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Copper–Zeolites as Catalysts for the Coupling of Terminal Alkynes: An Efficient Synthesis of Diynes

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Cu^I-modified zeolites, especially Cu^I–USY, proved to be very efficient catalysts for the homocoupling of terminal alkynes. Such heterogeneous catalysts offer a very simple (no added ligand) and convenient synthesis of diynes, including carbohydrate derivatives. A strong influence of the zeolite pore size has been observed, high (quantitative) yields being obtained with zeolites having large internal cages. The role of zeolite acidic sites in the reaction has been pointed out.

Introduction

The carbon–carbon triple bond represents one of the oldest known and most versatile functionalities in organic chemistry.[1] Compounds with more than one triple bond are known for around a century as natural products, but in the last two decades, they emerged as important tools in the areas of non-linear optics and organic conductors.[2] Among polyalkynylated compounds, diynes constitute an important class. Indeed, this motif can be found in natural products, usually exhibiting interesting and useful biological activities,[3] as well as in man-made derivatives towards numerous applications. Diynes have been used to build up length-defined oligomers[4,5] or polymers,[4,6] as well as annulenes[4,7] and carbon allotropes.[4,8] Diynes, as longer polyyne motifs, have been used to link organometallic complexes[9] or porphyrin derivatives.[10] In such compounds diynes and homologs act as conjugated connectors, modulating the redox and optoelectronic properties and also inducing fluorescence enhancement.[11] They thus behave as molecular wires.[12] Being rigid, diyne connectors also allow to build up large molecular clefts for specific binding in molecular recognition.[13]

With so many applications, the synthesis of diynes is clearly a key element in these areas. The synthesis of diynes is known since 1869 with the discovery of the oxidative coupling of copper acetylides by Glaser,[14] and then of alkynes in the presence of copper chloride and ammonium chloride.[15] In 1956, Eglinton and Galbraith improved the Glaser coupling reaction by using cupric salts in pyridine instead of ammoniacal cuprous salts.[16] Both methods were, however, not fully catalytic; but in 1962, Hay proposed a variant in which a CuCl–TMEDA complex under oxygen or air acts as an effective catalyst.[17] The Hay reaction was since the most commonly used protocol for oxidative homocoupling of alkynes, although palladium-catalyzed acetylenic homo- and cross-coupling methods have nowadays been developed and adjusted for the construction of complex di- and polyyne derivatives.[18]

Surprisingly, only a very few supported versions have been reported despite the usefulness and ecofriendliness of such variants, and all are recent. In 2007, a layered double hydroxide, hydrotalcite, containing cupric and aluminium ions has been prepared and used in an Eglington-type homocoupling of terminal alkynes.[19] Cupric salts adsorbed on alumina could promote alkyne coupling in the presence of either KF[20] or morpholine[21] under microwave activation. These methods rely on cupric salts, but so far none exists based on cuprous salts, probably due to the inherent instability of the latter. Zeolites, with their silicoaluminate frame, could act as ligand toward metal ions and especially cuprous ions by stabilizing them. Being heterogeneous, zeolites modified with Cu^I ions could thus offer an interesting and practical alternative to the Hay catalyst.

In this context, and in connection with our current interest in the development of zeolites, modified or not, as catalysts for organic synthesis,[22–23] we describe here the first Cu–zeolite-catalyzed synthesis of diynes (Scheme 1).

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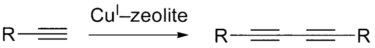


Scheme 1. Cu^I–zeolite catalyzed diyne synthesis.

Results and Discussion

Cu^I-Modified Zeolites as Catalyst for Homocoupling of Alkynes

In order to study the feasibility of alkyne homocoupling in zeolites, phenylacetylene (**1a**) was submitted to the commercially available USY zeolite modified by heating and CuCl treatment according to solid-state exchange procedures.[24] This zeolite was chosen as one of the most representative zeolites and as the one having the largest pore size, able to accommodate rod-shaped diynes.

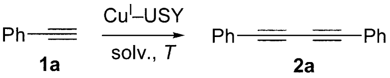
Preliminary experiments in various solvents revealed that the reaction was highly dependent on the solvent polarity. Indeed, at the same temperature, reaction performed in apolar toluene mostly returned the starting material, whereas in polar DMF, the expected diyne was obtained in excellent yield in a very clean reaction (Table 1, Entry 6 vs. 7). Other solvents of intermediate polarity did not allow for the transformation of the starting alkyne (Entries 3–5). Nevertheless, the temperature played a key role in this reaction, as revealed by a series of experiments carried out in DMF at various temperatures (Entries 7–10). At room temperature and below 50 °C no transformation occurred (Entries 9–10), and even at 80 °C the reaction was approximately one third slower than the one performed at 110 °C (Entry 8 vs. 7). Control experiments highlighted the role of oxygen as in the conventional Glaser–Eglington–Hay reactions (Entry 11 vs. 7).

Since control experiments showed that no reaction occurred with unmodified H-USY zeolite (Entry 19), these results demonstrated that Cu^I–USY acts as a true catalyst for the homocoupling of phenylacetylene (**1a**).

Under the Glaser-type acidic conditions, it has been shown that the rate increased with increasing cuprous ion concentration.[25] The same trend was observed in our hands with Cu^I–USY as catalyst since yields increased with cuprous loading (Entry 12 vs. 13 vs. 14). Quantitative yields were obtained with an amount of USY zeolite corresponding to around 30 mol-% of cuprous ions (Entry 14).[26]

This set of results suggests that Cu^I–USY behaves as acidic Glaser-type catalyst. It is worth noting that depending on the method the H/Cu^I exchange is performed, Cu^I–zeolites still contain some acidic sites left untouched. The Cu^I–USY used in the present study was prepared at 350 °C (see Exp. Sect.), and titration revealed that around 25% of acidic sites remained.[27] Since Cu^I–USY prepared at 650 °C did not contain residual acidic sites, such zeolite was examined as catalyst in the homocoupling of **1a**. Under the same conditions, but with this acid-free Cu^I–USY, only

Table 1. Search for optimal zeolite catalysts and conditions for homocoupling of phenylacetylene (**1a**).[a]



Entry	Catalyst	Catalyst loading	Atmosphere	Solvent	Temp.	Yield[b]	Acidic sites	Pore diameter	Topology
1	none	–	Ar or air	[c]	40–110 °C	0%[d,e]	–	–	–
2	CuCl		air	[c]	40–110 °C	0–60%[e,f]	–	–	–
3	Cu^I–USY	15	air	CH_2Cl_2	40 °C	0%[d,e]	4.39 mmol/g	7.4 × 7.4 Å	cage-type
4	"	"	"	THF	60 °C	traces	"	"	"
5	"	"	"	MeCN	80 °C	traces	"	"	"
6	"	"	"	PhMe	110 °C	traces	"	"	"
7	"	"	"	DMF	110 °C	95%	"	"	"
8	"	"		"	80 °C	29%	"	"	"
9	"	"	"	"	50 °C	traces	"	"	"
10	"	"	"	"	20 °C	0%[d,e]	"	"	"
11	"	"	Ar	"	110 °C	23%			
12	"	10	air	"	110 °C	78%	"	"	"
13	"	15	"	"	"	93%	"	"	"
14	"	30	"	"	"	97%	"	"	"
15	Cu^I–Y	"	"	"	"	84%	6.67 mmol/g	7.4 × 7.4 Å	cage-type
16	Cu^I–β	"	"	"	"	19%[e]	0.90–1.23 mmol/g	7.6 × 6.4 Å 5.5 × 5.5 Å	channel-type
17	Cu^I–ZSM5	"	"	"	"	12%[e]	1.04 mmol/g	5.1 × 5.5 Å 5.3 × 5.6 Å	"
18	Cu^I–MOR	"	"	"	"	5%[e]	1.48 mmol/g	6.5 × 7.0 Å 3.4 × 3.8 Å	"
19	H–USY	"	"	"	"	0%[d,e]	6.67 mmol/g	7.4 × 7.4 Å	cage-type

[a] Reaction performed overnight on 1 mmol of **1a** in 3 mL of solvent with 70 mg of Cu^I–zeolite (i.e. approximately 30 mol-% of Cu^I for Cu^I–USY[26]). [b] Yields of isolated pure product. [c] Dichloromethane, THF, acetonitrile, toluene and DMF were examined. [d] No transformation was observed. [e] The starting material was recovered. [f] No transformation occurred in most solvents, except in hot DMF where dimerization occurred but with decomposition.

around half of **1a** was converted into the corresponding diyne (52% isolated yield of **2a**). Therefore, it seems that acid sites might be required for optimum dimerization of alkynes in zeolites.

In order to improve the reaction conditions, we performed the same coupling under microwave activation. Unfortunately, the reaction stopped at around 30% conversion, due to zeolite alteration.[28]

Since pore size and shape play a key role in the zeolite reactivity and often give some shape selectivity, we screened other zeolites looking for optimal zeolite catalyst for alkyne homocoupling. Four other representative zeolites possessing different topology and pore size combinations, i.e. H–Y, H–MOR, H–ZSM5 and H–β, were modified by CuCl treatment.[24] Their behavior in oxidative dimerization reaction was examined with phenylacetylene (**1a**) under the conditions already set up for Cu^{I}–USY.

As expected for reactions in which rod-shaped molecules are formed, the zeolite nature had dramatic influences on reaction efficiency. The latter was high with zeolites having cages as an internal shape (Table 1, Entries 14–15) but low with channel-type zeolites (Table 1, Entries 16–18). Thus, the reaction efficiency is directly correlated with the pore size; the larger the pore size, the better the yield (Figure 1). These results are in favor of a reaction taking place *within* the zeolite framework and not on its external surface, where no such correlation could be expected. It is interesting to note that the reaction efficiency also correlated with the Si/Al ratios of the zeolites used as catalysts (Figure 1). Although very different in range, the same trend was observed in the cage as well as in the channel series; the higher the Si/Al ratio, the higher the yield. Since the Si/Al ratio is related to the number of acidic sites in zeolites, these results corroborated the role that acids seem to play in this Cu^{I}–zeolite-catalyzed dimerization of alkynes.

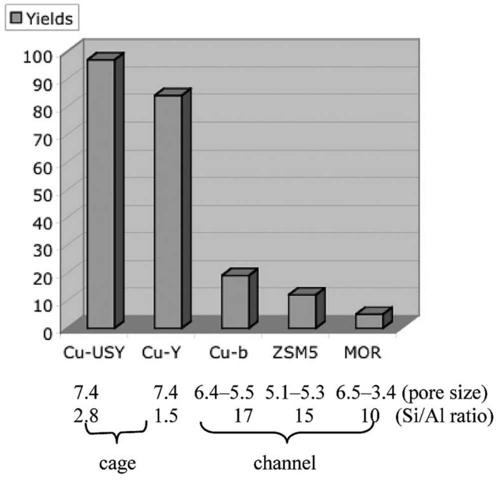


Figure 1. Efficiency of the Cu–zeolite-catalyzed homocoupling of phenylacetylene (**1a**) depending on the zeolite nature.

Since the release of the active species could be the actual catalyst, we also examined whether leaching of active species from the zeolite frame is occurring or not. To do so, Cu^{I}–USY was suspended in DMF and the mixture stirred overnight; the resulting suspension was then filtered off, leading to a clear solution. To this one, was added phenylacetylene (**1a**), and this mixture was heated as for the preceding homocoupling reaction (110 °C, 15 h). The starting material was the main compound and the diyne **2a** could not be detected or at best as traces (≤3%) (Figure 2). Since control experiments revealed that no traces of **2a** could be detected without Cu^{I}–USY catalyst or with untreated USY (Table 1, Entries 1–2 and 19), it seems that no leaching occurred in Cu^{I}–USY-catalyzed homocoupling of alkynes.

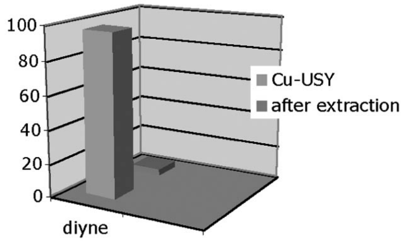


Figure 2. Leaching study: comparison of the homocoupling of **1a** in the presence of either Cu^{I}–USY or a solution coming from Cu^{I}–USY extraction.

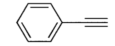
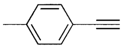
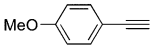
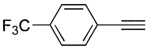
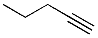
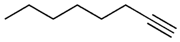
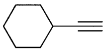
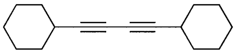
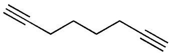
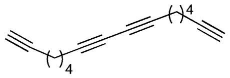
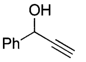
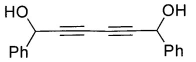
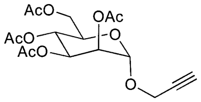
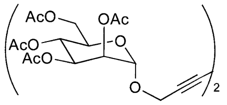
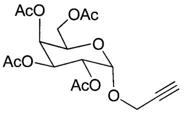
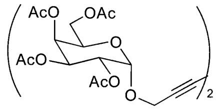
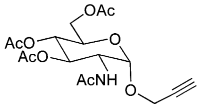
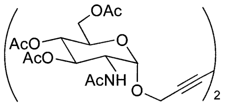
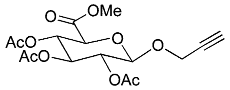
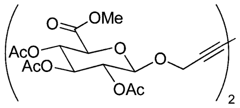
Scope of the Cu^{I}–USY-Catalyzed Homocoupling Reaction of Diynes

With these conditions in hand, we then explored the scope of this new Cu^{I}–zeolite-catalyzed dimerization of terminal alkynes with different series of alkynyl compounds (Table 2).

In the Glaser acidic reaction, it has been shown that the rates decreased with increasing alkyne conjugation and that this was correlated to the acidity of the acetylenic proton, whereas under Eglington-type basic conditions, the reverse was observed.[29] Therefore, the influence of electronic effects susceptible to modulate the alkyne acidity was investigated in order to correlate the behavior of Cu^{I}–USY to the well-known homocoupling conditions. For that, a series of phenylacetylene derivatives were submitted to the same conditions as before. Tolylacetylene (**1b**) behaved as phenylacetylene (**1a**) and gave the best results of this series (Entry 3 vs. 2). Surprisingly, with a stronger electrodonating substituent, as well as with an electron-withdrawing substituent (**1c** and **1d**, respectively), a slight but significant decrease in yields was observed (Entries 4 and 5, respectively, vs. 2). The d–π conjugation between the silicon atom and the carbon atom of an unsaturated bond is known to decrease the electronic density in silylacetylene derivatives.[30] The homocoupling of such compounds was thus expected to be similar to those of **1d**, and indeed, the results were almost identical with, for example, the (triisopropylsilyl)acetylene (**1e**) (Entry 6 vs. 5).

From these experiments, our Cu^{I}–USY conditions did not seem to correspond to any of the known Glaser, Eglington or Hay reactions. However, electronic effects may not be the major factor in the particular environment of zeo-

Table 2. Homocoupling of various alkynes catalyzed by Cu^I–USY.[a]

Entry	Alkyne		Catalyst loading	Yield[b]	Product	
1 2		**1a**	10 30	78 % 97 %	$C_6H_4-\equiv-\equiv-C_6H_4Me\text{-}4$	**2a**
3		**1b**	30	98 %	$C_6H_4-\equiv-\equiv-C_6H_4DMe\text{-}4$	**2b**
4		**1c**	30	89 %	$C_6H_4-\equiv-\equiv-C_6H_4CF_3\text{-}4$	**2c**
5		**1d**	30	91 %	$4\text{-}CF_3Ph-\equiv-\equiv-Ph\text{-}4\text{-}CF_3$	**2d**
6	$i\mathrm{Pr}_3\mathrm{Si}-\equiv$	**1e**	30	88 %	$i\mathrm{Pr}_3\mathrm{Si}-\equiv-\equiv-\mathrm{Si}i\mathrm{Pr}_3$	**2e**
7		**1f**	30	85 %	$n\mathrm{Pr}-\equiv-\equiv-n\mathrm{Pr}$	**2f**
8		**1g**	30	80 %	$n\mathrm{Hex}-\equiv-\equiv-n\mathrm{Hex}$	**2g**
9 10		**1h**	10 30	66 % 90 %		**2h**
11		**1i**	30	40 %[c]		**2i**
12		**1j**	30	20 %[d]		**2j**
13		**1k**	30	86 %		**2k**
14		**1l**	30	87 %		**2l**
15		**1m**	30	74 %		**2m**
16		**1n**	30	85 %		**2n**

[a] Reaction performed on 1 mmol in DMF at 110 °C during 15 h with Cu^I–USY loading corresponding to 30 mol-%.[26] [b] Yields of isolated pure products. [c] Oligomers were also formed. [d] Decomposition occurred.

lites, and sizes could be as important, as revealed by the dramatic influence of the zeolite internal shape (Figure 1). To look at this aspect, molecular calculations were performed, revealing that the dimerization products **2a**–**d** exhibited lengths from 11 to 17 Å depending on the substituent on the butadiyne moiety. Product sizes appeared thus larger than the 7.4 Å cage diameters of USY or Y. Interestingly, a clear correlation between product size and yields could be found (Figure 3), suggesting an optimum size for this reaction under the conditions used. This optimum size, between 12 and 15 Å, could result from the combination of two parameters. On one hand, the Cu^I–USY-catalyzed homocoupling only proceeded above 80 °C. Heating probably induced zeolite "breathing",[31] allowing large molecules to be accommodated within the zeolite frame. It is worth noting that heating was also required for Cu^I–zeolite-catalyzed click reactions of large molecules, whereas small ones reacted at room temperature (Table 2).[23] On the other hand, polyynes are not so rigid and can easily bend,[1] giving more flexibility to rod-shaped molecules like diynes.

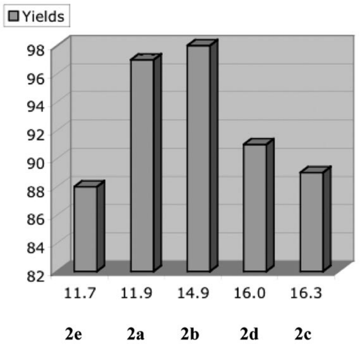


Figure 3. Correlation between diyne sizes [Å] and yields (%) obtained by using Cu^I–USY as catalyst.

The influence of conjugation was also examined by comparing the arylacetylene series with various alkylacetylene derivatives. With the latter, yields were comparable (Entries 7–10) with nevertheless a similar slight decrease (Entries 7–8, 10 vs. 2 and 9 vs. 1). As for phenylacetylene, better yields were obtained with higher catalyst loading (Entry 9 vs. 10). Such results are consistent with those reported with Eglington–Hay catalysts, for which phenylacetylene (**1a**) coupled faster than alkylacetylenes.[16,17]

From the comparison between experiments with cyclohexylacetylene (**1h**) and those with the linear alkylacetylenes **1f**,**g**, it seems that the more substituted the alkyne, the easier the reaction (Entry 10 vs. 7–8). However, the adjustment between product and pore sizes could also be responsible for such variations. Compound **2h** exhibits a calculated size of 11.9 Å, in the right range exemplified by Figure 3, whereas **2f** is shorter (11.1 Å) and **2g** longer (18.0 Å).

The dimerization of 1,7-octadiyne (**1i**) was examined to look at the role the zeolite shape could play in controlling the competition between the possible cyclization, oligomerization and polymerization. Interestingly, the dimeric derivative **2i** was the major isolable product (Entry 11).[32] Moreover, the isolated yield was good compared to other conventional homocoupling reactions, in which mixtures of cyclic dimer and trimer have been obtained besides oligomers under high-dilution conditions.[33]

The more functionalized 1-phenylprop-2-ynol (**1j**) or its dimerization product **2j** did not survive our conditions, and only around half of the mass balance could be recovered after the reaction, from which the diyne **2j** was isolated in modest yield (Entry 12).

With biological applications in mind, we envisaged to apply our Cu^{I}–zeolite-catalyzed homocoupling method to glycosylated alkynes. Indeed, carbohydrate derivatives containing a buta-1,3-diyne unit are compounds of high interest as cyclodextrin analogs,[34] oligo- or polysaccharide analogs[35] or as multivalent systems.[36] The latter are specially promising, since they mimic the multivalent interactions between carbohydrates and proteins responsible for numerous biological events, from virus-cell entry to cell recognitions and immunology. They can thus be applied as vaccines or drugs.[37]

The peracetylated propargyl glycosides **1k**–**n** were prepared by using known glycosylations with propargyl alcohol[38–40] and then submitted to the above-mentioned conditions. All of them gave the expected dimeric diynes in high yields (Entries 13–17), although the glucosamine derivative[39] **1m** appeared less reactive, giving the corresponding diyne **2m** with a slightly lower yield (Entry 15 vs. 13–14 and 16). Interestingly, epimerization occurred neither at the anomeric center nor at other positions, as revealed by NMR analysis of the diynes **2k**–**m**. Even the sensitive and usually poorly reactive glucuronate **1n** gave the expected dimer **2n** without epimerization and with high yield (Entry 16). It is worth noting that our conditions provided better results than those reported (78% for **2k** and 81% for **1l**).[41]

Conclusions

Cu^{I}-modified zeolites were used for the first time as catalysts for the synthesis of diynes by homocoupling of terminal alkynes. Zeolites exhibiting internal large cage frames, i.e. Cu^{I}–USY and Cu^{I}–Y, proved to be the best catalysts. High and usually quantitative yields were obtained with a large variety of alkynes, including carbohydrate derivatives. An interesting correlation between product size and pore size was observed, and the surprising role of zeolite acid sites in the reaction has been pointed out.

Further works are now in progress to expand the scope of this reaction and to decipher its mechanism.

Experimental Section

General: All starting materials were commercial and used as received. The reactions were monitored by thin-layer chromatography on silica plates (silica gel 60 F_{254}, Merck) using UV light and *p*-anisaldehyde, phosphomolybdic acid or Ce^{IV} 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. Evaporation of solvents was conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Melting points (m.p.) were measured in open capillary tubes and are uncorrected. IR spectra were recorded with an Alpha FT-IR spectrometer (neat), and values are reported in cm^{-1}. ^{1}H 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. Chemical shifts δ are reported relative to residual solvent as an internal standard ([D$_1$]chloroform: δ = 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Carbon multiplicities were determined by DEPT 135 experiments. Electron impact (EI) and electrospray (ESI) low/high-resolution mass spectra were obtained from the mass spectrometry department of the Institut de Chimie, Strasbourg. Molecular modeling has been performed with Hyperchem Professional Release 7.5. Geometry optimizations have been computed by using the MM+ force field in vacuo with the Polar-Ribiere algorithm and an RMS gradient of 0.001 kcal/Å mol as termination condition.

Preparation of Cu^{I}–USY: Commercial NH$_4$USY was loaded in an oven and heated at 550 °C during 4 h to give H–USY; 1 g of H–USY and 475 mg of CuCl (1.1 equiv.) were mixed by using a mortar and charged in a closed reactor. The mixture of powders was then heated at 350 °C under a nitrogen flow during 3 d to quantitatively yield Cu^{I}–USY.

General Procedure for the Cu^{I}–Zeolite-Catalyzed Homocoupling of Terminal Alkynes: To a suspension of Cu^{I}–USY (70 mg, 0.3 equiv.[26]) in dimethylformamide (3 mL) was added the alkyne (1 mmol, 1.0 equiv.). After vigorous stirring at 110 °C overnight (15 h), the mixture was taken up in dichloromethane (25 mL) and then filtered through nylon membranes (0.20 µm). The filtrate was washed 3 times with a 0.1 M HCl solution (25 mL each). The organic layer was dried with MgSO$_4$ and filtered. Solvent evaporation provided the resulting crude product, usually at >95% purity as judged by NMR spectroscopy. Column chromatography was performed when necessary. Most of the so formed compounds are known, and diynes **2a**,[42] **2b**,[42] **2c**,[42] **2d**,[42] **2e**,[43] **2f**,[44] **2g**,[45] **2h**,[46] **2j**,[47] **2k**[41] and **2l**[41] have been reported. The dimer **2i** of 1,7-octadiyne (**1i**) is also known,[48] but its NMR spectroscopic data have not been reported, so we provide these data.

Hexadeca-1,7,9,15-tetrayne (2i): ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.64 (m, 8 H), 1.94 (t, J = 2.7 Hz, 2 H), 2.21 (m, 4 H), 2.28 (m, 4 H) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 17.9 (2 C), 18.7 (2 C), 27.2 (2 C), 27.4 (2 C), 65.6 (2 C), 68.6 (2 C), 77.0 (2 C), 83.9 (2 C) ppm.

1,6-Di-*O*-(α-D-2-acetamido-2-deoxy-3,4,6-*O*-triacetylglucopyranosyl)-hexa-2,4-diyn-1,6-ol (2m): According to the general procedure, starting from propargyl α-D-2-acetamido-2-deoxy-3,4,6-*O*-triacetylglucoside (193 mg, 0.5 mmol), the expected diyne was isolated as a white solid (142 mg, 0.25 mmol). Yield 74%. M.p. 105 °C. $[\alpha]^{20}_{589} = +41.2$ ($c = 1.0$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3293, 2954, 1738, 1661, 1535, 1435, 1367, 1217, 1119, 1080, 1026\ \mathrm{cm^{-1}}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.76$ (d, $J_{NH,2} = 9.5$ Hz, 2 H, NH), 5.21 (t, $J_{3,4} = J_{3,2} = 9.5$ Hz, 2 H, H^3), 5.14 (t, $J_{4,3} = J_{4,5} = 9.5$ Hz, 2 H, H^4), 4.98 (d, $J_{1,2} = 3.7$ Hz, 2 H, H^1), (dt, $J_{2,3} = J_{NH\text{-}2} = 9.5$, $J_{2,1} = 3.7$ Hz, 2 H, H^2), 4.34 (s, 4 H, –CH_2–CC–), 4.24 (dd, $J_{6a,6b} = 12.4$, $J_{6a,5} = 4.2$ Hz, 2 H, H^{6a}), 4.10 (dd, $J_{6b,6a} = 12.4$, $J_{6b,5} = 2.4$ Hz, 2 H, H^{6b}), 3.97 (ddd, $J_{5,4} = 9.5$, $J_{5,6a} = 4.2$, $J_{5,6b} = 2.4$ Hz, 2 H, H^5), 2.09 (s, 6 H, –OAc), 2.02 (s, 6 H, –OAc), 2.01 (s, 6 H, –OAc), 1.97 (s, 6 H, –NHAc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.3$ (C=O acetate), 170.7 (C=O acetate), 170.0 (C=O acetate), 169.2 (C=O acetamide), 96.8 (C^1), 74.5 (–CH_2*C*C–), 70.9 (C^3), 70.7 (–CH_2C*C*–), 68.4 (C^5), 67.9 (C^4), 61.7 (–*C*H_2CC–), 56.0 (C^6), 51.6 (C^2), 23.2 (–*C*H_3 of –NHAc), 20.7 (–*C*H_3 of –OAc), 20.6 (–*C*H_3 of –OAc), 20.6 (–*C*H_3 of –OAc) ppm. HRMS (ESI, positive mode): *m*/*z* calcd. for $C_{34}H_{44}N_2O_{18}Li$ 775.2744; found 775.2782 $[M + Li]^+$.

1,6-Di-*O*-(α-D-2,3,4-*O*-triacetyl-6-methylglucuronyl)hexa-2,4-diyn-1,6-ol (2n): According to the general procedure, starting from propargyl α-D-2,3,4-*O*-triacetyl-6-methylglucuronide (186 mg, 0.5 mmol), the expected diyne was isolated as a white solid (158 mg, 0.25 mmol). Yield 85%. M.p. 179–182 °C. $[\alpha]^{20}_{589} = -75.0$ ($c = 0.5$, $CHCl_3$). IR (neat): $\tilde{\nu} = 2955, 1748, 1439, 1368, 1246, 1221, 1151, 1120, 1097, 1036\ \mathrm{cm^{-1}}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.27$ (dd, $J_{3,4} = 9.2$, $J_{3,2} = 9.0$ Hz, 2 H, H^3), 5.20 (dd, $J_{4,5} = 9.5$, $J_{4,3} = 9.2$ Hz, 2 H, H^4), 5.00 (dd, $J_{2,3} = 9.0$, $J_{2,1} = 7.6$ Hz, 2 H, H^2), 4.77 (d, $J_{1,2} = 7.6$ Hz, 2 H, H^1), 4.46 (s, 4 H, –CH_2CC–), 4.07 (d, $J_{5,4} = 9.5$ Hz, 2 H, H^5), 3.72 (s, 6 H, –OCH_3), 2.05 (s, 6 H, –OAc), 2.00 (s, 6 H, –OAc), 1.99 (s, 6 H, –OAc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.0$ (C=O acetate), 169.3 (C=O acetate), 169.2 (C=O acetate), 167.0 (C=O methyl ester), 98.2 (C^1), 74.0 (–CH_2*C*C–), 72.5 (C^2), 71.8 (C^3), 71.0 (–CH_2C*C*–), 70.8 (C^5), 69.2 (C^4), 56.5 (–*C*H_2CC–), 52.9 (–OCH_3), 20.6 (–*C*H_3 of –OAc), 20.5 (–*C*H_3 of –OAc), 20.4 (–*C*H_3 of –OAc) ppm. HRMS (ESI, positive mode): *m*/*z* calcd. for $C_{32}H_{38}O_{20}Li$ 749.2111; found 749.2026 $[M + Li]^+$.

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