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Zeo-Click Synthesis: Copper-Zeolite-Catalyzed Synthesis of Ynamides

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Abstract: Copper(I)-zeolites, especially copper(I)-ultra stable Y zeolite (USY), are very efficient heterogeneous catalysts for the coupling of functionalized 1-bromoalkynes and various nitrogen derivatives. Under these conditions, sulfonylated alkyl- or arylamines and various N-heterocycles, such as oxazolidinones or indoles, could be efficiently transformed into the corresponding *N*-alkynyl derivatives. However, imidazoles gave addition products rather than coupling products. The reaction conditions proved compatible with a variety of functional and protecting groups. Such zeolitic catalysts can be recycled and reused at least five times without significant deactivation. Low catalyst loading could be used (4 mol%) and as low as *0.8 mol%* of this heterogeneous copper catalyst still gave good conversion and yields.

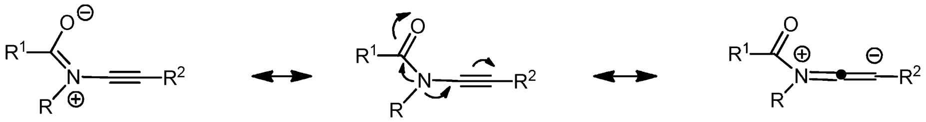
Keywords: copper; coupling; ynamides; zeolites

Introduction

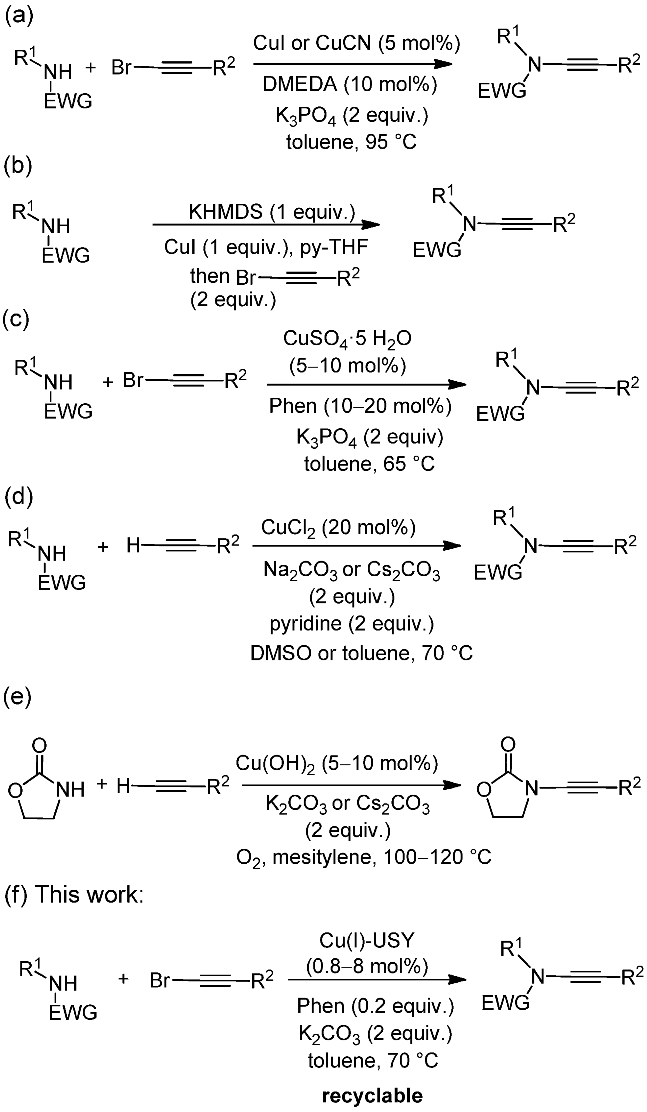
The last decade has witnessed the emergence of ynamides[1] as a powerful and versatile tool in organic synthesis.[2] Ynamides exhibit high reactivity due to the strong polarization of the triple bond induced by ynamine conjugation, while the electron-withdrawing group carried by the nitrogen atom modulates this reactivity (Scheme 1). Ynamides thus exhibit enhanced stability compared to ynamines,[3] and their reactivity can be tuned depending on the nature of the nitrogen substituent.

Although ynamines were not easily obtained,[3] ynamides can be readily produced either by elimination of β-bromo-, β-dichloro- or α-chloroenamides or by coupling reactions.[2] Among the latter, Ullman-type coupling reactions have been successfully extended to such compounds, providing a rapid and convenient access to ynamides from bromoalkynes and deactivated amines (Scheme 2).

Hsung and co-workers were the first to develop such copper-catalyzed couplings, but the use of *N,N'*-dimethyl-1,2-ethanediamine (DMEDA) as ligand and high temperatures led to limitations in terms of substrate scope, especially with sulfonamides and some heterocycles (Scheme 2a).[4] Danheiser and co-workers in part solved this problem by using stoichiometric amounts of copper iodide and potassium hexamethyldisilazane.[5] These reagents allowed the reaction to proceed at room temperature, but the strong base also led to limitations (Scheme 2b). After an extensive conditions screening, Hsung and co-workers later reported more general and milder conditions based on copper sulfate pentahydrate with 1,10-phenanthroline (Phen) as catalyst and potassium phosphate as base (Scheme 2c).[6] More recently, direct coupling



Scheme 1. Ynamides: stability and reactivity.



Scheme 2. Known ynamide syntheses and our proposal.

conditions have been proposed from terminal alkynes.[7] However, the latter required a large excess of amides and bases, non-convenient solvents and high temperatures (Scheme 2d–e) in order to limit the Glaser homo-coupling reaction.

Our interest in metallated zeolites,[8] especially Cu(I)-zeolites, as catalyst in organic synthesis led us to consider applying copper(I)-zeolites as convenient and recyclable catalysts for ynamide synthesis. As successfully shown for the "click" Huisgen reaction,[9] the cycloaddition of azomethine imines,[10] multicomponent Mannich-type reactions,[11] and alkyne homocoupling,[12] the zeolite frame could act as ligand toward copper(I) stabilizing this inherently labile species. Furthermore, the inherent heterogeneous nature of zeolites should greatly facilitate product recovery (through simple filtration) and recycling. We demonstrate here that such Cu(I)-zeolites could indeed be applied as catalysts in the synthesis of ynamides, providing a useful and interesting alternative to current methods (Scheme 2f).

Results and Discussion

Catalyst and Condition Screening

In a first set of experiments, we looked for the best combination of reagents and catalysts as well as for the best conditions. This study was performed starting from the readily available *N*-tosylbenzylamine and 1-bromo-4-phenyl-1-butyne as model substrates, and with copper(I)-ultra stable Y zeolite [Cu(I)-USY] as catalyst due to its high performance in other Cu(I)-zeolite-catalyzed reactions (Table 1).[9–12]

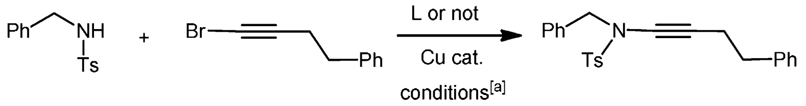
Under homogeneous conditions, these starting materials gave, as reported, the corresponding ynamide, but with 1,10-phenanthroline as ligand and potassium carbonate as base – the best conditions achieved with Cu(I)-zeolite catalyst (*vide infra*) – high yields were obtained without complete conversion (entries 1 and 2). With Cu(I)-USY as catalyst and without additive or with just a base, no reaction occurred whatever the solvent (entry 3 or 4). Upon addition of various ligands, the expected transformation could be achieved depending on the nature of the ligand (entries 5–9), but only *N,N'*-dimethyl-1,2-ethanediamine and 1,10-phenanthroline gave full conversion and satisfactory high yields of ynamide (entries 8 and 9). Shifting from potassium carbonate to the phosphate or to cesium carbonate led to a sharp decrease in conversion and thus in yields (entries 10 and 11). Similarly, variations in the relative amounts of either base or ligand also reduced conversion, but less drastically giving still reasonable yields (entries 12 and 13). Interestingly, decreasing the amount of catalyst (and accordingly of ligand) did not dramatically influence the reaction (entries 14–16). Only a slight conversion lowering was observed and, with *less than 1 mol% of heterogeneous copper catalyst*, around 70% of ynamide could still be isolated (entry 16).

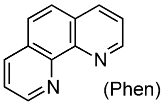
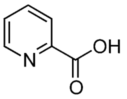
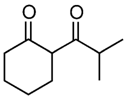
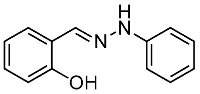
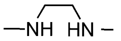
The reaction could also be performed in various solvents (entries 17–19), among which THF and DMF proved almost as efficient as toluene (entries 17 and 18 *vs.* 9). These interesting results provided thus excellent alternative conditions in case of solubility problems with one or the other coupling partner. It is worth mentioning that such flexibility in solvent use is not so common in homogeneous conditions.

Control experiments showed that the native H-USY, with or without additive, was unable to promote any transformation (entries 20 and 21).

For comparison purposes, we prepared other Cu(I)-zeolites with different internal shapes, sizes and Si/Al ratio, and we examined their behaviour as catalyst

Table 1. Screening of conditions for the Cu(I)-zeolite catalyzed ynamide synthesis.



Entry	Catalyst	Ligand	Base	Yield[b]
1	$CuSO_4$		K_3PO_4	68[c,d]
2	CuBr		K_2CO_3	81[c,d]
3	Cu(I)-USY	–	–	0
4	Cu(I)-USY	–	K_2CO_3	0
5	Cu(I)-USY		K_2CO_3	0
6	Cu(I)-USY		K_2CO_3	0
7	Cu(I)-USY		K_2CO_3	3
8	Cu(I)-USY		K_2CO_3	89
9	Cu(I)-USY	Phen	K_2CO_3	92
10	Cu(I)-USY	Phen	K_3PO_4	36[e]
11	Cu(I)-USY	Phen	Cs_2CO_3	45[e]
12	Cu(I)-USY	Phen (10 mol%)	K_2CO_3	58[f]
13	Cu(I)-USY	Phen	K_2CO_3 (1 equiv.)	68[f]
14	Cu(I)-USY (6 mol%)	Phen	K_2CO_3	87
15	Cu(I)-USY (4 mol%)	Phen	K_2CO_3	87[g]
16	Cu(I)-USY (0.8 mol%)	Phen	K_2CO_3	67
17	Cu(I)-USY	Phen	K_2CO_3	91[h]
18	Cu(I)-USY	Phen	K_2CO_3	87[i]
19	Cu(I)-USY	Phen	K_2CO_3	82[j]
20	H-USY	Phen	K_2CO_3	0
21	H-USY	–	–	0

[a] Performed with Cu-zeo (8 mol%), ligand (L) (20 mol%) and base (2 equiv.) in toluene at 70 °C for 20 h, unless otherwise noted.
[b] Isolated pure product.
[c] Homogeneous conditions.
[d] 83–87% conversion.
[e] Modest conversion (40–50%).
[f] 65–70% conversion.
[g] 95% conversion.
[h] In THF.
[i] In DMF.
[j] In dioxane.

(Figure 1). Surprisingly, Cu(I)-Y proved less effective than Cu(I)-USY despite its structural similarity (see the Supporting Information). In contrast, the Cu(I)-doped mordenite proved almost as effective as Cu(I)-USY, despite structural differences, although conversion was lower. The Cu(I)-doped beta and ZSM5 zeolites behaved similarly, giving reasonable but nevertheless lower yields of ynamide and with a lower conversion than with Cu(I)-USY.

These results suggest that the zeolites' internal sizes and shapes did not play a large role since the largest cage-type Y and USY zeolites behave quite differently, while the smaller channel-type zeolites gave results similar to those of Y. Such phenomena could be explained both by the flexible molecular shapes of the starting materials and products allowing them to fit within either cages or channels,[13,14] and by mobility differences in each zeolite (confinement effects).[15] Nevertheless, a surface catalysis due to Cu(I) species

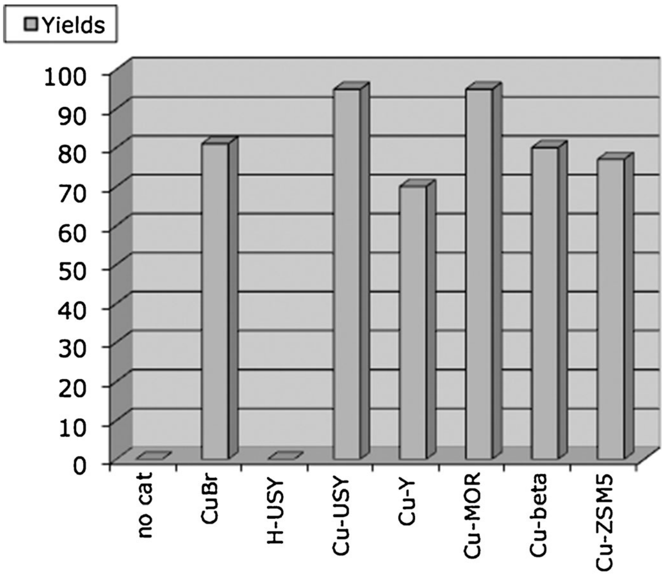


Figure 1. Comparison of various Cu(I)-zeolites as catalyst in the ynamide synthesis, and shapes and sizes of their framework. *USY:* cage – 7.4 Å; *Y:* cage – 7.4 Å; *MOR:* channels – 6.5×3.4; *Beta:* channels – 6.5×5.5; *ZSM5:* channels – 5.5×5.3.

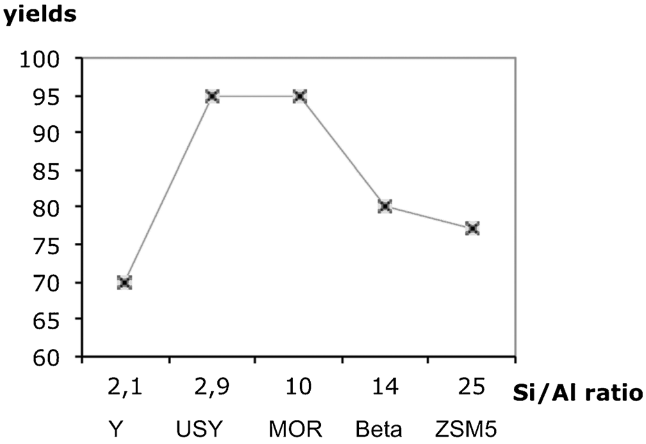


Figure 2. Correlation of the zeolite Si/Al ratios with coupling efficiency.

(agglomerates) can still be envisaged. The latter could, however, be ruled out since EDX mapping revealed a homogeneous distribution of copper in zeolites.

It has been shown that the number and the position of Al atoms in a zeolite framework play a crucial role in determining the type of Cu coordination, inducing different activation and confinement effects, both acting on reactivity.[16] These phenomena have been confirmed for acetylene binding to Cu(I)-zeolites.[17] Therefore, we looked for a possible correlation between the different Si/Al ratios of the present Cu-zeolites and their reactivity. Too low or too high ratios indeed proved not appropriate for the present catalysis with a clear optimum for ratios between 3 to 10 (Figure 2). This observation suggests the value of tuning the zeolite structural and functional parameters in order to improve the catalysis efficiency.[18]

Recycling

With a heterogeneous and efficient catalyst in hand for the coupling of deactivated amines and 1-bromoalkynes, it was worthwhile to look at its properties as heterogeneous catalyst, and especially its recyclability and stability. This was performed with the coupling of *N*-tosylbenzylamine and 1-bromo-4-phenylbut-1-yne under the conditions set out above.

The catalyst was recovered after the reaction by filtration and washed to remove the added base and any organic component. After drying and calcination, the catalyst was reused for the next reaction run. As shown in Figure 3, the catalyst remained very efficient over at least five runs. A slight decrease was nevertheless observed after the three first runs, but the yields of recovered ynamide after isolation were still high after the fifth reuse (78%).

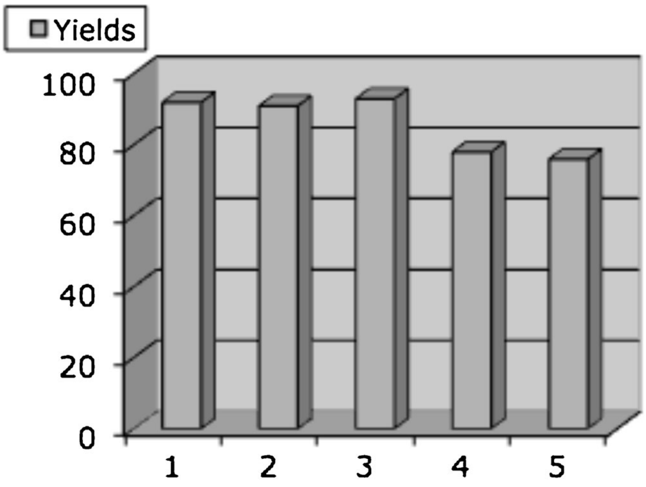


Figure 3. Recycling of the Cu(I)-USY catalyst in the ynamide synthesis.

The possible leaching of copper species was also evaluated. After having heated mixtures containing Cu(I)-USY and phenanthroline in toluene, with or without potassium carbonate, filtration over Nylon micromembranes provided a clear solution. To the latter were added *N*-tosylbenzylamine and 1-bromo-5-silyloxypent-1-yne, with or without further phenanthroline and potassium carbonate. Upon heating again, NMR monitoring did not show any compounds other than the starting materials, supporting the true heterogeneous nature of such catalysts.

As mentioned above, the presence of Cu agglomerates on the zeolite surface can be excluded. Nevertheless, one cannot exclude catalysis due to a release and catch mechanism. To try to get some clues on one or the other catalysis mechanism, we investigated in more detail the Cu(I)-zeolite before and after recycling. Due to its high sensitivity and large element coverage, X-fluorescence was finally selected, allowing us to monitor to some extent the Cu concentration within the catalyst, and it turned out that a small amount (1–2%) of copper is lost after recycling.[19]

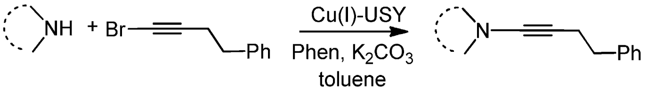
Taken together, these results tend to support a release and catch mechanism. Indeed, incomplete catching of Cu species may explain the small erosion observed upon recycling. Such phenomena have been observed with other metals and supports,[20] and seem related to hydrogen-bonding and acid sites.[20c,21] However, such a mechanism cannot account for the large reactivity differences observed with the various zeolites examined. It is nevertheless difficult to conclude since the actual mechanism of ynamide coupling is unknown. Related to the Ullmann reaction, it may involve a Cu(I)/Cu(III) cycle.[22] Interestingly, it has recently been shown that protonation should facilitate the reductive elimination step, especially with nitrogen ligands.[23] Cu(I)-zeolites may act as such, since they exhibit residual acidity due to incomplete exchange (~80%) of acid sites by Cu(I). This would be in line with the correlation we observed upon Si/Al ratios and thus zeolite acidity (see Figure 2).

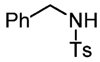
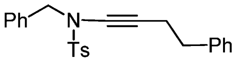
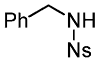
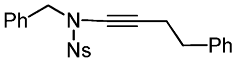
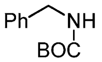
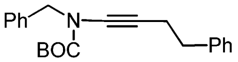
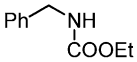
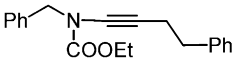
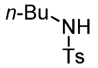
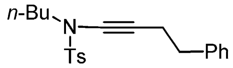
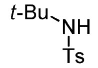
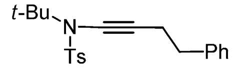
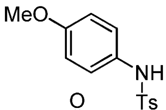
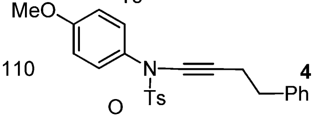
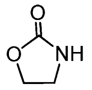
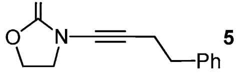
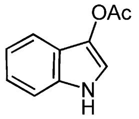
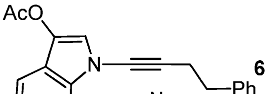
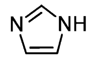
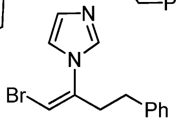
Scope

In order to make a comparison with the homogeneous version, we then examined what partners could be engaged in this Cu(I)-zeolite-catalyzed ynamide synthesis. Different amines, amides, and various nitrogen heterocycles, as well as various 1-bromoalkynes were thus prepared (when necessary) and submitted to the best conditions described above (Table 2 and Table 3, respectively).

Various nitrogen derivatives were first evaluated as possible substrates (Table 2). The nature of the electron-withdrawing group carried by the nitrogen atom was first examined (entries 1–4). The more electron-withdrawing this group, the more effective was the coupling, as shown by the quantitative coupling seen with the *N-para*-nitrophenylsulfonyl (nosyl; Ns) benzylamine compared to its tosyl analogue (entry 2 *vs.* 1). Carbamates may not be electron-withdrawing enough, since no reaction occurred despite higher heating and longer reaction time (entries 3 and 4). Interestingly, simple tosylated alkylamines readily reacted under the optimized conditions. The tosylated *n*-butylamine quantitatively gave the coupling product (entry 5), while its *tert*-butyl analogue only slowly reacted and moreover decomposed (entry 6). Arylated sulfonamides also gave the expected coupling *N*-arylynamide in high yields (entry 7).

Table 2. Cu(I)-zeolite-catalyzed ynamide synthesis: screening of nitrogen derivatives as coupling partner.[a]



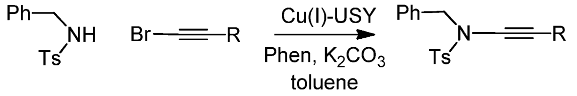
Entry	Amine	Conditions [h; °C]	Product		Yield[b] [%]
1		20; 65		**1a**	92
2		20; 65		**1b**	97
3		30; 110			0
4		30; 110			0
5		26; 85		**2**	97
6		30; 110		**3**	11[c]
7		30; 110		**4**	91
8		30; 110		**5**	95
9		24; 110		**6**	93
10		24; 110		**7**	68

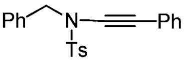
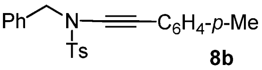
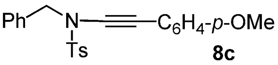
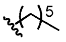
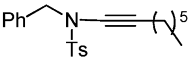
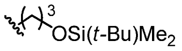
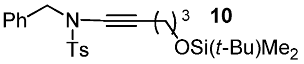
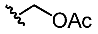
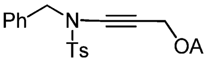
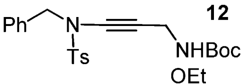
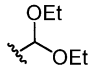
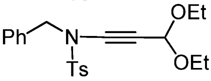
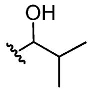
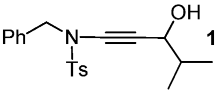
[a] Performed with Cu(I)-USY (8 mol%), 1,10-phen (20 mol%) and K_2CO_3 (2 equiv.) in toluene.
[b] Isolated pure product.
[c] Decomposition occurred.

Since some nitrogen heterocycles have been successfully engaged in Hsung coupling, we also examined the behaviour of such heterocycles in the presence of Cu(I)-zeolites. Oxazolidinone readily reacted in the presence of Cu(I)-USY, giving the expected *N*-alkynyloxazolidinone in very high yield, opening up the way to chiral ynamides (entry 8).[6] Indoles could also be engaged in such a coupling, as shown by the very efficient formation of *N*-alkynylindole (entry 9). However, imidazole gave the product resulting from addition to the starting bromoalkyne (entry 10). Such addition products have already been observed.[24]

Various 1-bromoalkynes were then examined as substrates in the presence of *N*-tosylbenzylamine as coupling partner (Table 3).

Table 3. Cu(I)-zeolite catalyzed ynamide synthesis: screening of 1-bromoalkynes as coupling partner.[a]



Entry	Alkyne R	Conditions [h; °C]	Product	Yield[b] [%]
1	—Ph	24; 110	 **8a**	97[c]
2	—C_6H_4-*p*-Me	20; 70	 **8b**	82
3	—C_6H_4-*p*-OMe	20; 70	 **8c**	82
4		20; 85	 **9**	97
5		7; 110	 **10**	89
6		20; 85	 **11**	98[d]
7		20; 85	 **12**	96
8		20; 85	 **13**	96
9		20; 85	 **14**	95

[a] Performed with Cu(I)-USY (8 mol%), 1,10-phen (20 mol%) and K_2CO_3 (2 equiv.) in toluene.
[b] isolated pure product.
[c] 2 equiv. of bromoalkyne were used for volatility reasons.
[d] 1.7 equiv. of bromoalkyne were used for volatility reasons.

Bromides derived from phenylacetylene derivatives gave the expected ynamides in high yields (entries 1–3). The simple 1-bromo-1-octyne quantitatively gave the corresponding ynamide (entry 4). Remarkably, analogues functionalized at various positions could also be readily coupled. Noteworthy are acetate, ketal, carbamate, ester and free or silylated hydroxy groups, which even at propargylic positions, were well tolerated, giving the corresponding ynamides in very high, sometimes quantitative yields (entries 5–9).

Conclusions

In conclusion, copper-doped zeolites, especially Cu(I)-USY, are very efficient catalysts for the coupling of nitrogen derivatives and 1-bromoalkynes. Various deactivated amines and nitrogen heterocycles, as well as numerous functional groups are compatible with these heterogeneous coupling conditions. Furthermore, the catalyst can be recycled at least five times without dramatic loss of activity.

Experimental Section

General Procedure for the Formation of Ynamides

In a 10-mL tube with a screw stopper, sulfonamide (0.57 mmol) was added to a solution of bromoalkyne (0.63 mmol, 1.1 equiv.) in dry and degassed toluene (1.5 mL). Dry potassium carbonate (1.14 mmol, 2 equiv.) was added, followed by 1,10-phenanthroline (0.114 mmol, 0.2 equiv.) and Cu-zeolite (mass corresponding to 8 mol% of copper). The mixture was then stirred and heated at 65–110 °C for appropriate time (see the appropriate Tables). After cooling to room temperature, the solid was filtered over a pad of celite or a Nylon membrane (0.2 μm), and washed with ethyl acetate. The filtrate was then evaporated under vacuum. The product was purified by flash column chromatography (cyclohexane/ethyl acetate).

Recycling Procedure

At the end of the run, the solid (mixture of Cu-zeolite and inorganic salts from the base) was recovered by filtration over a Nylon membrane (0.2 μm), washed with ethyl acetate, water (20 mL), dried at 100 °C for 4 h, and then calcinated at 350 °C for 4 h.

Ynamides **2**,[6b] **5**,[25] **8a**,[26] **8b**,[27] **8c**,[28] **9**[29] and **11**[30] are known compounds and exhibit spectroscopic data identical to those reported in the literature. Data of the other ynamides are provided in the Supporting Information.

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8 Zeo-Click Synthesis: Copper-Zeolite-Catalyzed Synthesis of Ynamides

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