1	none	rt	96	<5[d]
2	none	110	48	70[e]
3	CuCl	rt	48	70[f]
4	$\mathrm{Cu^{I}}$-USY	rt	15	83
5	$\mathrm{Cu^{I}}$-USY	110	5	87
6	$\mathrm{Cu^{I}}$-Y	rt	15	68
7	$\mathrm{Cu^{I}}$-Y	110	5	75
8	$\mathrm{Cu^{I}}$-MOR	rt	15	69
9	$\mathrm{Cu^{I}}$-MOR	110	5	79
10	$\mathrm{Cu^{I}}$-ZSM5	rt	15	63
11	$\mathrm{Cu^{I}}$-ZSM5	110	5	79
12	$\mathrm{Cu^{I}}$-β	rt	15	47
13	$\mathrm{Cu^{I}}$-β	110	5	73
14	H-USY	rt	15	−[d]

[a] Reagents and reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv), solution concentration (1 M), 10 mol % of catalyst,[13] toluene. [b] Yields of isolated pure product **3a** after complete conversion unless otherwise stated (see Supporting Information). [c] Only the 1,4-adduct was formed and isolated unless otherwise noted. [d] Mainly recovery of the starting materials. [e] 1:1 mixture of regioisomers. [f] Incomplete conversion.

Table 2. Optimization of the Solvent[a]



entry	solvent	yield (%)[b,c]
1	$PhCH_3$	83
2	PhH	64
3	CH_2Cl_2	82[d]
4	THF	62[d]
5	CH_3CN	61[d]
6	CH_3OH	61[d,e]

[a] Reagents and reaction conditions: **1a** (1.2 equiv), **2a** (1.0 equiv), solution concentration (1 M), 10 mol % of catalyst,[13] 15 h, rt. [b] Yields of isolated pure product **3a**. [c] Only the 1,4-adduct was formed and isolated unless otherwise noted. [d] Unidentified byproducts were formed. [e] Incomplete conversion even after 48 h.

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(5) Triazoles exhibit interesting properties. (a) In liquid crystals, see: Gallardo, H.; Ely, F.; Bortoluzzi, A. J.; Conte, G. *Liq. Cryst.* **2005**, *32*, 667−671. (b) In multipolar chromophores, see: Parent, M.; Mongin, O.; Kamada, K.; Katan, C.; Blanchard-Desce, M. *Chem. Commun.* **2005**, 2029−2031. (c) As β-turn mimics, see: Oh, K.; Guan, Z. *Chem. Commun.* **2006**, 3069−3071.

(6) (a) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152−9153. (b) Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.*−*Eur. J.* **2006**, *12*, 7558−7564.

(7) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210−216.

(8) A polymer-supported catalyst, involving a $\mathrm{Cu^{I}}$−nitrogen ligand combination, has recently been reported. See: (a) Girard, C.; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689−1692. For copper catalysts avoiding the use of an additive ligand or reducing agent, see: (b) Pachon, L. D.; van Maarseveen, J. H.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 811−815. (c) Molteni, G.; Bianchi, C. L.; Marinoni, G.; Santod, N.; Ponti, A. *New J. Chem.* **2006**, *30*, 1137−1139.

(9) For recent examples, see: (a) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Chem. Commun.* **2004**, 1754−1755. (b) Haouas, M.; Walspurger, S.; Taulelle, F.; Sommer, J. *J. Am. Chem. Soc.* **2004**, *126*, 599−606. (c) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391−8394. (d) Walspurger, S.; Sun, Y.; Sani Souna Sido, A.; Sommer, J. *J. Phys. Chem. B* **2006**, *110*, 18368−18373. (e) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *J. Mol. Catal. A* **2006**, *245*, 231−234.

(10) (a) Lamberti, C.; Turnes Palomino, G.; Bordiga, S.; Berlier, G.; D'Acapito, F.; Zecchina, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2138−2141. (b) Turnes Palomino, G.; Bordiga, S.; Zecchina, A.; Marra, G. L.; Lamberti, C. *J. Phys. Chem. B* **2000**, *104*, 8641−8651. (c) Bolis, V.; Meda, L.; D'Acapito, F.; Turnes Palomino, G.; Bordiga, S. *J. Chem. Phys.* **2000**, *113*, 9248−9261. (d) Lamberti, C.; Bordiga, S.; Bonino, F.; Prestipino, C.; Berlier, G.; Capello, L.; D'Acapito, F.; Llabrés i Xamena, F. X.; Zecchina, A. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4502−4509. (e) Prestipino, C.; Capello, L.; D'Acapito, F.; Lamberti, C. *Phys. Chem. Chem. Phys.* **2005**, *7*, 1743−1746. For a recent review, see: (f) Berthomieu, D.; Delahay, G. *Catal. Rev.* **2006**, *48*, 269−313.

(11) Characteristics of H-zeolites are given in Supporting Information.

(12) For the preparation of $\mathrm{Cu^{I}}$-zeolites, we adopted the solid-state exchange procedure reported in: Li, Z.; Xie, K.; Slade, R. C. T. *Appl. Catal. A: Gen.* **2001**, *209*, 107−115.

the best system (entries 4 and 5 vs 6−13). Furthermore, an experiment performed on native H-USY did not yield any expected adduct **3a**, highlighting the key role of copper loaded in the zeolite (entry 14 vs 4).

These data thus show that the Cu^{I} catalytic activity is significantly enhanced in the presence of modified zeolites.

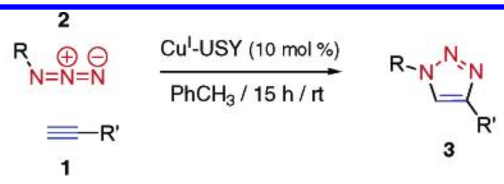
After selection of the most efficient catalyst, we screened different solvents to adjust the reaction conditions (Table 2). Among the solvents examined, toluene and benzene were the only ones where reactions proceeded without detectable formation of byproducts. Toluene proved to be the best solvent, being more effective than benzene (Table 2, entry 1 vs 2). In dichloromethane, the yield was very similar to the one in toluene (entry 3), but the reaction was however less clean. More polar solvents such as tetrahydrofuran, acetonitrile, and methanol led to lower yields and to the formation of undesirable byproducts (entries 4−6). In the case of toluene and benzene, purity of the crude adduct was more than 95% as judged by ^{1}H NMR (see Supporting Information). With other solvents, chromatography purification was required to obtain pure **3a** (entries 3−6). We also examined the recycling of the catalyst. It is noteworthy that, under the optimized reaction conditions (i.e., Cu-USY catalyst in toluene), the catalyst was reused three times without dramatic yield loss.

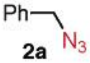
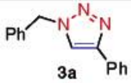
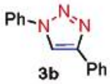
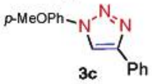
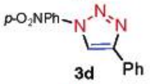
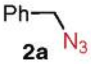
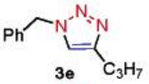
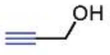
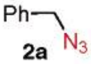
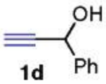
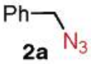
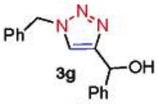
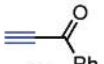
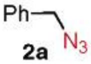
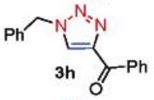
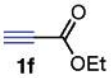
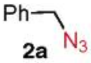
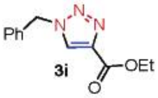
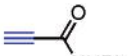
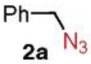
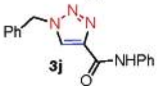
To explore the scope of this reaction, simple alkynes bearing different functional groups **1b**−**g** were submitted to various azides **2b**−**d** in the presence of Cu^{I}-USY as catalyst (Table 3, entries 1−10).

Simple nonfunctionalized alkynes such as **1b** reacted with benzyl azide **2a** very efficiently, giving the expected adduct **3e** as a single regioisomer in excellent yield (Table 3, entry 5). Hydroxy-substituted alkynes such as **1c** and **1d** also gave the expected adducts **3f**,**g** as a single regioisomer in good to high yields (Table 3, entries 6 and 7).

Electronic effects are known to influence cycloadditions.[14,15] Although the mechanism of the Cu^{I}-catalyzed Huisgen reaction is probably different from a classical [3 + 2]-cycloaddition,[16] we nevertheless investigated on one hand the reaction of terminal alkynes substituted by either an electron-donating or -withdrawing group (entries 1 and 5−10) and on the other hand the reaction of phenyl azides bearing or not an electron-donating or -withdrawing group at the para position (entries 2−4).

Table 3. Scope of the Catalytic System^{a}



entry	alkyne	azide	product	yield (%)^{b,c}
1	$\equiv$—Ph **1a**	 **2a**	 **3a**	83
2	$\equiv$—Ph **1a**	Ph—N$_3$ **2b**	 **3b**	59
3	$\equiv$—Ph **1a**	*p*-MeOPh—N$_3$ **2c**	 **3c**	61
4	$\equiv$—Ph **1a**	*p*-O$_2$NPh—N$_3$ **2d**	 **3d**	traces^{d}
5	$\equiv$—C$_3$H$_7$ **1b**	 **2a**	 **3e**	85
6	 **1c**	 **2a**	 **3f**	64
7	 **1d**	 **2a**	 **3g**	83
8	 **1e**	 **2a**	 **3h**	52^{e}
9	 **1f**	 **2a**	 **3i**	76^{e}
10	 **1g**	 **2a**	 **3j**	87

^{a} Reagents and reaction conditions: **1** (1.2 equiv), **2** (1.0 equiv), solution concentration (1 M), 10 mol % of Cu^{I}-USY,[13] toluene, 15 h, rt. ^{b}Yields of isolated pure product **3**. ^{c}Only the 1,4-adduct was formed and isolated unless otherwise noted. ^{d}Mainly recovery of the starting materials. ^{e}Unidentified byproducts were formed.

With benzyl azide **2a**, no significant difference was observed with acetylenes substituted with an alkyl, a phenyl, or an electron-withdrawing group (entries 1, 5, and 10). With phenylacetylene **1a**, phenyl azide itself **2b** gave the expected 1,4-diphenyl-1,2,3-triazole **3b** in good yield after chromatography (entry 2). Its *para*-methoxy analogue **2c** reacted similarly (entry 3). However, the corresponding *para*-nitrophenyl azide **2d** did not react under the same conditions and only traces of the expected adduct could be detected, revealing a deleterious effect of electron-withdrawing substitutents on the reaction (entry 4).

Acetylenes conjugated with either an amide or an ester group such as **1f** and **1g** reacted without any problem with benzyl azide. The corresponding triazoles **3i** and **3j** were obtained in high yields (entries 9 and 10). However, 1-phenylpropynone **1e** seemed to decompose under the reaction conditions, even at room temperature, and byproducts were formed. The yield of triazole **3h** was therefore lower (entry 8).

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(13) Concerning Cu^{I}-zeolite, 10 mol % of catalyst corresponds to 10 mol % of Cu^{I} species based on the theoretical number of native acidic sites of the corresponding H-zeolite. For a recent method of determination of Brönsted acid sites on zeolites, see: Louis, B.; Walspurger, S.; Sommer, J. *Catal. Lett.* **2004**, *93*, 81−84.

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In conclusion, we have reported *for the first time* an original use of Cu^I-modified zeolites as catalysts in organic synthesis. With such catalysts, we have developed a simple and efficient method for the [3 + 2]-cycloaddition of terminal alkynes with azides. Moreover, a single regioisomer, the 1,4-diphenyl-1,2,3-triazole, was formed. These results thus broaden the scope of this so-called click chemistry.

Further work is now underway to expand the use of modified zeolites as catalysts in organic synthesis and to better understand the role of the zeolite core in these reactions.

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Supporting Information Available: General procedure and ^{13}C NMR spectra of known compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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