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Copper Zeolites as Green Catalysts for Multicomponent Reactions of Aldehydes, Terminal Alkynes and Amines: An Efficient and Green Synthesis of Propargylamines

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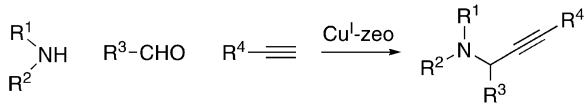
Cu^I-modified zeolites, especially Cu^I-USY, have proved to be very efficient catalysts in multicomponent reactions, allowing for a solvent-free synthesis of propargylamines from aldehydes, amines, and terminal alkynes. With a heterogeneous catalyst and in the absence of solvent, this process is among the greenest ever reported. A mechanism has been proposed for this three-component reaction.

Introduction

One of the fundamental aspects in (green) chemistry is linked to the number of steps in organic synthesis as well as atom economy. As mentioned by Marek, the Guest Editor for a recent special issue of Tetrahedron Symposium-in-Print on Multicomponent Reactions,[1] "the practical construction techniques available to prepare elaborate products are still woefully inadequate. A seemingly trivial but rather serious limitation in practice is set by the mere number of steps accumulating in linear sequences". Multicomponent reactions (MCRs) are thus becoming an increasingly important class of reactions as they allow several starting materials to be combined usually to form a single compound and in a one-pot operation.[2] They therefore exhibit an economy of steps and often atom economy, most of the incoming atoms being linked together in a single product.

Combining these aspects with heterogeneity and catalysis would reinforce the "greenness" of such reactions. In order to offer solutions to such problems, we are currently applying zeolites, modified or unmodified, to organic synthesis.[3] In this work, we describe a solvent-free zeolite-catalyzed synthesis of propargylic amines through a three-component reaction (Scheme 1).



Scheme 1. Cu^I-zeolite-catalyzed three-component synthesis of propargylamines.

Propargylamines are high-value building blocks in organic synthesis[4] and their structural motif has been found in various natural products[5] and in compounds of pharmaceutical[6] or phytoprotective[7] importance. They can be obtained by the addition of alkynes to imines,[4] but as imines are easily formed from aldehydes and amines, three-component versions of the reaction are known, either as such[8] or promoted by various transition metals.[9] A few supported reactions or reactions based on heterogeneous catalysts have recently been described, but no zeolite-catalyzed reaction has so far been reported.[10]

Results and Discussion

Cu^I-Modified Zeolites as Catalysts in MCRs

To search for the optimal zeolite catalyst, five representative zeolites, that is, H-USY, H-Y, H-MOR, H-ZSM5, and H-β, were modified by CuCl treatment according to a reported solid-state exchange procedure.[11] Their behavior in MCRs was screened by using a classical reaction, the synthesis of propargylamines (Scheme 1).

To screen the zeolite catalysts and the reaction conditions, we selected first a commonly used amine, piperidine (**1a**), a reactive aldehyde, benzaldehyde (**2a**), and phenylacetylene (**3a**) as one of the simplest alkynes. The results are collected in Table 1.

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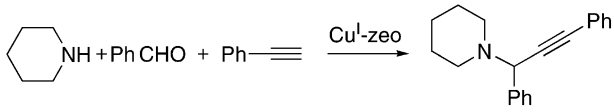
Table 1. Search for optimal zeolite catalysts and reaction conditions.[a]



Entry	Catalyst	Solvent	Temp. [°C]	Yield[b] [%]	Number of acidic sites [mmol/g]	Pore diameter [Å]	Topology
1	Cu^I-USY	DMF	60	40	4.39	7.4 × 7.4	cage-type
2	Cu^I-USY	toluene	60	37	4.39	7.4 × 7.4	cage-type
3	Cu^I-USY	toluene	80	72	4.39	7.4 × 7.4	cage-type
4	Cu^I-USY	THF	60	41	4.39	7.4 × 7.4	cage-type
5	Cu^I-USY	THF	80	79	4.39	7.4 × 7.4	cage-type
6	Cu^I-USY	MeCN	60	35	4.39	7.4 × 7.4	cage-type
7	Cu^I-USY	MeCN	80	71	4.39	7.4 × 7.4	cage-type
8	Cu^I-USY	none	80	95	4.39	7.4 × 7.4	cage-type
9	Cu^I-Y	none	80	92	6.67	7.4 × 7.4	cage-type
10	Cu^I-β	none	80	90	0.90–1.23	7.6 × 6.4 5.5 × 5.5	channel-type
11	Cu^I-ZSM5	none	80	80	1.04	5.1 × 5.5 5.3 × 5.6	channel-type
12	Cu^I-MOR	none	80	71	1.48	6.5 × 7.0 3.4 × 3.8	channel-type
13	H-USY	none	80	–[c]	6.67	7.4 × 7.4	cage-type
14	CuCl	none	80	40–90[c]	–	–	–
15	none	none	80	–[d]	–	–	–

[a] Reaction performed with 1 mmol of each component for 15 h with a zeolite loading of 20 mg.[12] [b] Yields were evaluated by NMR analysis of the crude mixture. [c] Upon mixing without solvent, intense heat was evolved leading to decomposition, whereas in solvent good yields were obtained.[8,9] [d] No transformation was observed.

Preliminary experiments in various solvents revealed that the reaction was more dependent on temperature than on solvent polarity (Table 1, Entries 1–7). Indeed, reaction yields were similar in nonpolar or slightly polar solvents (Entries 2 and 4) as well as in polar solvents (Table 1, Entries 1 and 6) at 60 °C. At a higher temperature, the reaction was best performed in THF (Entry 5) rather than in nonpolar or polar solvents (Entries 3 and 7, respectively). Gratifyingly, the reaction was far more efficient *without solvent*, being almost quantitative under such conditions (Entry 8).

Under these solvent-free conditions, the zeolite nature proved to be critical (Table 1, Entries 8–12). As expected for MCRs in which three molecules have to meet within the zeolites, the internal shapes of the zeolites have a marked influence on the reaction efficiency. Cage-type zeolites were observed to be better catalysts than zeolites containing channel pores (Entries 8 and 9 vs. 10–12). In the latter series, the reaction efficiency seemed directly correlated with the pore size (compare Entries 10–12). In this MCR, the three starting reagents have to meet and react within the internal pores of the zeolites, and the observed results fit with this logic. Indeed, the larger cage systems, which could better accommodate three molecules together and their intermediates than the channel systems, which usually have smaller diameters, gave better results (Entries 8 and 9 vs. 10–12). For the zeolites with channel systems, the smaller the diameter, the less efficient is the reaction (Entries 10–12).

With an unmodified zeolite, no reaction took place (Entry 13). Likewise, no reaction occurred in the absence of a catalyst (Entry 15). CuCl alone did give the product,[8,9] but as expected without solvent, a significant increase in temperature occurred upon mixing the products that led to decomposition (Entry 14). Moreover, CuCl is almost insoluble under such peculiar conditions. These results clearly emphasize the role of the zeolite itself and of the copper within the zeolite.

Cu^I-Zeolite Catalyst Recycling

Heterogeneous catalysts offer ease of handling and purification through simple filtration. They also allow catalyst recovery and recycling, another interesting eco-friendly aspect of these catalysts. In order to examine this possibility, we performed the condensation reaction between piperidine (**1a**), benzaldehyde (**2a**), and phenylacetylene (**3a**) several times with the same Cu^I-USY catalyst, the latter being filtered and reused after each run with reactivation.[13] As shown in Figure 1, the Cu^I-USY catalyst could be recycled up to four times. However, the product yield was reduced on the fifth reuse of the catalyst (Run 5 vs. 1–4).[13]

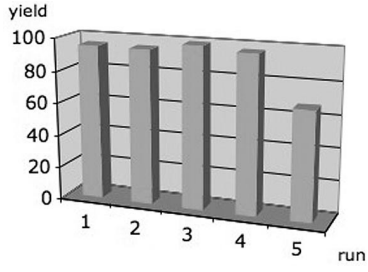
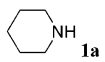
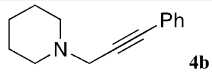
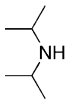
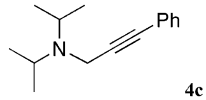
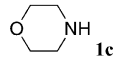
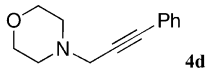
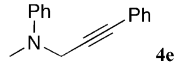
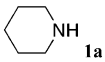
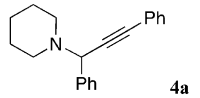
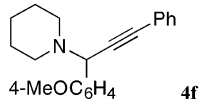
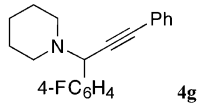
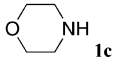
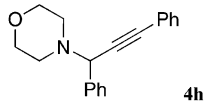
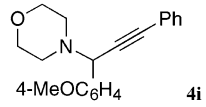
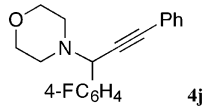
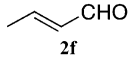
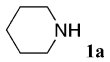
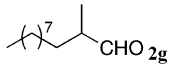
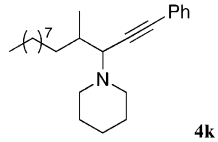
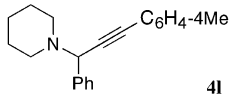
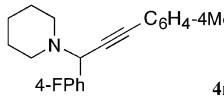
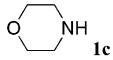
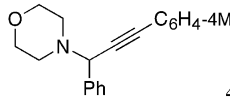
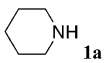
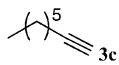
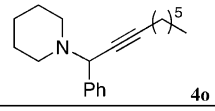


Figure 1. Recovery studies: Condensation of phenylacetylene (**3a**) with benzaldehyde (**1a**) and piperidine (**2a**) successively catalyzed by the same recovered Cu^I-USY upon reactivation.

Table 2. Scope of the condensation reaction catalyzed by Cu^{I}-modified zeolites.[a]

Entry	Amine	Aldehyde	Alkyne	Product	Yield [%][b]
1	 **1a**	H–CHO **2b**	Ph–≡ **3a**	 **4b**	90
2	 **1b**	"	"	 **4c**	80
3	 **1c**	"	"	 **4d**	83
4	 **1d**	"	"	 **4e**	60
5	 **1a**	Ph–CHO **2a**	Ph–≡ **3a**	 **4a**	80
6	"	4-$MeOC_6H_4$–CHO **2c**	"	 **4f**	77
7	"	4-FC_6H_4–CHO **2d**	"	 **4g**	86
8	"	4-$O_2NC_6H_4$–CHO **2e**	"	–	dec.[c]
9	 **1c**	Ph–CHO **2a**	Ph–≡ **3a**	 **4h**	70
10	"	4-$MeOC_6H_4$–CHO **2c**	"	 **4i**	68
11	"	4-FC_6H_4–CHO **2d**	"	 **4j**	79
12	"	4-$O_2NC_6H_4$–CHO **2e**	"	–	dec.[c]
13	"	 **2f**	"	–	dec.[c]
14	 **1a**	 **2g**	"	 **4k**	60[d]
15	"	Ph–CHO **2a**	4-MePh–≡ **3b**	 **4l**	85
16	"	4-FC_6H_4–CHO **2d**	"	 **4m**	55
17	 **1c**	Ph–CHO **2a**	"	 **4n**	82
18	 **1a**	Ph–CHO **2a**	 **3c**	 **4o**	81

[a] Reaction performed with 1 mmol of each component for 15 h with a zeolite loading of 20 mg, that is, ca. 0.08 mmol Cu^{I}.[12] [b] Yields of isolated products after chromatography. [c] Decomposition was observed. [d] Unidentified byproducts were also formed.

Scope of the Three-Component Reaction Catalyzed by Cu^{I}-Modified Zeolites

With these "green" conditions in hand, we then explored the scope of this new Cu^{I}-zeolite-catalyzed MCR. We also investigated the role of each reagent in this three-component condensation (Table 2).

The effect of the amine was examined by submitting amines of increasing bulkiness or of decreasing nucleophilicity to the reaction with benzaldehyde (**2a**) or formaldehyde (**2b**) and phenylacetylene (**3a**) (Table 2, Entries 1–5 and 9). Piperidine (**1a**) gave the corresponding propargylamines **4a**,**b** in excellent isolated yields, the smaller aldehyde giving the highest yield (Entry 1 vs. 5). The more bulky diisopropylamine (**1b**) also gave the expected propargylamine **4c**, but as expected, the yield of isolated product was lower (Entry 2 vs. 1). With its electron-withdrawing oxygen atom in β-position to the nitrogen atom in a cyclohexyl structure, morpholine (**1c**) is less nucleophilic than piperidine (**1a**). Indeed, when submitted to the above-mentioned conditions, the yield of the corresponding propargylamine **4d** was significantly lowered (Entry 3 vs. 1). The same effect was also observed with benzaldehyde (Entry 9 vs. 5). With the even less nucleophilic *N*-methylaniline (**1d**), the yield was even lower (Entry 4 vs. 1).

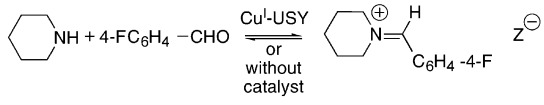
The effect of the aldehyde was then examined on mechanistic grounds. Owing to the mechanism of this condensation reaction under conventional conditions, the more electrophilic the aldehyde, the easier the reaction, and the reverse should also be true. This is indeed what was observed in this reaction with a series of benzaldehyde derivatives. Piperidine (**1a**) was again used as well as phenylacetylene (**3a**). With these reagents, benzaldehyde (**2a**) gave a high isolated yield of the expected adduct **4a**, whereas the more electron-rich *p*-anisaldehyde (**2c**) led to a slightly lower yield of **4f** and the more electron-poor *p*-fluorobenzaldehyde (**2d**) gave the best results (Entry 7 vs. 6 and 5). However, *p*-nitrobenzaldehyde (**2e**) did not give any adduct, and only a mixture of resinous compounds was observed. The same behavior was observed with the less nucleophilic morpholine **1c** (Entries 9–12).

With conjugated but nonaromatic aldehydes, for example, **2f**, the expected adduct could not be obtained. It seemed that under the reaction conditions only decomposition occurred, with mainly polymerization of the starting conjugated aldehyde (Entry 13). However, with nonconjugated aldehydes such as 2-methylundecanal (**2g**), the MCR proceeded smoothly with piperidine and phenylacetylene leading to the expected adduct in good yield (Entry 14).

The effect of the alkyne on this Cu^{I}-zeolite-catalyzed MCR was also investigated. As already shown above, phenylacetylene (**3a**) was highly reactive, usually giving good to high yields of adducts depending on the co-reacting amine and aldehyde (Entries 1–7, 9–11, and 14). Tolylacetylene (**3b**) was almost as effective as phenylacetylene (**3a**), giving the expected adducts in high yields with benzaldehyde (**2a**) and various amines (Entries 15 and 17). Surprisingly, its reaction with *p*-fluorobenzaldehyde (**2d**) only gave a modest yield of the corresponding adduct **4m**, despite the favorable electron density of this aldehyde (Entry 16 vs. 7 and 11). Aliphatic alkynes reacted as well as aromatic ones, as exemplified with 1-octyne (**3c**), which gave the expected adduct **4o** in a high yield, similar to that obtained with tolyl- or phenylacetylene (Entry 18 vs. 15 or 5).

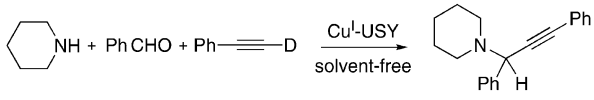
Mechanistic Studies

In such MCRs, the reaction proceeds through the initial formation of an iminium intermediate from the starting amine and aldehyde. This iminium compound then reacts with the alkyne, usually in the presence of a metal as catalyst. However, the iminium formation, which proceeds through an aminal, is equilibrated, and this equilibrium could be influenced by the zeolite. The residual acidity[14] of the exchanged zeolite could indeed favor iminium formation (cf. Scheme 4), and interactions of the oxygen or nitrogen atoms with the zeolite frame could also facilitate the reaction. To check for this possibility, we monitored by NMR spectroscopy the evolution of a mixture of piperidine and *p*-fluorobenzaldehyde in the presence or absence of Cu^{I}-USY (Scheme 2). At 80 °C, the signal at $\delta \approx 9$ ppm, typical of an iminium proton, gradually grew, and its relative integration reached a plateau. These results and the fact that the proportion of the iminium species was significantly higher in the presence of zeolite than in its absence (24 ± 3 vs. 14 ± 2%, respectively) tends to support an active role of the zeolite in the formation of this intermediate.



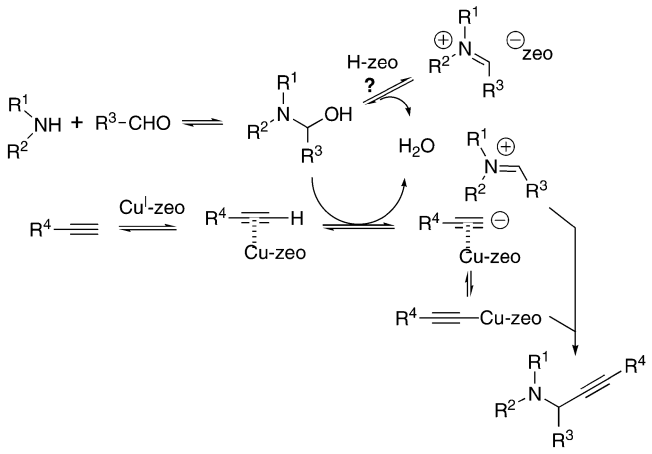
Scheme 2. Equilibrium mixture obtained from piperidine and *p*-fluorobenzaldehyde in the presence or absence of Cu^{I}-USY.

Under our conditions, the copper ions present in the exchanged zeolite probably act as the catalyst. Upon coordination, the alkyne is probably deprotonated,[15] either by the starting amine or the intermediate aminal. The copper acetylide thus formed could then add concomitantly to the iminium compound produced within the zeolite (cf. Scheme 4). Accordingly, a reaction performed with deuteriated phenylacetylene in the presence of benzaldehyde and piperidine yielded the expected adduct without any deuterium (Scheme 3).



Scheme 3. Cu^{I}-USY-catalyzed reaction between piperidine, benzaldehyde, and 1-deuterio-2-phenylacetylene.

These results support the mechanism presented in Scheme 4.



Scheme 4. Proposed mechanism for the MCR catalyzed by Cu^{I}-USY.

Conclusions

Cu-modified zeolites, especially Cu-USY, proved to be very efficient catalysts for the synthesis of propargylamines from aldehydes, amines, and alkynes. Moreover, no solvent is required for this reaction, and upon filtration the adduct is usually obtained as a single compound. Therefore, with a heterogeneous catalyst, which can be reused, this multicomponent reaction fulfills most of the principles of green chemistry. Preliminary mechanistic investigations suggest that this reaction proceeds via an iminium intermediate, probably assisted by zeolite, and that this formation is combined with the formation of acetylide within the zeolite pores, leading to an efficient 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) using UV light and *p*-anisaldehyde for visualization. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck) by using mixtures of ethyl acetate and cyclohexane as eluents. Solvents were removed by evaporation under reduced pressure at temperatures below 30 °C unless otherwise noted. IR spectra were recorded with a Perkin-Elmer FTIR 1600 spectrometer (KBr disc), and values are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with 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. The chemical shifts are reported relative to the residual solvent as an internal standard ([D_1]chloroform: δ = 7.26 ppm for ^1H and 77.0 ppm for ^{13}C; [D_4]methanol: δ = 3.31 ppm for ^1H and 49.15 ppm for ^{13}C). Carbon multiplicities were determined by DEPT 135 experiments. Electron impact (EI) and electrospray (ESI) low- and high-resolution mass spectra were recorded at the mass spectrometry department of the Institut de Chimie, Strasbourg.

Preparation of Cu^{I}-USY: Commercial NH_4-USY was loaded in an oven and heated at 550 °C for 4 h to give H-USY. H-USY (1 g) and CuCl (475 mg, 1.1 equiv.) were mixed by using a mortar and charged in a closed reactor. The mixture of powders was heated at 350 °C for 3 d under a nitrogen flow, quantitatively yielding Cu^{I}-USY.

General Procedure for the Cu^{I}-Zeolite-Catalyzed Condensation of Amines, Aldehydes, and Terminal Alkynes: Amines **1a**–**d** (1.0 mmol, 1.0 equiv.), aldehydes **2a**–**f** (1.0 mmol, 1.0 equiv.), and then alkynes **3a**,**b** (1.2 mmol, 1.2 equiv.) were successively added to Cu^{I}-USY (20 mg, 0.07 equiv.). After stirring at 80 °C for 15 h, the mixture was diluted with dichloromethane (5 mL). After removing the catalyst by filtration, solvent evaporation provided the resulting crude product usually at ca. 95% purity as judged by NMR spectroscopy. Column chromatography was then performed. Most of the adducts thus formed are known compounds, and propargylamines **4a**,[10a,10b] **4b**,[9a,10a] **4c**,[10f,16] **4d**,[9e] **4e**,[9e,10f] **4f**,[9k,10a] **4g**,[9k] **4h**,[10a,10d] **4i**,[10c] **4j**,[9k] **4l**,[9k,10b] **4n**,[10c] and **4o**[9k,10b] have been reported previously.

4-Methyl-3-(piperidin-1-yl)-1-phenyltridec-1-yne (4k): A 1:1 mixture of diastereoisomers as a yellowish oil. IR (neat): $\tilde{\nu}$ = 2360, 2340, 1465, 1376, 1157, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.44–7.50 (m, 2 × 2 H), 7.27–7.33 (m, 2 × 3 H), 3.09 and 3.13 (2 d, J = 9 Hz, 2 × 1 H), 2.63–2.71 (m, 2 × 2 H), 2.43–2.50 (m, 2 × 2 H), 1.78–1.86 (m, 2 × 3 H), 1.58–1.70 (m, 2 × 4 H), 1.42–1.52 (m, 2 × 2 H), 1.21–1.40 (br. s, 2 × 16 H), 1.04 and 1.13 (2d, J = 6 Hz, 2 × 3 H), 0.92–0.95 (m, 2 × 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 131.73, 128.18, 127.76, 123.93, 88.05, 86.04, 64.56, 64.38, 51.19, 51.06, 50.86, 35.50, 34.87, 34.38, 33.19, 32.01, 30.24, 29.74, 29.25, 26.98, 26.58, 26.39, 24.83, 23.92, 22.78, 21.77, 17.50, 16.58, 14.18 ppm. MS: *m*/*z* (%) = 354 (100) $[M + 1]^+$, 283 (4), 240 (2). HRMS: calcd. 354.3155; found 354.3148.

1-(4-Fluorophenyl)-1-(piperidin-1-yl)-3-(*p*-tolyl)prop-2-yne (4m): Yellowish oil. IR (neat): $\tilde{\nu}$ = 2360, 2320, 1604, 1506, 1222, 1154, 815 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.64 (br. dd, J = 9, 6 Hz, 2 H), 7.44 (d, J = 7 Hz, 2 H), 7.15 (d, J = 7 Hz, 2 H), 7.05 (br. dd, J = 9, 8 Hz, 2 H), 4.78 (s, 1 H), 2.56 (br. t, J = 6 Hz, 4 H), 2.38 (s, 3 H), 1.52–1.70 (m, 4 H), 1.42–1.51 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.14 ($J_{C,F}$ = 244 Hz, C), 138.16 (C), 134.46 ($J_{C,F}$ = 2.5 Hz, C), 131.62 (CH), 129.98 ($J_{C,F}$ = 8 Hz, CH), 128.99 (CH), 120.03 (C), 114.72 ($J_{C,F}$ = 20.9 Hz, CH), 88.14 (C), 84.49 (C), 61.60 (CH), 50.51 (CH_2), 26.19 (CH_2), 24.38 (CH_2), 21.40 (CH_3) ppm. MS: *m*/*z* (%) = 308 (100) $[M + 1]^{2+}$, 223 (45). HRMS: calcd. 308.1736; found 308.1897.

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[1] I. Marek, *Tetrahedron* **2005**, *61*, 11309–11519.
[2] a) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; b) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
[3] a) A. Sani-Souna-Sido, S. Chassaing, P. Pale, J. Sommer, *Appl. Catal., A* **2008**, *336*, 101–108; b) S. Chassaing, M. Kumarraja, P. Pale, J. Sommer, *Org. Lett.* **2007**, *9*, 3889–3892; c) A. Sani Souna Sido, S. Chassaing, M. Kumarraja, P. Pale, J. Sommer, *Tetrahedron Lett.* **2007**, *48*, 5911–5914; d) S. Chassaing, M. Kumarraja, A. Sani Souna Sido, P. Pale, J. Sommer, *Org. Lett.* **2007**, *9*, 883–886.
[4] For a review, see: L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275.
[5] a) M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. VanDuyne, J.

Clardy, *J. Antibiot.* **1989**, *42*,1449–1451; b) M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. VanDuyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715–3721.

[6] a) T.-S. Hu, R. Tannert, H.-D. Arndt, H. Waldmann, *Chem. Commun.* **2007**, 3942–3944; b) H.-B. Jeon, Y. Lee, C. Qiao, H. Huang, L. M. Sayre, *Bioorg. Med. Chem.* **2003**, *11*, 4631–4641; c) J. L. Wright, T. F. Gregory, S. P. Kesten, P. A. Boxer, K. A. Serpa, L. T. Meltzer, L. D. Wise, S. A. Espitia, C. S. Konkoy, E. R. Whittemore, R. M. Woodward, *J. Med. Chem.* **2000**, *43*, 3408–3419; d) P. J. Connolly, S. K. Wetter, K. N. Beers, S. C. Hamel, R. H. K. Chen, M. P. Wachter, J. Ansell, M. M. Singer, M. Steber, D. M. Ritchie, D. C. Argentieri, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 979–984; e) P. H. Yu, B. A. Davies, A. A. Boulton, *J. Med. Chem.* **1992**, *35*, 3705–3713; f) R. Salvador, D. Z. Simon, L. Leonard, PCT Int. Appl. WO9320804, **1993**; g) F. N. Shirota, E. G. DeMaster, H. T. Nagasawa, *J. Med. Chem.* **1979**, *22*, 463–464.

[7] C. Swithenbank, P. J. McNulty, K. L. Viste, *J. Agric. Food Chem.* **1971**, *19*, 417–442.

[8] a) L.Brandsma, *Preparative Acetylene Chemistry*, Elsevier, Amsterdam, **1971**; b) M. B. Smith, J. March *Advanced Organic Chemistry*, 5th ed., Wiley, New York, **2001**.

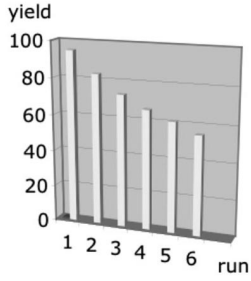
[9] For Cu-catalyzed reactions, see: a) O. Russo, S. Messaoudi, A. Hamze, N. Olivi, J.-F. Peyrat, J.-D. Brion, S. Sicsic, I. Berque-Bestel, M. Alami, *Tetrahedron* **2007**, *63*, 10671–10683; b) N. Gommermann, P. Knochel, *Chem. Eur. J.* **2006**, *12*, 4380–4392; c) Z.-Y. Yan, Y.-B. Zhao, M.-J. Fan, W.-M. Liu, Y.-M. Liang, *Tetrahedron* **2005**, *61*, 9331–9337; d) N. Olivi, P. Spruyt, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* **2004**, *45*, 2607–2610; e) L. W. Bieber, M. F. Da Silva, *Tetrahedron Lett.* **2004**, *45*, 8281–8283; f) B. Sreedhar, P. Surendra Reddy, B. Veda Prakash, A. Ravindra, *Tetrahedron Lett.* **2005**, *46*, 7019–7022; for Ag-catalyzed reactions, see: g) Z. Li, C. Wei, L. Chen, R. S. Varma, C.-J. Li, *Tetrahedron Lett.* **2004**, *45*, 2443–2447; h) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473–4475; for Au-catalyzed reactions, see: i) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*, 1529–1532; j) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; for Zn-catalyzed reactions, see: k) E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, *Tetrahedron Lett.* **2007**, *48*, 7184–7190; for Ru-catalyzed reactions, see: l) V. Cadierno, J. Gimeno, N. Nebra, *Chem. Eur. J.* **2007**, *13*, 9973–9998.

[10] a) P. Li, L. Wang, *Tetrahedron* **2007**, *63*, 5455–5459; b) M. L. Kantam, V. Balasubrahmanyam, K. B. S. Kumar, G. T. Venkanna, *Tetrahedron Lett.* **2007**, *48*, 7332–7334; c) B. Sreedhar, P. S. Reddy, C. S. V. Krishna, P. V. Babu, *Tetrahedron Lett.* **2007**, *48*, 7882–7886; d) P. R. Likhar, S. Roy, M. Roy, M. S. Subhas, M. L. Kantam, R. L. De, *Synlett* **2007**, 2301–2303; e) K. Mohan Reddy, N. Seshu Babu, I. Suryanarayana, P. S. Sai Prasad, N. Lingaiah, *Tetrahedron Lett.* **2006**, *47*, 7563–7566; f) B. M. Choudary, C. Sridhar, M. L. Kantam, B. Sreedhar, *Tetrahedron Lett.* **2004**, *45*, 7319–7321; g) A. Sharifi, H. Farhangian, F. Mohsenzadeh, M. R. Naimi-Jamal *Monatsh. Chem.* **2002**, *133*, 199–204; during the submission-revision of the present manuscript, a similar reaction was reported, see: R. Maggi, A. Bello, C. Oro, G. Sartori, L. Soldi, *Tetrahedron* **2008**, *64*, 1435–1439.

[11] Z. Li, K. Xie, R. C. T. Slade, *Appl. Catal., A* **2001**, *209*, 107–115.

[12] 10 mol-% catalyst corresponds to 10 mol-% Cu^{I} species based on the theoretical number of native acidic sites of the corresponding H-zeolite. For recent methods of determination of Brønsted acid sites on zeolites, see: B. Louis, S. Walspurger, J. Sommer, *Catal. Lett.* **2004**, *93*, 81–84; S. Walspurger, B. Louis, *Appl. Catal. A-Gen.* **2007**, *336*, 109–115.

[13] The catalyst was reactivated by calcination at 300 °C in a stream of air for 1 h. With practical synthetic aspects in mind, the zeolite catalyst was also reused as such, without reactivation. In this case, a slow but regular decrease in efficiency was observed (see Figure). It is known that deactivation occurred by coke slowly building up in the zeolite pores.



[14] Applying the H/D titration method that we developed for the determination of acidic sites in zeolites[12] to H-USY treated with CuCl revealed that the H/Cu exchange process was not complete and ca. 20% of the acidic sites remained.

[15] Such a coordination/deprotonation/acetylide formation sequence has been demonstrated for silver ions, see: U. Halbes-Letinois, P. Pale, S. Berger, *J. Org. Chem.* **2005**, *70*, 9185–9190.

[16] H. Nakamura, T. Kamakura, M. Ishikura, J.-F. Biellmann, *J. Am. Chem. Soc.* **2004**, *126*, 5958–5959.

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