IMPROVED PROTOCOLS FOR MICROWAVE-ASSISTED CU(I)-CATALYZED HUISGEN 1,3-DIPOLAR CYCLOADDITIONS

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Dedicated to Professor Štefan Toma, a close friend and great scientist, on the occasion of his 70th birthday.

The Huisgen 1,3-dipolar cycloaddition of azides and acetylenes catalyzed by Cu(I) salts, leading to 1,2,3-triazoles, is one of the most versatile "click reactions". We have developed a series of optimized protocols and new applications of this reaction starting from several substrates, comparing heterogeneous vs homogeneous catalysis, conventional heating vs microwave irradiation or simultaneous microwave/ultrasound irradiation. Both non-conventional techniques strongly promoted the cycloaddition (bromide → azide → triazole), that could be conveniently performed in a one-pot procedure. This was feasible even with such bulky molecules as functionalized β-cyclodextrins (β-CD), starting from 6^1-*O*-tosyl-β-CD or from heptakis[6-*O*-(*tert*-butyldimethylsilyl)]-2^1-*O*-propargyl-β-CD. "Greener" heterogeneous catalysis with charcoal-supported Cu(II) or Cu(I) (prepared under ultrasound) was advantageously employed.

Keywords: Click chemistry; Microwave; Huisgen cyclization; Heterogeneous catalysis; Ultrasound; Sonochemistry; Azides; Alkynes; Triazoles; Cyclodextrins.

Click chemistry, introduced by Sharpless a few years ago[1], has emerged as an efficient and time-saving synthetic method. Although in their seminal contribution Sharpless and associates identified a handful of simple and versatile reactions requiring little or no purification of products, the Huisgen 1,3-dipolar cycloaddition of azides and alkynes has become the veritable paradigm of click reactions. The classic Huisgen cycloaddition[2] leads to both 1,4- and 1,5-disubstituted 1,2,3-triazoles, with poor or no selectivity. However, in the Cu(I)-catalyzed click variant, azides and terminal

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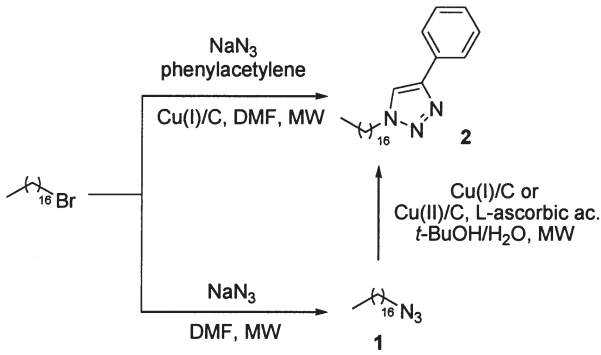
acetylenes react regiospecifically to give 1,4-disubstituted 1,2,3-triazoles; the process is widely applicable and experimentally straightforward. The triazole core thus offers a universal means of ligation and an attractive isosteric replacement in the search for new leads. These features are now promoting this powerful synthetic tool in the fields of polymer and materials science, as well as drug discovery[3]. The catalyst is usually prepared in situ by reduction of Cu(II) salts (that are less expensive and often purer than Cu(I) salts), usually employing L-ascorbic acid or sodium L-ascorbate. Examples of click reactions mediated by heterogeneous Cu(I) catalysis are rare[4]. Recently Lipshutz et al.[5] found that copper supported on charcoal (Cu(II)/C) was an efficient catalyst for the Huisgen 1,3-dipolar cycloaddition. Van der Eycken et al.[6] successfully carried out the same cycloaddition under microwave (MW) irradiation, dramatically cutting down the reaction time.

The present work aimed to optimize the reaction protocol by comparing the efficacy of soluble copper catalysts with that of heterogeneous catalysis based on charcoal-supported Cu(II) or Cu(I). Our investigation also covered role of the solvent, effect of temperature, and physical activation achieved by exposure to MW or simultaneous irradiation with MW and high-intensity ultrasound (US). In other words, we studied this Cu-catalyzed three-component reaction under both homogeneous and heterogeneous conditions in the search for a fast and efficient protocol leading to 1,4-disubstituted 1,2,3-triazoles. In addition, we extended our strategy to the selective functionalization of cyclodextrins (CDs), a target of great practical interest that we had already exploited for diagnostic applications[7].

Our preliminary trials started with benzyl bromide and phenylacetylene, two conventional substrates for the Huisgen reaction, which we carried out either in two steps (nucleophilic substitution with NaN_3 followed by cyclization) or one-pot reaction. Working in *t*-BuOH–H_2O at 80–85 °C, we compared results obtained under both conventional heating and MW irradiation. We obtained very good yields with Cu(II) sulfate and L-ascorbic acid as well as under heterogeneous catalysis with charcoal-supported Cu(II) or Cu(I). In all cases MW dramatically accelerated the reaction. To broaden the scope of this study, we performed the reaction of phenylacetylene with heptadecyl bromide either one-pot or in two steps, the first one being the preparation of the azide (Scheme 1).

As reported in Table I, the cyclization starting from the azide was carried out in the presence of Cu(II)/C and L-ascorbic acid. MW irradiation improved yields up to 83%, cutting the reaction time down to 10 min (entry 2). Recycling of the catalyst was feasible, and its reuse in the same



SCHEME 1

reaction afforded the same yields found in the first cycle, even though the reducing agent was omitted (entry 3); thus the addition of L-ascorbic acid and Et_3N to the recycled catalyst (as recommended by Lipshutz[5]) could be dispensed with. This finding led us to investigate from the very beginning the role of the reducing agent. When the reaction was carried out in the absence of L-ascorbic acid under simple heating (oil bath), conversion was poor and yields very low (entry 4); on the contrary, under MW irradiation complete conversion took place and an 81% yield was obtained after 45 min (entry 5). Although the catalysis with Cu(I) salts was reported to require a co-solvent such as acetonitrile and the presence of an amine[8], we

TABLE I
Huisgen 1,3-dipolar cycloadditions under heterogeneous catalysis

Entry	Catalyst 10 mole %	Operating conditions 85 °C	Reaction time min	Yield %
1	Cu^{II}/C, L-ascorbic acid	oil bath	120	79
2	Cu^{II}/C, L-ascorbic acid	MW	10	83
3	recycled Cu^{II}/C[a]	MW	30	84
4	Cu^{II}/C	oil bath	180	30
5	Cu^{II}/C	MW	45	81
6	Cu^{I}/C	oil bath	120	78
7	Cu^{I}/C	MW	10	89
8	Cu^{I}/C	MW/US	10	93

[a] Reaction carried out in the presence of recycled catalyst from the reaction listed as entry 2.

found that charcoal-supported Cu(I) catalyzed the reaction in *t*-BuOH–H_2O without any addition of amine. Cu(I)/C was prepared by impregnation of activated charcoal with CuI following the Lipshutz protocol. Cu(I)/C catalysis under MW irradiation gave excellent results: after 10 min the final product was isolated in 89% yield, no further purification being required (entry 7). A small improvement was found with simultaneous MW/US irradiation[9], achieved by inserting into the MW oven a non-metallic US horn (made of Pyrex, fused quartz or PEEK, i.e. poly(ether–ether ketone))[9,10].

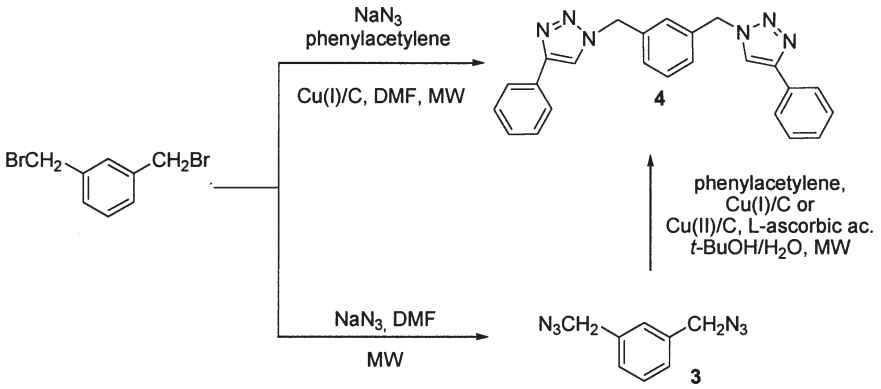
Working under heterogeneous catalysis (Cu(I)/C or Cu(II)/C) MW irradiation proved to be crucial for the one-pot reaction, when the azide was generated in situ from the corresponding halide (Scheme 1). With the exception of highly reactive benzyl bromide, usually the reaction was much slower compared with standard click reactions and its rate depended on the nature of the alkyl bromide. As shown in Table II, under MW benzyl bromide reacted faster but the yield was unaffected. 1-Bromoheptadecane in *t*-BuOH–H_2O at 85 °C gave a very poor yield, which even under MW did not reach 50%. However, the same reaction, when performed under MW irradiation in DMF at 110 °C, afforded in a few minutes the desired product **2** in good yield (Table II, entries 5, 6).

TABLE II
One-pot Huisgen 1,3-dipolar cycloadditions under heterogeneous catalysis (Cu(I)/C, 0.1 equiv.)

Entry	Substrate	Solvent	Operating conditions	Reaction time min	Yield %
1	benzyl bromide	*t*-BuOH–H_2O	oil bath, 85 °C	90	94
2	benzyl bromide	*t*-BuOH–H_2O	MW, 85 °C	20	95
3	1-bromoheptadecane	*t*-BuOH–H_2O	oil bath, 85 °C	90	28
4	1-bromoheptadecane	*t*-BuOH–H_2O	MW, 85 °C	45	47
5	1-bromoheptadecane	DMF	MW, 110 °C	25	85
6	1-bromoheptadecane	DMF	MW/US, 110 °C	20	80

These encouraging results prompted us to try the synthesis of the corresponding bistriazole derivative from dibromo-*m*-xylene and phenylacetylene, as a first step towards an easy method for cross-linking two acetylenic moieties. After some preliminary trials carried out in two steps, we turned to the one-pot reaction under homogeneous catalysis, which

gave product **4** in good yield (Scheme 2). This procedure, using a soluble Cu(II) salt, required a silica gel column purification for the removal of copper traces from the product. When Cu(II)/C was used as catalyst, the reaction time was longer and, besides **4**, a small amount of the corresponding monotriazole was also obtained. Because in *t*-BuOH–H_2O benzyl bromide underwent partial degradation, we repeated the reaction in anhydrous DMF in the presence of Cu(I)/C. The final product **4** was isolated in 78% yield when the process was carried out under MW; traces of the monotriazole derivative were formed (Table III).



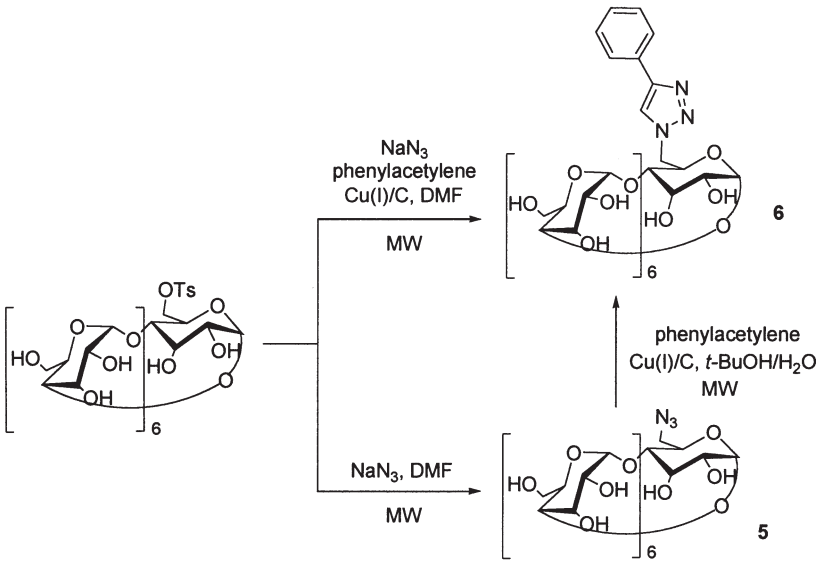
SCHEME 2

TABLE III
One-pot Huisgen 1,3-dipolar cycloadditions with soluble or insoluble catalyst

Entry	Catalyst 10 mole %	Solvent	Operating conditions	Reaction time min	Yield %
1	$CuSO_4$, L-ascorbic acid	*t*-BuOH–H_2O	oil bath, 85 °C	120	63
2	$CuSO_4$, L-ascorbic acid	*t*-BuOH–H_2O	MW, 85 °C	30	71
3	$CuSO_4$, L-ascorbic acid	*t*-BuOH–H_2O	MW/US, 85 °C	20	76
4	Cu^{II}/C, L-ascorbic acid	*t*-BuOH–H_2O	oil bath, 85 °C	240	20
5	Cu^{II}/C, L-ascorbic acid	*t*-BuOH–H_2O	MW, 85 °C	30	50
6	Cu^{I}/C	DMF	oil bath, 110 °C	240	40
7	Cu^{I}/C	DMF	MW, 110 °C	30	78

As the click Huisgen cycloaddition shows a high tolerance to many functional groups and proceeds to completion in a large variety of solvents including aqueous *tert*-butyl alcohol, we decided to apply it to β-cyclodextrin (β-CD) derivatives. To the best of our knowledge, only one example of click chemistry concerning β-CD has appeared in the literature, viz. a copperless MW-assisted procedure that afforded a mixture of heptakis-4-[poly(ε-caprolactone)]-1*H*-1,2,3-triazol-1-yl-β-CD and heptakis-5-[poly(ε-caprolactone)]-1*H*-1,2,3-triazol-1-yl-β-CD [11].

Formation of triazole-substituted CDs has now been investigated under both homogeneous and heterogeneous Cu catalysis. To this end, 6^1-azido-6^1-deoxy-β-CD and heptakis[6-*O*-(*tert*-butyldimethylsilyl)]-2^1-*O*-propargyl-β-CD were prepared as described previously[12] and reacted with phenylacetylene and heptadecyl azide, respectively (Scheme 3). Both reactions were catalyzed either with 3% $CuSO_4$ plus L-ascorbic acid (protocol A) or with Cu(I)/C (protocol B). 6^1-Azido-6^1-deoxy-β-CD reacted (A) with phenylacetylene to afford 6^1-deoxy-6^1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-β-CD (**6**). The reaction proceeded to completion at 80 °C in 4 h; the final product was isolated in 73% yield by precipitation with acetone–water. When the reaction was carried out in the presence of Cu(I)/C (protocol B), the triazolyl derivative **6** was isolated in high yield by filtration (Table IV, entries 1, 2).



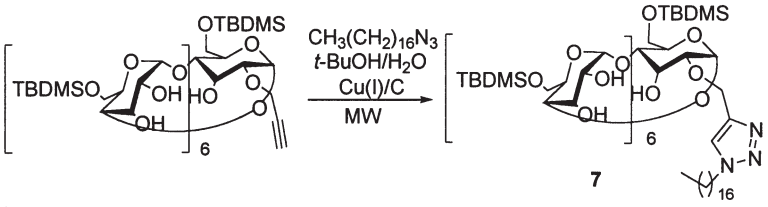
SCHEME 3

We also investigated the feasibility of the one-pot reaction using 6^1-*O*-tosyl-β-CD in DMF under conventional heating and MW irradiation (entries 3, 4). The latter gave an overall yield of 77%.

TABLE IV
Cycloadditions on β-CD derivatives under heterogeneous catalysis (Cu(I)/C, 0.1 equiv.)

Entry	Substrate	Solvent	Operating conditions	Reaction time min	Yield %
1	6^1-azido-6^1-deoxy-β-CD	*t*-BuOH–H_2O	oil bath, 80 °C	90	94
2	6^1-azido-6^1-deoxy-β-CD	*t*-BuOH–H_2O	MW, 80 °C	20	95
3	6^1-*O*-tosyl-β-CD	DMF	oil bath, 85 °C	240	31
4	6^1-*O*-tosyl-β-CD	DMF	MW, 85 °C	20	77

We also applied our optimized procedure to heptakis[6-*O*-(*tert*-butyldimethylsilyl)]-2^1-*O*-propargyl-β-CD in order to evaluate the reactivity of the acetylenic group at position 2 of β-CD. The reaction was performed with 1-azidoheptadecane **1** using Cu(I)/C as catalyst. After 20 min of MW irradiation at 85 °C, conversion was complete and compound **7** was isolated in 60% yield (Scheme 4).



SCHEME 4

In conclusion, the present work demonstrates that MW irradiation substantially improves the Cu-catalyzed Huisgen cycloaddition under both homogeneous and heterogeneous conditions. Bulky and functionalized molecules such as CD derivatives are equally susceptible to triazole cycloaddition without appreciable loss of reactivity. Work is in progress to evaluate the ability of CD derivative **6** to self-assemble by the formation of inclusion complexes between the phenyl group and the inner cavity of the host.

EXPERIMENTAL

Commercially available reagents and solvents were used without further purification unless otherwise noted. β-CD was kindly provided by Wacker Chemie (Germany). Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or by heating after spraying of 5% H_2SO_4 in ethanol or phosphomolybdic acid. Silica gel (Merck) was used for column chromatography (CC). The sonochemical apparatus was developed in our laboratory, model with immersion horn[13] and a modified cup-horn model called a "cavitating tube" because it features a thin titanium tube fixed on the transducer[14]. Both reactors were equipped with efficient cooling systems; all critical parameters (power, frequency, reaction temperature and composition of the modified atmosphere) were monitored. MW-promoted reactions were carried out in a professional oven, MicroSYNTH-Milestone (Italy). IR spectra (ν in cm^{-1}) were recorded with a Shimadzu FT-IR 8001 spectrophotometer. Unless otherwise stated, NMR spectra were recorded on a Bruker 300 Avance (300 and 75 MHz for ^1H and ^{13}C, respectively) at 25 °C; chemical shifts were calibrated to residual proton and carbon resonances of the solvents, $CDCl_3$ (δ_H 7.26, δ_C 77.0), DMSO-d_6 (δ_H 2.54) and $(CD_3)_2CO$ (δ_H 2.05). Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Low-resolution mass spectra were recorded on a Finnigan-MAT TSQ70 apparatus in electron impact (EI) and chemical ionization (CI) modes with isobutane as reactant gas; ESI-MS were recorded on a Waters Micromass ZQ apparatus equipped with ESI source. MALDI-TOF MS were measured on a Bruker Reflex III spectrometer. The elemental analysis was determined on a thermo Electron Flash EA1112 CHNS-O Analyzer.

1-Azidoheptadecane (**1**)

The reaction was carried out under magnetic stirring in the MW oven, the temperature being monitored with an optical-fiber thermometer. 1-Bromoheptadecane (1 g, 3.14 mmol) and sodium azide (224 mg, 3.4 mmol) were dissolved in a mixture of DMF–H_2O (5 ml, 95:5). The mixture was irradiated with MW (200 W) at 85 °C for 15 min, then it was diluted with water (25 ml) and extracted with ethyl acetate (3 × 25 ml). The product was collected as a transparent oil (805 mg, 91% yield). IR: 2924, 2855, 2094 (N_3), 1687, 1466, 1259. ^1H NMR (300 MHz, $CDCl_3$): 3.26 t, 2 H, J(1,2) = 6.6 (H-1); 1.53–1.67 m, 2 H (H-2); 1.18–1.41 m, 28 H (CH_2 aliphatic); 0.887 t, 3 H, J(17,16) = 6.9 (H-17). MS (EI, m/z): 252, 112, 98. MS (CI, m/z): 282 $[M + H]^+$, 254. For $C_{17}H_{35}N_3$ (281.3) calculated: 72.54% C, 12.53% H, 14.93% N; found: 72.48% C, 12.21% H, 14.74% N.

1,3-Bis(azidomethyl)benzene (**3**)

The reaction was carried out under magnetic stirring in the MW oven, the temperature being monitored with an optical-fiber thermometer. In a 25-ml two-necked round-bottomed flask equipped with a condenser and an optical-fiber thermometer, 1,3-bis(bromomethyl)-benzene (1 g, 3.79 mmol) and sodium azide (0.98 g, 15.1 mmol) were dissolved in a mixture of DMF (10 ml) and water (0.5 ml). The mixture was irradiated at 100 W for 5 min, the temperature increased up to 80 °C. The reaction was monitored by TLC (hexane–EtOAc 9:1). The reaction mixture was diluted with EtOAc, washed with water (3 × 30 ml) and brine, then dried (Na_2SO_4) and evaporated to give 0.47 g of **3** as a yellow oil (yield 66%). IR: 2099 (N_3), 1447, 1344, 1264, 706. ^1H NMR (300 MHz, $CDCl_3$): 7.45–7.40 m, 1 H (H-5); 7.32–7.27 m,

3 H (H-2,4,6); 4.38 s, 4 H (-N-C**H**$_2$-Ph). MS (CI, *m/z*): 189 $[M + H]^+$. For $C_8H_8N_6$ (188.1) calculated: 51.06% C, 4.28% H, 44.66% N; found: 51.15% C, 4.32% H, 44.74% N.

6^1-Azido-6^1-deoxy-β-CD (**5**)

The reaction was carried out under magnetic stirring in the MW oven, the temperature being monitored with an optical-fiber thermometer. Sodium azide (181 mg, 2.79 mmol) was suspended in DMF (20 ml), and 6^1-*O*-tosyl-β-CD (2 g, 1.55 mmol) was added. The mixture was irradiated with MW at 85 °C (200 W) for 2 min, then acetone (20 ml) was added and the formed precipitate was filtered. After crystallization from water–acetone 9:1, 1.35 g of pure 6^1-azido-6^1-deoxy-β-CD was obtained (75% yield). M.p. > 221 °C (dec.). IR: 3400, 2104 (N_3), 1663, 1437, 1412, 1333, 1300, 1157,1030, 915. ^{1}H NMR (300 MHz, DMSO-d_6): 5.56–5.76 m, 14 H (OH-2,3); 4.87 shoulder, 1 H (H-1); 4.81 br s, 6 H (H-1); 4.4–4.56 m, 6 H (OH-6); 3.48–3.81 m, 28 H; 3.23–3.44 m, overlaps with H_2O. MS (MALDI-TOF, *m/z*): 1198.59 $[M + K]^+$. For $C_{42}H_{69}N_3O_{33}$ (1159.4) calculated: 44.10% C, 6.08% H, 3.67% N; found: 44.41% C, 6.22% H, 3.74% N.

Preparation of Cu(I)/C

Activated carbon (5 g) was suspended with CuI (556 mg) in H_2O (70 ml), the suspension was degassed and sonicated for 2 h (20.4 kHz, 150 W). Water was distilled off and the remaining solid heated to 200 °C for 20 min. Finally it was washed with toluene and dried under vacuum.

Cu-Catalyzed Huisgen 1,3-Dipolar Cycloadditions. General Procedure

Two-step procedure. In a 25-ml two-necked round-bottomed flask (equipped with an optical-fiber thermometer for reactions under MW or combined MW/US) the copper catalyst ($CuSO_4$ or Cu(II)/C or Cu(I)/C, both containing 10 mole % of Cu) was suspended in a mixture of *t*-BuOH–H_2O (5 ml, 1:1). The alkyl azide (1 mmol) and the acetylenic derivative (1 mmol, if not otherwise stated) were added; a further addition of 20 mole % of L-ascorbic acid was made only when the catalyst was based on Cu(II). The mixture was heated or irradiated with MW or MW/US as indicated in the tables. The reaction outcome was monitored by TLC until complete conversion of the starting material was observed. When the reaction was performed under heterogeneous catalysis, the catalyst was filtered off, washed and recovered. The liquid was partially evaporated, diluted with water (20 ml), extracted with ethyl acetate (3 × 30 ml), and finally dried (Na_2SO_4) and the solvent evaporated under vacuum.

One-pot procedure. In a 25-ml two-necked round-bottomed flask (equipped with an optical-fiber thermometer for reactions under MW or combined MW/US), the alkyl bromide or the tosylate (1 mmol) and sodium azide (1.5 mmol) were dissolved in a mixture of *t*-BuOH–H_2O (5 ml, 1:1) or DMF. When *t*-BuOH–H_2O was used as solvent, the flask was equipped with a reflux condenser. The catalyst ($CuSO_4$ or Cu(II)/C or Cu(I)/C, both containing 10 mole % of Cu) and the acetylenic derivative (1 mmol) were added. L-Ascorbic acid (20 mole %) was added only when the catalyst was based on Cu(II). The mixture was heated or irradiated with MW or MW/US as indicated in the tables. The reaction outcome was monitored by TLC until complete conversion of the starting material and the azide intermediate was observed. When the reaction was performed under heterogeneous catalysis, the catalyst was filtered off, washed, and recovered. The liquid was partially evaporated, diluted with wa-

ter (20 ml), extracted with ethyl acetate (3 × 30 ml), and finally dried (Na_2SO_4) and evaporated under vacuum.

1-Heptadecyl-4-phenyl-1H-1,2,3-triazole (**2**). This compound was synthesized using both general procedures and in no case further purification was necessary. The two-step procedure started from 1-azidoheptadecane (**1**) and was done in the presence of 10 mole % of Cu(I)/C, irradiation with MW at 85 °C for 10 min). The desired product was obtained in 89% yield. The one-pot procedure started from 1-bromoheptadecane (DMF, 10 mole % of Cu(I)/C, irradiation with MW at 110 °C for 25 min). The desired product was obtained in 85% yield. M.p. 94 °C. IR: 2918, 2941, 2847, 2096 (N_3), 1464, 1217, 1080, 1053, 976, 912, 841, 726, 734, 694. ^{1}H NMR (300 MHz, $CDCl_3$): 7.88 d, 2 H, *J*(2′,3′Ph) = 7.2 (H-2′,6′ Ph); 7.74 s, 1 H (H-5); 7.21–7.45 m 3 H (H-3′,4′,5′ Ph); 4.34 t, 2 H, *J*(1′,2′) = 7.2 (H-1′); 1.88–2.01 m, 2 H (H-2′); 1.52–1.63 m, 2 H (H-3′); 1.13–1.42 m, 26 H (CH_2 aliphatic); 0.88 t, 3 H, *J*(17′,16′) = 6.9 (H-17′). MS (EI, *m/z*): 383 $[M]^+$, 354, 172, 145. MS (CI, *m/z*): 384 $[M + H]^+$. For $C_{25}H_{41}N_3$ (383.3) calculated: 78.27% C, 10.77% H, 10.95% N; found: 78.15% C, 10.52% H, 11.10% N.

1,3-Bis[(4-phenyl-1H-1,2,3-triazol-1-yl)methyl]benzene (**4**). This compound was synthesized using both general procedures and in no case further purification was necessary. The two-step procedure started from 1,3-bis(azidomethyl)benzene (**3**) using acetylenic compound (2 mmol), sodium azide (3 mmol), 10 mole % of Cu(II)/C and 20 mole % of L-ascorbic acid (irradiation with MW at 85 °C for 20 min). The desired product was obtained in 85% yield. The one-pot procedure started from dibromo-*m*-xylene (10 mole % of Cu(I)/C, irradiation with MW at 110 °C for 30 min). The desired product was recovered in 78% yield. M.p. 145 °C. IR: 3088, 2941, 2860, 2099 (N_3), 1460, 1441, 1221, 1200, 1078, 1049, 837, 820, 762, 692. ^{1}H NMR (300 MHz, acetone-d_6): 8.37 s, 2 H (H-5); 7.86 d, 4 H, *J*(2′,3′Ph) = 6.9 (H-2′,6′); 7.49–7.28 m, 10 H (H-2,4,5,6 Bz, H-3′,4′,5′ Ph); 5.70 s, 4 H (-N-C**H**$_2$-Ph). MS (CI, *m/z*): 393 $[M + H]^+$. For $C_{24}H_{20}N_6$ (392.2) calculated: 73.45% C, 5.14% H, 21.41% N; found: 73.25% C, 5.32% H, 21.19% N.

6^1-Deoxy-6^1-(4-phenyl-1H-1,2,3-triazol-1-yl)-β-*CD* (**6**). This compound was synthesized using both general procedures and purification specified further was used. The two-step procedure started from 6^1-azido-6^1-deoxy-β-CD (**5**), solution of azido derivative (1 mmol), acetylenic compound (5 mmol) and 10 mole % of Cu(I)/C (irradiation with MW at 85 °C for 20 min). The catalyst was filtered off and washed with water, the filtrate was partially evaporated and precipitated with acetone, the product was washed with the same solvent and obtained in 95% yield. The one-pot procedure started from 6^1-*O*-tosyl-β-CD (DMF, 10 mole % of Cu(I)/C, irradiation with MW at 85 °C for 20 min). The catalyst was filtered off and washed with water, the filtrate was partially evaporated and precipitated with acetone, the product was washed with the same solvent and obtained in 77% yield. M.p. > 235 °C (dec.). IR: 3420, 2926, 2104 (N_3), 1655, 1458, 1367, 1333, 1157, 1097, 1028, 947, 756. ^{1}H NMR (300 MHz, DMSO-d_6): 8.52 s, 1 H (H-5′ triazole); 7.80 d, 2 H, *J*(2′,3′Ph) = 7.5 (H-2′,6′ Ph); 7.42 t, 2 H, *J* = 7.5 (H-3′,5′ Ph); 7.32 d, 1 H, *J* = 7.5 (H-4′ Ph); 5.9–5.52 m, 14 H (OH-2,3); 4.85–4.61 m, 7 H (H-1); 4.35–4.65 m, 6 H (OH-6); 3.43–3.78 m, 28 H (H-3,5,6a,6b); 3.15–3.42 (m, overlaps with H_2O). ESI-MS: 1284.3 $[M + Na]^+$. For $C_{50}H_{75}N_3O_{34}$ (1261.4) calculated: 47.58% C, 5.99% H, 3.33% N; found: 47.79% C, 5.72% H, 3.40% N.

Heptakis[6-O-(tert-butyldimethylsilyl)]-2^1-O-(1-heptadecyl-1H-1,2,3-triazol-1-yl)methyl-β-*CD* (**7**). The compound was synthesized from heptakis[6-*O*-(*tert*-butyldimethylsilyl)]-2^1-*O*-propargyl-β-CD (1 mmol) by the two-step procedure in the presence of 10 mole % of Cu(I)/C and 1-bromoheptadecane (1 mmol) (irradiation with MW at 85 °C for 20 min). The catalyst was

filtered off, and washed with CH_2Cl_2. The filtrate was diluted with CH_2Cl_2, washed with water and brine, and finally dried (Na_2SO_4). The crude residue after evaporation of the solvent under reduced pressure was purified by column chromatography ($CHCl_3$–CH_3OH 9:1) to yield 60% of the desired product as a white powder. M.p. 182 °C. IR: 3420, 1362, 1472, 1252, 1086, 1040, 835. ^{1}H NMR (300 MHz, $CDCl_3$): 4.9–4.7 m, 9 H (H-1 overlapped triazole-C**H**$_2$-O); 4.3 t, 2 H, *J*(1′,2′) = 6.9 (H-1′); 4.1–3.9 m, 14 H (H-3,6b); 3.78–3.6 m, 28 H (H-2,4,5,6a); 1.8–1.7 m, 4 H (H-2′, H-3′); 1.3–1.2 m, 26 H (CH_2 aliphatic); 0.88 s, 66 H (*t*-Bu overlapped H-17′); 0.05 s, 42 H (Si-CH_3). ESI-MS: 1145.6 $[M + Na + H]^{2+}$, 1156.6 $[M + 2\ Na]^{2+}$. For $C_{104}H_{205}N_3O_{35}Si_7$ (2252.3) calculated: 55.41% C, 9.17% H, 1.86% N, 8.72% Si; found: 55.56% C, 9.21% H, 1.71% N, 8.91% Si.

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